

20-1025 (Lead); 20-1138 (Consolidated)

**UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT**

ENVIRONMENTAL HEALTH TRUST; CONSUMERS FOR SAFE CELL
PHONES; ELIZABETH BARRIS; THEODORA SCARATO

CHILDREN'S HEALTH DEFENSE; MICHELE HERTZ; PETRA BROKKEN;
DR. DAVID O. CARPENTER; DR. PAUL DART; DR. TORIL H. JELTER; DR.
ANN LEE; VIRGINIA FARVER, JENNIFER BARAN; PAUL STANLEY, M.Ed.

Petitioners

v.

FEDERAL COMMUNICATIONS COMMISSION;
UNITED STATES OF AMERICA

Respondents

Petition for Review of Order Issued by the
Federal Communications Commission

DEFERRED JOINT APPENDIX**VOLUME 18**

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repetition rates ranging from 0.5 to 110 pps, or it was applied as a continuous wave (CW). When subjected to pulsed waves (PW), rapid, burst-like changes in the firing rate of neurons occurred at SARs of a few W/kg. If the burst-like irregularity was present in the firing rate under control conditions, irradiation enhanced its probability of occurrence. The effect was dependent on modulation, but not on modulation frequency, and it had a threshold SAR near 0.5 W/kg. CW radiation had no effect on the firing rate pattern at the same SAR. Mediator-induced, current activation of acetylcholine, dopamine, serotonin, or gamma-aminobutyric-acid receptors of the neuronal soma was not altered during CW or PW exposures and, hence, could not have been responsible for the bursting effect.

Cao Z, Liu J, Li S, Zhao X. [Effects of electromagnetic radiation from handsets of cellular telephone on neurobehavioral function] Wei Sheng Yan Jiu 29(2):102-103, 2000. [Article in Chinese]

In order to study the effects of electromagnetic radiation from handsets of cellular telephone on neurobehavioral function, 81 staff with handsets of cellular telephone and 63 staff without handsets of cellular telephone from corporations were selected as the subjects. The subjects were investigated by questionnaire on their general health, lifestyle habit, suppress of spirit, handset using of cellular telephone, environmental exposure, morbidity, and the neurobehavioral core test battery(NCTB). The data was analyzed by chi-square, stepwise regression analysis and covariance statistics. The results showed that the average reaction time in user's group was longer than that in control group ($P < 0.01$). The time of using handset was negatively associated with corrected reaction number ($P < 0.01$). The fast reaction time and the slowest reaction time were positively associated with the length of handset using ($P < 0.01$, $P < 0.05$). The results suggested that the handset using could cause adverse health effects in neurobehavioral function.

D'Costa H, Trueman G, Tang L, Abdel-rahman U, Abdel-rahman W, Ong K, Cosic I. Human brain wave activity during exposure to radiofrequency field emissions from mobile phones. Australas Phys Eng Sci Med. 26(4):162-167, 2003.

The aim of this study was to determine whether there is an effect of mobile phone electromagnetic field emissions on the human electroencephalograph (EEG). EEG recordings from ten awake subjects were taken during exposure to radiofrequency (RF) emissions from a mobile phone positioned behind the head. Two experimental trials were conducted. In the first trial, RF exposures were generated by a GSM mobile phone with the speaker disabled and configured to transmit at full-radiated power. During the second trial, exposures were generated by a non-modified GSM mobile phone in active standby mode. For each trial, subjects were exposed in five minute intervals to a randomized, interrupted sequence of five active and five sham exposures. The experiment was conducted under single-blind conditions. The average EEG band power in active exposure recordings was compared to corresponding sham recordings. Statistical tests indicated significant difference in the full-power mode trial within the EEG alpha (8-13 Hz) and beta (13-32 Hz) bands. A subsequent statistical analysis of

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median spectral power in discrete EEG rhythms revealed significant differences in 7 of the 32 distinct frequencies overall. In conclusion, the results of this study lend support to EEG effects from mobile phones activated in talk-mode.

Ammari M, Brillaud E, Gamez C, Lecomte A, Sakly M, Abdelmelek H, de Seze R. Effect of a chronic GSM 900MHz exposure on glia in the rat brain. *Biomed Pharmacother.* 62(4):273-281, 2008.

Extension of the mobile phone technology raises concern about the health effects of 900MHz microwaves on the central nervous system (CNS). In this study we measured GFAP expression using immunocytochemistry method, to evaluate glial evolution 10 days after a chronic exposure (5 days a week for 24 weeks) to GSM signal for 45min/day at a brain-averaged specific absorption rate (SAR)=1.5W/kg and for 15min/day at a SAR=6W/kg in the following rat brain areas: prefrontal cortex (Pfcx), caudate putamen (Cpu), lateral globus pallidus of striatum (LGP), dentate gyrus of hippocampus (DG) and cerebellum cortex (CCx). In comparison to sham or cage control animals, rats exposed to chronic GSM signal at 6W/kg have increased GFAP stained surface areas in the brain ($p<0.05$). But the chronic exposure to GSM at 1.5W/kg did not increase GFAP expression. Our results indicated that chronic exposure to GSM 900MHz microwaves (SAR=6W/kg) may induce persistent astroglia activation in the rat brain (sign of a potential gliosis).

Ammari M, Lecomte A, Sakly M, Abdelmelek H, de-Seze R. Exposure to GSM 900 MHz electromagnetic fields affects cerebral cytochrome c oxidase activity. *Toxicology.* 250(1):70-74, 2008.

The world-wide and rapidly growing use of mobile phones has raised serious concerns about the biological and health-related effects of radio frequency (RF) radiation, particularly concerns about the effects of RFs upon the nervous system. The goal of this study was conducted to measure cytochrome oxidase (CO) levels using histochemical methods in order to evaluate regional brain metabolic activity in rat brain after exposure to a GSM 900 MHz signal for 45 min/day at a brain-averaged specific absorption rate (SAR) of 1.5 W/Kg or for 15 min/day at a SAR of 6 W/Kg over seven days. Compared to the sham and control cage groups, rats exposed to a GSM signal at 6 W/Kg showed decreased CO activity in some areas of the prefrontal and frontal cortex (infralimbic cortex, prelimbic cortex, primary motor cortex, secondary motor cortex, anterior cingulate cortex areas 1 and 2 (Cg1 and Cg2)), the septum (dorsal and ventral parts of the lateral septal nucleus), the hippocampus (dorsal field CA1, CA2 and CA3 of the hippocampus and dental gyrus) and the posterior cortex (retrosplenial agranular cortex, primary and secondary visual cortex, perirhinal cortex and lateral entorhinal cortex). However, the exposure to GSM at 1.5 W/Kg did not affect brain activity. Our results indicate that 6 W/Kg GSM 900 MHz microwaves may affect brain metabolism and neuronal activity in rats.

Ammari M, Gamez C, Lecomte A, Sakly M, Abdelmelek H, De Seze R. GFAP expression in the rat brain following sub-chronic exposure to a 900 MHz electromagnetic field

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signal. Int J Radiat Biol. 86(5):367-375, 2010.

PURPOSE: The rapid development and expansion of mobile communications contributes to the general debate on the effects of electromagnetic fields emitted by mobile phones on the nervous system. This study aims at measuring the glial fibrillary acidic protein (GFAP) expression in 48 rat brains to evaluate reactive astrogliosis, three and 10 days after long-term head-only sub-chronic exposure to a 900 MHz electromagnetic field (EMF) signal, in male rats. **METHODS:** Sprague-Dawley rats were exposed for 45 min/day at a brain-averaged specific absorption rate (SAR) = 1.5 W/kg or 15 min/day at a SAR = 6 W/kg for five days per week during an eight-week period. GFAP expression was measured by the immunocytochemistry method in the following rat brain areas: Prefrontal cortex, cerebellar cortex, dentate gyrus of the hippocampus, lateral globus pallidus of the striatum, and the caudate putamen. **RESULTS:** Compared to the sham-treated rats, those exposed to the sub-chronic GSM (Global System for mobile communications) signal at 1.5 or 6 W/kg showed an increase in GFAP levels in the different brain areas, three and ten days after treatment. **CONCLUSION:** Our results show that sub-chronic exposures to a 900 MHz EMF signal for two months could adversely affect rat brain (sign of a potential gliosis).

Ammari M, Gamez C, Lecomte A, Sakly M, Abdelmelek H, De Seze R. GFAP expression in the rat brain following sub-chronic exposure to a 900 MHz electromagnetic field signal. Int J Radiat Biol. 86(5):367-375, 2010.

PURPOSE: The rapid development and expansion of mobile communications contributes to the general debate on the effects of electromagnetic fields emitted by mobile phones on the nervous system. This study aims at measuring the glial fibrillary acidic protein (GFAP) expression in 48 rat brains to evaluate reactive astrogliosis, three and 10 days after long-term head-only sub-chronic exposure to a 900 MHz electromagnetic field (EMF) signal, in male rats. **METHODS:** Sprague-Dawley rats were exposed for 45 min/day at a brain-averaged specific absorption rate (SAR) = 1.5 W/kg or 15 min/day at a SAR = 6 W/kg for five days per week during an eight-week period. GFAP expression was measured by the immunocytochemistry method in the following rat brain areas: Prefrontal cortex, cerebellar cortex, dentate gyrus of the hippocampus, lateral globus pallidus of the striatum, and the caudate putamen. **RESULTS:** Compared to the sham-treated rats, those exposed to the sub-chronic GSM (Global System for mobile communications) signal at 1.5 or 6 W/kg showed an increase in GFAP levels in the different brain areas, three and ten days after treatment. **CONCLUSION:** Our results show that sub-chronic exposures to a 900 MHz EMF signal for two months could adversely affect rat brain (sign of a potential gliosis).

Barth A, Winker R, Ponocny-Seliger E, Mayrhofer W, Ponocny I, Sauter C, Vana N. A meta-analysis for neurobehavioral effects due to electromagnetic field exposure emitted by GSM mobile phones. Occup Environ Med. 65(5):342-6, 2008.

BACKGROUND AND OBJECTIVE: Numerous studies have investigated the potential effects of electromagnetic fields (EMFs) emitted by GSM mobile phones (~900 MHz to ~1800 MHz) on cognitive functioning, but results have been equivocal. In order to try

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and clarify this issue, the current study carried out a meta-analysis on nineteen experimental studies. DESIGN: meta-analysis METHODS: Nineteen studies were taken into consideration. Ten of them were included in the meta-analysis as they fulfil several minimum requirements; for example, single-blind or double-blind experimental study design and documentation of means and standard deviation of the dependent variables. The meta-analysis aimed at comparing exposed with non-exposed subjects assuming that there is a common population effect so that one single effect size could be calculated. When homogeneity for single effect sizes was not given, an own population effect for each study and a distribution of population effects was assumed. RESULTS: Attention measured by the subtraction task seems to be affected in regard of decreased reaction time. Working memory measured by the N-back test seems to be affected too: Under condition 0-back target response time is lower under exposure, while under condition 2-back target response time increases. The number of errors under condition 2-back non-targets appears to be higher under exposure. CONCLUSION: Results of the meta-analysis suggest that EMFs may have a small impact on human attention and working memory.

Papageorgiou CC, Nanou ED, Tsiafakis VG, Kapareliotis E, Kontoangelos KA, Capsalis CN, Rabavilas AD, Soldatos CR. Acute mobile phone effects on pre-attentive operation. Neurosci Lett 397(1-2):99-103, 2006.

There is a debate whether electromagnetic field (EMF) emitted by mobile phones (MP) have an effect on cognitive functions. Since the auditory P50 component of event-related potentials (ERPs) reflects pre-attentive processing and working memory (WM) operation, the present study was designed to investigate whether the exposure to MP-EMF affects the patterns of the P50 component of ERPs elicited during a WM test. The P50 elicited during a WM task and evoked by two warning stimuli low and high frequency (500 and 3000Hz) has been assessed in 19 normal subjects (10 women and 9 men) both without and with exposure to a 900MHz signal, emitted by a dipole antenna placed near the subjects. Results showed that the presence of MP-EMFs induced statistically significant increase in the amplitude of P50 evoked by the low frequency stimuli, at Fp1 and O1 electrode leads as compared to themselves without MP-EMF exposure. In contrast the exposure to MP-EMFs revealed statistically significant decrease of the amplitude of P50 evoked by the high frequency stimuli, at Fp1 electrode lead as compared to themselves without MP-EMF exposure. These findings provide evidence that the MP-EMF emitted by mobile phone affect pre-attentive information processing as it is reflected in P50 evoked potential. The basis of such an effect is unclear, although several possibilities exist and call for potential directions of future research.

Papageorgiou CC, Nanou ED, Tsiafakis VG, Capsalis CN, Rabavilas AD. Gender related differences on the EEG during a simulated mobile phone signal. Neuroreport. 15(16):2557-2560, 2004.

The present study investigated the gender-related influence of electromagnetic fields (EMF), similar to that emitted by mobile phones, on brain activity. Ten women and nine

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men performed a short memory task (Wechsler test), both without (baseline) and with exposure to a 900 MHz signal. The EEG energy of the total waveform and the alpha, beta, delta and theta; rhythms were calculated from the recordings of 15 scalp electrodes. Baseline EEG energy of males was greater than that of females, while exposure to EMF decreased EEG energy of males and increased that of females. Memory performance was invariant to EMF exposure and gender influences. These findings indicate that EMF may exert a gender-related influence on brain activity.

Effects on Brain

Aalto S, Haarala C, Bruck A, Sipila H, Hamalainen H, Rinne JO. Mobile phone affects cerebral blood flow in humans. *J Cereb Blood Flow Metab.* 26(7):885-890, 2006.

Mobile phones create a radio-frequency electromagnetic field (EMF) around them when in use, the effects of which on brain physiology in humans are not well known. We studied the effects of a commercial mobile phone on regional cerebral blood flow (rCBF) in healthy humans using positron emission tomography (PET) imaging. Positron emission tomography data was acquired using a double-blind, counterbalanced study design with 12 male subjects performing a computer-controlled verbal working memory task (letter 1-back). Explorative and objective voxel-based statistical analysis revealed that a mobile phone in operation induces a local decrease in rCBF beneath the antenna in the inferior temporal cortex and an increase more distantly in the prefrontal cortex. Our results provide the first evidence, suggesting that the EMF emitted by a commercial mobile phone affects rCBF in humans. These results are consistent with the postulation that EMF induces changes in neuronal activity.

Megha K, Deshmukh PS, Banerjee BD, Tripathi AK, Abegaonkar MP. Microwave radiation induced oxidative stress, cognitive impairment and inflammation in brain of Fischer rats. *Indian J Exp Biol.* 50(12):889-896, 2012.

Public concerns over possible adverse effects of microwave radiation emitted by mobile phones on health are increasing. To evaluate the intensity of oxidative stress, cognitive impairment and inflammation in brain of Fischer rats exposed to microwave radiation, male Fischer-344 rats were exposed to 900 MHz microwave radiation (SAR = 5.953×10^{-4} W/kg) and 1800 MHz microwave radiation (SAR = 5.835×10^{-4} W/kg) for 30 days (2 h/day). Significant impairment in cognitive function and induction of oxidative stress in brain tissues of microwave exposed rats were observed in comparison with sham exposed groups. Further, significant increase in level of cytokines (IL-6 and TNF-alpha) was also observed following microwave exposure. Results of the present study indicated that increased oxidative stress due to microwave exposure may contribute to cognitive impairment and inflammation in brain.

Maskey D, Kim M, Aryal B, Pradhan J, Choi IY, Park KS, Son T, Hong SY, Kim SB, Kim HG, Kim MJ. Effect of 835 MHz radiofrequency radiation exposure on calcium binding

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proteins in the hippocampus of the mouse brain. Brain Res.1313:232-241, 2010.

Worldwide expansion of mobile phones and electromagnetic field (EMF) exposure has raised question of their possible biological effects on the brain and nervous system. Radiofrequency (RF) radiation might alter intracellular signaling pathways through changes in calcium (Ca(2+)) permeability across cell membranes. Changes in the expression of calcium binding proteins (CaBP) like calbindin D28-k (CB) and calretinin (CR) could indicate impaired Ca(2+)homeostasis due to EMF exposure. CB and CR expression were measured with immunohistochemistry in the hippocampus of mice after EMF exposure at 835 MHz for different exposure times and absorption rates, 1 h/day for 5 days at a specific absorption rate (SAR)=1.6 W/kg, 1 h/day for 5 days at SAR=4.0 W/kg, 5 h/day for 1 day at SAR=1.6 W/kg, 5 h/day for 1 day at SAR=4.0 W/kg, daily exposure for 1 month at SAR=1.6 W/kg. Body weights did not change significantly. CB immunoreactivity (IR) displayed moderate staining of cells in the cornu ammonis (CA) areas and prominently stained granule cells. CR IR revealed prominently stained pyramidal cells with dendrites running perpendicularly in the CA area. Exposure for 1 month produced almost complete loss of pyramidal cells in the CA1 area. CaBP differences could cause changes in cellular Ca(2+)levels, which could have deleterious effect on normal hippocampal functions concerned with neuronal connectivity and integration.

Tong J, Chen S, Liu XM, Hao DM. [Effect of electromagnetic radiation on discharge activity of neurons in the hippocampus CA1 in rats]. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 29(5):423-427, 2013. [Article in Chinese]

OBJECTIVE: In order to explore effect of electromagnetic radiation on learning and memory ability of hippocampus neuron in rats, the changes in discharge patterns and overall electrical activity of hippocampus neuron after electromagnetic radiation were observed. METHODS: Rat neurons discharge was recorded with glass electrode extracellular recording technology and a polygraph respectively. Radiation frequency of electromagnetic wave was 900 MHz and the power was 10 W/m². In glass electrode extracellular recording, the rats were separately irradiated for 10, 20, 30, 40, 50 and 60 min, every points repeated 10 times and updated interval of 1h, observing the changes in neuron discharge and spontaneous discharge patterns after electromagnetic radiation. In polygraph recording experiments, irradiation group rats for five days a week, 6 hours per day, repeatedly for 10 weeks, memory electrical changes in control group and irradiation group rats when they were feeding were repeatedly monitored by the implanted electrodes, observing the changes in peak electric digits and the largest amplitude in hippocampal CA1 area, and taking some electromagnetic radiation sampling sequence for correlation analysis. RESULTS: (1) Electromagnetic radiation had an inhibitory role on discharge frequency of the hippocampus CA1 region neurons. After electromagnetic radiation, discharge frequency of the hippocampus CA1 region neurons was reduced, but the changes in scale was not obvious. (2) Electromagnetic radiation might change the spontaneous discharge patterns of hippocampus CA1 region neurons, which made the explosive discharge pattern increased obviously. (3) Peak potential total number within 5 min in irradiation group was significantly reduced, the largest

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amplitude was less than that of control group. (4) Using mathematical method to make the correlation analysis of the electromagnetic radiation sampling sequence, that of irradiation group was less than that of control group, indicating that there was a tending to be inhibitory connection between neurons in irradiation group after electromagnetic radiation. CONCLUSION: Electromagnetic radiation may cause structure and function changes of transfer synaptic in global, make hippocampal CA1 area neurons change in the overall discharge characteristic and discharge patterns, thus lead to decrease in the ability of learning and memory.

Aboul Ezz HS, Khadrawy YA, Ahmed NA, Radwan NM, El Bakry MM. The effect of pulsed electromagnetic radiation from mobile phone on the levels of monoamine neurotransmitters in four different areas of rat brain. Eur Rev Med Pharmacol Sci. 17(13):1782-1788, 2013.

BACKGROUND: The use of mobile phones is rapidly increasing all over the world. Few studies deal with the effect of electromagnetic radiation (EMR) on monoamine neurotransmitters in the different brain areas of adult rat. **AIM:** The aim of the present study was to investigate the effect of EMR on the concentrations of dopamine (DA), norepinephrine (NE) and serotonin (5-HT) in the hippocampus, hypothalamus, midbrain and medulla oblongata of adult rats. **MATERIALS AND METHODS:** Adult rats were exposed daily to EMR (frequency 1800 MHz, specific absorption rate 0.843 W/kg, power density 0.02 mW/cm², modulated at 217 Hz) and sacrificed after 1, 2 and 4 months of daily EMR exposure as well as after stopping EMR for 1 month (after 4 months of daily EMR exposure). Monoamines were determined by high performance liquid chromatography coupled with fluorescence detection (HPLC-FD) using their native properties. **RESULTS:** The exposure to EMR resulted in significant changes in DA, NE and 5-HT in the four selected areas of adult rat brain. CONCLUSIONS: The exposure of adult rats to EMR may cause disturbances in monoamine neurotransmitters and this may underlie many of the adverse effects reported after EMR including memory, learning, and stress.

Ning W, Xu SJ, Chiang H, Xu ZP, Zhou SY, Yang W, Luo JH. Effects of GSM 1800 MHz on dendritic development of cultured hippocampal neurons. Acta Pharmacol Sin. 28(12):1873-1880, 2007.

AIM: To evaluate the effects of global system for mobile communications (GSM) 1800 MHz microwaves on dendritic filopodia, dendritic arborization, and spine maturation during development in cultured hippocampal neurons in rats. **METHODS:** The cultured hippocampal neurons were exposed to GSM 1800 MHz microwaves with 2.4 and 0.8 W/kg, respectively, for 15 min each day from 6 days in vitro (DIV6) to DIV14. The subtle structures of dendrites were displayed by transfection with farnesylated enhanced green fluorescent protein (F-GFP) and GFP-actin on DIV5 into the hippocampal neurons. **RESULTS:** There was a significant decrease in the density and mobility of dendritic filopodia at DIV8 and in the density of mature spines at DIV14 in the neurons exposed to GSM 1800 MHz microwaves with 2.4 W/kg. In addition, the average length of dendrites per neuron at DIV10 and DIV14 was decreased, while the dendritic

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arborization was unaltered in these neurons. However, there were no significant changes found in the neurons exposed to the GSM 1800 MHz microwaves with 0.8 W/kg. **CONCLUSION:** These data indicate that the chronic exposure to 2.4 W/kg GSM 1800 MHz microwaves during the early developmental stage may affect dendritic development and the formation of excitatory synapses of hippocampal neurons in culture.

Eser O, Songur A, Aktas C, Karavelioglu E, Caglar V, Aylak F, Ozguner F, Kanter M. The effect of electromagnetic radiation on the rat brain: an experimental study. Turk Neurosurg. 23(6):707-715, 2013.

AIM: The aim of this study is to determine the structural changes of electromagnetic waves in the frontal cortex, brain stem and cerebellum. MATERIAL and METHODS: 24 Wistar Albino adult male rats were randomly divided into four groups: group I consisted of control rats, and groups II-IV comprised electromagnetically irradiated (EMR) with 900, 1800 and 2450 MHz. The heads of the rats were exposed to 900, 1800 and 2450 MHz microwaves irradiation for 1h per day for 2 months. RESULTS: While the histopathological changes in the frontal cortex and brain stem were normal in the control group, there were severe degenerative changes, shrunken cytoplasm and extensively dark pyknotic nuclei in the EMR groups. Biochemical analysis demonstrated that the Total Antioxidative Capacity level was significantly decreased in the EMR groups and also Total Oxidative Capacity and Oxidative Stress Index levels were significantly increased in the frontal cortex, brain stem and cerebellum. IL-1 β level was significantly increased in the EMR groups in the brain stem. **CONCLUSION:** EMR causes to structural changes in the frontal cortex, brain stem and cerebellum and impair the oxidative stress and inflammatory cytokine system. This deterioration can cause to disease including loss of these areas function and cancer development.

Motawi TK, Darwish HA, Moustafa YM, Labib MM. Biochemical Modifications and Neuronal Damage in Brain of Young and Adult Rats After Long-Term Exposure to Mobile Phone Radiations. Cell Biochem Biophys. 2014 May 7. [Epub ahead of print]

This study investigated the effect of exposure to mobile phone radiations on oxidative stress and apoptosis in brain of rats. Rats were allocated into six groups (three young and three adult). Groups 1 and 4 were not subjected to the radiation source and served as control groups. In groups 2 and 5, the mobile phones were only connected to the global system for mobile communication, while in groups 3 and 6, the option of calling was in use. Microwaves were generated by a mobile test phone (SAR = 1.13 W/kg) during 60 days (2 h/day). Significant increments in conjugated dienes, protein carbonyls, total oxidant status, and oxidative stress index along with a significant reduction of total antioxidant capacity levels were evident after exposure. Bax/Bcl-2 ratio, caspase-3 activity, and tumor necrosis factor-alpha level were enhanced, whereas no DNA fragmentation was detected. The relative brain weight of young rats was greatly affected, and histopathological examination reinforced the neuronal damage. The study highlights the detrimental effects of mobile phone radiations on brain during young and adult ages. The interaction of these radiations with brain is via dissipating its antioxidant status and/or triggering apoptotic cell death.

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Lv B, Su C, Yang L, Xie Y, Wu T. Whole brain EEG synchronization likelihood modulated by long term evolution electromagnetic fields exposure. Conf Proc IEEE Eng Med Biol Soc. 2014:986-989, 2014.

In this paper, we aimed to investigate the possible interactions between human brain and radiofrequency electromagnetic fields (EMF) with electroencephalogram (EEG) technique. Unlike the previous studies which mainly focused on EMF effect on local brain activities, we attempted to evaluate whether the EMF emitted from Long Term Evolution (LTE) devices can modulate the functional connectivity of brain electrical activities. Ten subjects were recruited to participate in a crossover, double-blind exposure experiment which included two sessions (real and sham exposure). In each session, LTE EMF exposure (power on or off) lasted for 30 min and the EEG signals were collected with 32 channels throughout the experiment. Then we applied the synchronization likelihood method to quantify the neural synchronization over the whole brain in different frequency bands and in different EEG record periods. Our results illustrated that the short-term LTE EMF exposure would modulate the synchronization patterns of EEG activation across the whole brain.

Lv B, Chen Z, Wu T, Shao Q, Yan D, Ma L, Lu K, Xie Y. The alteration of spontaneous low frequency oscillations caused by acute electromagnetic fields exposure. Clin Neurophysiol. 2013 Sep 4. pii: S1388-2457(13)00976-0. doi: 10.1016/j.clinph.2013.07.018. [Epub ahead of print]

OBJECTIVE: The motivation of this study is to evaluate the possible alteration of regional resting state brain activity induced by the acute radiofrequency electromagnetic field (RF-EMF) exposure (30min) of Long Term Evolution (LTE) signal. **METHODS:** We designed a controllable near-field LTE RF-EMF exposure environment. Eighteen subjects participated in a double-blind, crossover, randomized and counterbalanced experiment including two sessions (real and sham exposure). The radiation source was close to the right ear. Then the resting state fMRI signals of human brain were collected before and after the exposure in both sessions. We measured the amplitude of low frequency fluctuation (ALFF) and fractional ALFF (fALFF) to characterize the spontaneous brain activity. **RESULTS:** We found the decreased ALFF value around in left superior temporal gyrus, left middle temporal gyrus, right superior temporal gyrus, right medial frontal gyrus and right paracentral lobule after the real exposure. And the decreased fALFF value was also detected in right medial frontal gyrus and right paracentral lobule. CONCLUSIONS: The study provided the evidences that 30min LTE RF-EMF exposure modulated the spontaneous low frequency fluctuations in some brain regions. **SIGNIFICANCE:** With resting state fMRI, we found the alteration of spontaneous low frequency fluctuations induced by the acute LTE RF-EMF exposure.

Salford LG, Brun AR, Eberhardt JL, Malmgren L, Persson BRR, Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones. Environ Health Persp 111:881-883, 2003.

The possible risks of radio-frequency electromagnetic fields for the human body is a growing concern for the society. We have earlier shown that weak pulsed microwaves

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give rise to a significant leakage of albumin through the blood-brain barrier (BBB). Now we have investigated whether a pathological leakage over the BBB might be combined with damage to the neurons. Three groups of each 8 rats were exposed for 2 hours to GSM mobile phone electromagnetic fields of different strengths. We found, and present here for the first time, highly significant ($p < 0.002$) evidence for neuronal damage in both the cortex, the hippocampus and the basal ganglia in the brains of exposed rats.

Noor NA, Mohammed HS, Ahmed NA, Radwan NM. Variations in amino acid neurotransmitters in some brain areas of adult and young male albino rats due to exposure to mobile phone radiation. Eur Rev Med Pharmacol Sci. 15(7):729-742, 2011.

BACKGROUND AND OBJECTIVES: Mobile phone radiation and health concerns have been raised, especially following the enormous increase in the use of wireless mobile telephony throughout the world. The present study aims to investigate the effect of one hour daily exposure to electromagnetic radiation (EMR) with frequency of 900 Mz (SAR 1.165 w/kg, power density 0.02 mW/cm²) on the levels of amino acid neurotransmitters in the midbrain, cerebellum and medulla of adult and young male albino rats.

MATERIALS AND METHODS: Adult and young rats were divided into two main groups (treated and control). The treated group of both adult and young rats was exposed to EMR for 1 hour daily. The other group of both adult and young animals was served as control. The determination of amino acid levels was carried out after 1 hour, 1 month, 2 months and 4 months of EMR exposure as well as after stopping radiation. **RESULTS:** Data of the present study showed a significant increase in both excitatory and inhibitory amino acids in the cerebellum of adult and young rats and midbrain of adult animals after 1 hour of EMR exposure. In the midbrain of adult animals, there was a significant increase in glycine level after 1 month followed by significant increase in GABA after 4 months. Young rats showed significant decreases in the midbrain excitatory amino acids. In the medulla, the equilibrium ratio percent (ER%) calculations showed a state of neurochemical inhibition after 4 months in case of adult animals, whereas in young animals, the neurochemical inhibitory state was observed after 1 month of exposure due to significant decrease in glutamate and aspartate levels. This state was converted to excitation after 4 months due to the increase in glutamate level. **CONCLUSION:** The present changes in amino acid concentrations may underlie the reported adverse effects of using mobile phones.

Deshmukh PS, Megha K, Banerjee BD, Ahmed RS, Chandna S, Abegaonkar MP, Tripathi AK. Detection of Low Level Microwave Radiation Induced Deoxyribonucleic Acid Damage Vis-à-vis Genotoxicity in Brain of Fischer Rats. Toxicol Int. 20(1):19-24, 2013.

BACKGROUND: Non-ionizing radiofrequency radiation has been increasingly used in industry, commerce, medicine and especially in mobile phone technology and has become a matter of serious concern in present time. **OBJECTIVE:** The present study was designed to investigate the possible deoxyribonucleic acid (DNA) damaging effects of low-level microwave radiation in brain of Fischer rats. **MATERIALS AND METHODS:** Experiments were performed on male Fischer rats exposed to microwave radiation for 30 days at three different frequencies: 900, 1800 and 2450 MHz. Animals were divided

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into 4 groups: Group I (Sham exposed): Animals not exposed to microwave radiation but kept under same conditions as that of other groups, Group II: Animals exposed to microwave radiation at frequency 900 MHz at specific absorption rate (SAR) 5.953×10^{-4} W/kg, Group III: Animals exposed to 1800 MHz at SAR 5.835×10^{-4} W/kg and Group IV: Animals exposed to 2450 MHz at SAR 6.672×10^{-4} W/kg. At the end of the exposure period animals were sacrificed immediately and DNA damage in brain tissue was assessed using alkaline comet assay. RESULTS: In the present study, we demonstrated DNA damaging effects of low level microwave radiation in brain. CONCLUSION: We concluded that low SAR microwave radiation exposure at these frequencies may induce DNA strand breaks in brain tissue.

Maby E, Le Bouquin Jeannes R, Faucon G. Short-term effects of GSM mobiles phones on spectral components of the human electroencephalogram. Conf Proc IEEE Eng Med Biol Soc. 1:3751-3754, 2006.

The aim of the study was to investigate whether the GSM (global system for mobile) signals affect the electrical activity of the human brain. Nine healthy subjects and six temporal epileptic patients were exposed to radiofrequencies emitted by a GSM mobile phone signals. Electroencephalographic (EEG) signals were recorded using surface electrodes with and without radiofrequency. In order to obtain a reference, a control session was also carried out. The spectral attributes of the EEG signals recorded by surface electrodes were analyzed. The significant decrease of spectral correlation coefficients under radiofrequency influence showed that the GSM signal altered the spectral arrangement of the EEG activity for healthy subjects as well as epileptic patients. For the healthy subjects, the EEG spectral energy decreased on the studied frequency band [0-40 Hz] and more precisely on occipital electrodes for the alpha-band. For the epileptic patients, these modifications were demonstrated by an increase of the power spectral density of the EEG signal. Nevertheless, these biological effects on the EEG are not sufficient to put forward some electrophysiological hypothesis.

Saikhedkar N, Bhatnagar M, Jain A, Sukhwal P, Sharma C, Jaiswal N. Effects of mobile phone radiation (900 MHz radiofrequency) on structure and functions of rat brain. Neurol Res. 2014 May 26:1743132814Y0000000392. [Epub ahead of print]

Objectives: The goals of this study were: (1) to obtain basic information about the effects of long-term use of mobile phone on cytological makeup of the hippocampus in rat brain (2) to evaluate the effects on antioxidant status, and (3) to evaluate the effects on cognitive behavior particularly on learning and memory. Methods: Rats (age 30 days, 120 ± 5 g) were exposed to 900 MHz radio waves by means of a mobile hand set for 4 hours per day for 15 days. Effects on anxiety, spatial learning, and memory were studied using open field test, elevated plus maze, Morris water maze (MWM), and classic maze test. Effects on brain antioxidant status were also studied. Cresyl violet staining was done to assess the neuronal damage. Result: A significant change in behavior, i.e., more anxiety and poor learning was shown by test animals as compared to controls and sham group. A significant change in level of antioxidant enzymes and non-enzymatic antioxidants, and increase in lipid peroxidation were observed in test rats. Histological

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examination showed neurodegenerative cells in hippocampal sub regions and cerebral cortex. Discussion: Thus our findings indicate extensive neurodegeneration on exposure to radio waves. Increased production of reactive oxygen species due to exhaustion of enzymatic and non-enzymatic antioxidants and increased lipid peroxidation are indicating extensive neurodegeneration in selective areas of CA1, CA3, DG, and cerebral cortex. This extensive neuronal damage results in alterations in behavior related to memory and learning.

Sirav B, Seyhan N. Effects of radiofrequency radiation exposure on blood-brain barrier permeability in male and female rats. *Electromagn Biol Med.* 30(4):253-260, 2011.

During the last several decades, numerous studies have been performed aiming at the question of whether or not exposure to radiofrequency radiation (RFR) influences the permeability of the blood-brain barrier (BBB). The objective of this study was to investigate the effect of RFR on the permeability of BBB in male and female Wistar albino rats. Right brain, left brain, cerebellum, and total brain were analyzed separately in the study. Rats were exposed to 0.9 and 1.8 GHz continuous-wave (CW) RFR for 20 min (at SARs of 4.26 mW/kg and 1.46 mW/kg, respectively) while under anesthesia. Control rats were sham-exposed. Disruption of BBB integrity was detected spectrophotometrically using the Evans-blue dye, which has been used as a BBB tracer and is known to be bound to serum albumin. Right brain, left brain, cerebellum, and total brain were evaluated for BBB permeability. In female rats, no albumin extravasation was found in the brain after RFR exposure. A significant increase in albumin was found in the brains of the RF-exposed male rats when compared to sham-exposed male brains. These results suggest that exposure to 0.9 and 1.8 GHz CW RFR at levels below the international limits can affect the vascular permeability in the brain of male rats. The possible risk of RFR exposure in humans is a major concern for the society. Thus, this topic should be investigated more thoroughly in the future.

Soderqvist F, Carlberg M, Hardell L. Mobile and cordless telephones, serum transthyretin and the blood-cerebrospinal fluid barrier: a cross-sectional study. *Environ Health.* 8(1):19, 2009.

ABSTRACT: BACKGROUND: Whether low-intensity radiofrequency radiation damages the blood-brain barrier has long been debated, but little or no consideration has been given to the blood-cerebrospinal fluid barrier. In this cross-sectional study we tested whether long-term and/or short-term use of wireless telephones was associated **with changes in the serum transthyretin level, indicating altered transthyretin concentration in the cerebrospinal fluid, possibly reflecting an effect of radiation.** METHODS: One thousand subjects, 500 of each sex aged 18-65 years, were randomly recruited using the population registry. Data on wireless telephone use were assessed by a postal questionnaire and blood samples were analyzed for serum transthyretin concentrations determined by standard immunonephelometric techniques on a BN Prospec(R) instrument. RESULTS: The response rate was 31.4%. Logistic regression of dichotomized TTR serum levels with a cut-point of 0.31 g/l on wireless telephone use yielded increased odds ratios that were statistically not significant. Linear regression of

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time since first use overall and on the day that blood was withdrawn gave different results for males and females: for men significantly higher serum concentrations of TTR were seen the longer an analogue telephone or a mobile and cordless desktop telephone combined had been used, and in contrast, significantly lower serum levels were seen the longer an UMTS telephone had been used. Adjustment for fractions of use of the different telephone types did not modify the effect for cumulative use or years since first use for mobile telephone and DECT, combined. For women, linear regression gave a significant association for short-term use of mobile and cordless telephones combined, indicating that the sooner blood was withdrawn after the most recent telephone call, the higher the expected transthyretin concentration.

CONCLUSIONS: In this hypothesis-generating descriptive study time since first use of mobile telephones and DECT combined was significantly associated with higher TTR levels regardless of how much each telephone type had been used. Regarding short-term use, significantly higher TTR concentrations were seen in women the sooner blood was withdrawn after the most recent telephone call on that day.

Lopez-Martin E, Relova-Quinteiro JL, Gallego-Gomez R, Peleteiro-Fernandez M, Jorge-Barreiro FJ, Ares-Pena FJ. GSM radiation triggers seizures and increases cerebral c-Fos positivity in rats pretreated with subconvulsive doses of picrotoxin. *Neurosci Lett.*398(1-2):139-144,2006.

This study investigated the effects of mobile-phone-type radiation on the cerebral activity of seizure-prone animals. When rats transformed into an experimental model of seizure-proneness by acute subconvulsive doses of picrotoxin were exposed to 2h GSM-modulated 900MHz radiation at an intensity similar to that emitted by mobile phones, they suffered seizures and the levels of the neuronal activity marker c-Fos in neocortex, paleocortex, hippocampus and thalamus increased markedly. Non-irradiated picrotoxin-treated rats did not suffer seizures, and their cerebral c-Fos counts were significantly lower. Radiation caused no such differences in rats that had not been pretreated with picrotoxin. We conclude that GSM-type radiation can induce seizures in rats following their facilitation by subconvulsive doses of picrotoxin, and that research should be pursued into the possibility that this kind of radiation may similarly affect brain function in human subjects with epileptic disorders.

Kwon MS, Vorobyev V, Kännälä S, Laine M, Rinne JO, Toivonen T, Johansson J, Teräs M, Lindholm H, Alanko T, Hämäläinen H. GSM mobile phone radiation suppresses brain glucosemetabolism. *J Cereb Blood Flow Metab.* 31(12):2293-2301, 2011.

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We investigated the effects of mobile phone radiation on cerebral glucose metabolism using high-resolution positron emission tomography (PET) with the (18)F-deoxyglucose (FDG) tracer. A long half-life (109 minutes) of the (18)F isotope allowed a long, natural exposure condition outside the PET scanner. Thirteen young right-handed male subjects were exposed to a pulse-modulated 902.4 MHz Global System for Mobile Communications signal for 33 minutes, while performing a simple visual vigilance task. Temperature was also measured in the head region (forehead, eyes, cheeks, ear canals) during exposure. (18)F-deoxyglucose PET images acquired after the exposure showed that relative cerebral metabolic rate of glucose was significantly reduced in the temporoparietal junction and anterior temporal lobe of the right hemisphere ipsilateral to the exposure. Temperature rise was also observed on the exposed side of the head, but the magnitude was very small. The exposure did not affect task performance (reaction time, error rate). Our results show that short-term mobile phone exposure can locally suppress brain energy metabolism in humans.

Nittby H, Brun A, Eberhardt J, Malmgren L, Persson BR, Salford LG. Increased blood-brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone. Pathophysiology. 16(2-3):103-112, 2009.

Microwaves were for the first time produced by humans in 1886 when radio waves were broadcasted and received. Until then microwaves had only existed as a part of the cosmic background radiation since the birth of universe. By the following utilization of microwaves in telegraph communication, radars, television and above all, in the modern mobile phone technology, mankind is today exposed to microwaves at a level up to 10(20) times the original background radiation since the birth of universe. Our group has earlier shown that the electromagnetic radiation emitted by mobile phones alters the permeability of the blood-brain barrier (BBB), resulting in albumin extravasation immediately and 14 days after 2h of exposure. In the background section of this report, we present a thorough review of the literature on the demonstrated effects (or lack of effects) of microwave exposure upon the BBB. Furthermore, we have continued our own studies by investigating the effects of GSM mobile phone radiation upon the blood-brain barrier permeability of rats 7 days after one occasion of 2h of exposure. Forty-eight rats were exposed in TEM-cells for 2h at non-thermal specific absorption rates (SARs) of 0mW/kg, 0.12mW/kg, 1.2mW/kg, 12mW/kg and 120mW/kg. Albumin extravasation over the BBB, neuronal albumin uptake and neuronal damage were assessed. Albumin extravasation was enhanced in the mobile phone exposed rats as compared to sham controls after this 7-day recovery period (Fisher's exact probability test, $p=0.04$ and Kruskal-Wallis, $p=0.012$), at the SAR-value of 12mW/kg (Mann-Whitney, $p=0.007$) and with a trend of increased albumin extravasation also at the SAR-values of 0.12mW/kg and 120mW/kg. There was a low, but significant correlation between the exposure level (SAR-value) and occurrence of focal albumin extravasation ($r(s)=0.33$; $p=0.04$). The present findings are in agreement with our earlier studies where we have seen increased BBB permeability immediately and 14 days after exposure. We here discuss the present findings as well as the previous results of altered BBB permeability from our and other laboratories.

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Volkow ND, Tomasi D, Wang GJ, Vaska P, Fowler JS, Telang F, Alexoff D, Logan J, Wong C. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. JAMA. 305(8):808-813, 2011.

CONTEXT: The dramatic increase in use of cellular telephones has generated concern about possible negative effects of radiofrequency signals delivered to the brain.

However, whether acute cell phone exposure affects the human brain is unclear.

OBJECTIVE: To evaluate if acute cell phone exposure affects brain glucose metabolism, a marker of brain activity.

DESIGN, SETTING, AND PARTICIPANTS:

Randomized crossover study conducted between January 1 and December 31, 2009, at a single US laboratory among 47 healthy participants recruited from the community. Cell phones were placed on the left and right ears and positron emission tomography with ((18)F)fluorodeoxyglucose injection was used to measure brain glucose metabolism twice, once with the right cell phone activated (sound muted) for 50 minutes ("on" condition) and once with both cell phones deactivated ("off" condition). Statistical parametric mapping was used to compare metabolism between on and off conditions using paired t tests, and Pearson linear correlations were used to verify the association of metabolism and estimated amplitude of radiofrequency-modulated electromagnetic waves emitted by the cell phone. Clusters with at least 1000 voxels (volume >8 cm³) and P < .05 (corrected for multiple comparisons) were considered significant.

MAIN OUTCOME MEASURE: Brain glucose metabolism computed as absolute metabolism ($\mu\text{mol}/100\text{ g per minute}$) and as normalized metabolism (region/whole brain).

RESULTS: Whole-brain metabolism did not differ between on and off conditions. In contrast, metabolism in the region closest to the antenna (orbitofrontal cortex and temporal pole) was significantly higher for on than off conditions (35.7 vs 33.3 $\mu\text{mol}/100\text{ g per minute}$; mean difference, 2.4 [95% confidence interval, 0.67-4.2]; P = .004). The increases were significantly correlated with the estimated electromagnetic field amplitudes both for absolute metabolism (R = 0.95, P < .001) and normalized metabolism (R = 0.89; P < .001). **CONCLUSIONS:** In healthy participants and compared with no exposure, 50-minute cell phone exposure was associated with increased brain glucose metabolism in the region closest to the antenna. This finding is of unknown clinical significance.

Ragy MM. Effect of exposure and withdrawal of 900-MHz-electromagnetic waves on brain, kidney and liver oxidative stress and some biochemical parameters in male rats. Electromagn Biol Med. 2014 Apr 8. [Epub ahead of print]

Increasing use of mobile phones in daily life with increasing adverse effects of electromagnetic radiation (EMR), emitted from mobile on some physiological processes, cause many concerns about their effects on human health. Therefore, this work was designed to study the effects of exposure to mobile phone emits 900-MHz EMR on the brain, liver and kidney of male albino rats. Thirty male adult rats were randomly divided into four groups (10 each) as follows: control group (rats without exposure to EMR), exposure group (exposed to 900-MHz EMR for 1 h/d for 60 d) and withdrawal group (exposed to 900-MHz electromagnetic wave for 1 h/d for 60 d then left for 30 d without exposure). EMR emitted from mobile phone led to a significant increase in

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malondialdehyde (MDA) levels and significant decrease total antioxidant capacity (TAC) levels in brain, liver and kidneys tissues. The sera activity of alanine transaminase (ALT), aspartate aminotransferase (AST), urea, creatinine and corticosterone were significantly increased ($p < 0.05$), while serum catecholamines were insignificantly higher in the exposed rats. These alterations were corrected by withdrawal. In conclusion, electromagnetic field emitting from mobile phone might produce impairments in some biochemicals changes and oxidative stress in brain, liver and renal tissue of albino rats.

Dasdag S, Akdag MZ, Kizil G, Kizil M, Cakir DU, Yokus B. Effect of 900 MHz radio frequency radiation on beta amyloid protein, protein carbonyl, and malondialdehyde in the brain. *Electromagn Biol Med.* 31(1):67-74, 2012.

Recently, many studies have been carried out in relation to 900 MHz radiofrequency radiation (RF) emitted from a mobile phone on the brain. However, there is little data concerning possible mechanisms between long-term exposure of RF radiation and biomolecules in brain. Therefore, we aimed to investigate long-term effects of 900 MHz radiofrequency radiation on beta amyloid protein, protein carbonyl, and malondialdehyde in the rat brain. The study was carried out on 17 Wistar Albino adult male rats. The rat heads in a carousel were exposed to 900 MHz radiofrequency radiation emitted from a generator, simulating mobile phones. For the study group ($n = 10$), rats were exposed to the radiation 2 h per day (7 days a week) for 10 months. For the sham group ($n = 7$), rats were placed into the carousel and the same procedure was applied except that the generator was turned off. In this study, rats were euthanized after 10 months of exposure and their brains were removed. Beta amyloid protein, protein carbonyl, and malondialdehyde levels were found to be higher in the brain of rats exposed to 900 MHz radiofrequency radiation. However, only the increase of protein carbonyl in the brain of rats exposed to 900 MHz radiofrequency radiation was found to be statistically significant ($p < 0.001$). In conclusion, 900 MHz radiation emitted from mobile/cellular phones can be an agent to alter some biomolecules such as protein. However, further studies are necessary.

Spichtig S, Scholkmann F, Chin L, Lehmann H, Wolf M. Assessment of intermittent UMTS electromagnetic field effects on blood circulation in the human auditory region using a near-infrared system. *Bioelectromagnetics.* 33(1):40-54, 2012.

The aim of the present study was to assess the potential effects of intermittent Universal Mobile Telecommunications System electromagnetic fields (UMTS-EMF) on blood circulation in the human head (auditory region) using near-infrared spectroscopy (NIRS) on two different timescales: short-term (effects occurring within 80 s) and medium-term (effects occurring within 80 s to 30 min). For the first time, we measured potential immediate effects of UMTS-EMF in real-time without any interference during exposure. Three different exposures (sham, 0.18 W/kg, and 1.8 W/kg) were applied in a controlled, randomized, crossover, and double-blind paradigm on 16 healthy volunteers. In addition to oxy-, deoxy-, and total haemoglobin concentrations ([O(2) Hb], [HHb], and [tHb], respectively), the heart rate (HR), subjective well-being, tiredness, and counting speed were recorded. During exposure to 0.18 W/kg, we found a significant short-term

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increase in $\Delta[\text{O}(2) \text{Hb}]$ and $\Delta[\text{tHb}]$, which is small ($\approx 17\%$) compared to a functional brain activation. A significant decrease in the medium-term response of $\Delta[\text{HHb}]$ at 0.18 and 1.8 W/kg exposures was detected, which is in the range of physiological fluctuations. The medium-term ΔHR was significantly higher (+1.84 bpm) at 1.8 W/kg than for sham exposure. The other parameters showed no significant effects. Our results suggest that intermittent exposure to UMTS-EMF has small short- and medium-term effects on cerebral blood circulation and HR.

Persson BRR, Salford LG, Brun A, Blood-brain barrier permeability in rats exposed to electromagnetic fields used in wireless communication. *Wireless Network* 3:455-461, 1997.

Biological effects of radio frequency electromagnetic fields (EMF) on the blood-brain barrier (BBB) have been studied in Fischer 344 rats of both sexes. The rats were not anesthetised during the exposure. The brains were perfused with saline for 3-4 minutes, and thereafter perfusion fixed with 4% formaldehyde for 5-6 minutes. Whole coronal sections of the brains were dehydrated and embedded in paraffin and sectioned at 5 micrometers. Albumin and fibinogen were demonstrated immunochemically and classified as normal versus pathological leakage. In the present investigation we exposed male and female Fischer 344 rats in a Transverse Electromagnetic Transmission line chamber to microwaves of 915 MHz as continuous wave (CW) and pulse-modulated with different pulse power and at various time intervals. The CW-pulse power varied from 0.001 W to 10 W and the exposure time from 2 min to 960 min. In each experiment we exposed 4-6 rats with 2-4 controls randomly placed in excited and non-excited TEM cells, respectively. We have in total investigated 630 exposed rats at various modulation frequencies and 372 controls. The frequency of pathological rats is significantly increased ($P < 0.0001$) from 62/372 (ratio 0.17 + 0.02) for control rats to 244/630 (ratio: 0.39 + 0.043) in all exposed rats. Grouping the exposed animals according to the level or specific absorption energy (J/kg) give significant difference in all levels above 1.5 J/kg. The exposure was 915 MHz microwaves either pulse modulated (PW) at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width or continuous wave (CW). The frequency of pathological rats (0.17) among controls in the various groups is not significantly different. The frequency of pathological rats was 170/480 (0.35 + 0.03) among rats exposed to pulse modulated (PW) and 74/149 (0.50 + 0.07) among rats exposed to continuous wave exposure (CW). These results are both highly significantly different to their corresponding controls ($p < 0.0001$) and the frequency of pathological rats after exposure to pulsed radiation (PW) is significantly less ($p < 0.002$) than after exposure to continuous wave radiation (CW).

Rağbetli MC, Aydinlioğlu A, Koyun N, Rağbetli C, Bektas S, Ozdemir S. The effect of mobile phone on the number of Purkinje cells: A stereological study. *Int J Radiat Biol.*86(7):548-54, 2010

Purpose: The World Health Organisation proposed an investigation concerning the exposure of animals to radiofrequency fields because of the possible risk factor for health. At power frequencies there is evidence to associate both childhood leukaemia

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and brain tumours with magnetic field exposures. There is also evidence of the effect of mobile phone exposure on both cognitive functions and the cerebellum. Purkinje cells of the cerebellum are also sensitive to high dose microwave exposure in rats. The present study investigated the effect of exposure to mobile phone on the number of Purkinje and granule neurons in the developing cerebellum. Material and methods: Male and female Swiss albino mice were housed as control and mobile phone-exposed groups. Pregnant animals in the experimental group were exposed to Global System for Mobile Communication (GSM) mobile phone radiation at 890-915 MHz at 0.95 W/Kg specific absorption rate (SAR). The cerebella were processed by frozen microtome. The sections obtained were stained with Haematoxylin-eosin and cresyl violet. For cell counting by the optical fractionator method, a pilot study was firstly performed. Cerebellar areas were analysed by using Axiovision software running on a personal computer. The optical dissectors were systematically spaced at random, and focused to the widest profile of the neuron cell nucleus. Results: A significant decrease in the number of Purkinje cells and a tendency for granule cells to increase in cerebellum was found. Conclusion: Further studies in this area are needed due to the popular use of mobile telephones and relatively high exposure on developing brain.

Sonmez OF, Odaci E, Bas O, Kaplan S. Purkinje cell number decreases in the adult female rat cerebellum following exposure to 900 MHz electromagnetic field. *Brain Res.* 1356:95-101, 2010.

The biological effects of electromagnetic field (EMF) exposure from mobile phones have growing concern among scientists since there are some reports showing increased risk for human health, especially in the use of mobile phones for a long duration. In the presented study, the effects on the number of Purkinje cells in the cerebellum of 16-week (16 weeks) old female rats were investigated following exposure to 900 MHz EMF. Three groups of rats, a control group (CG), sham exposed group (SG) and an electromagnetic field exposed group (EMFG) were used in this study. While EMFG group rats were exposed to 900 MHz EMF (1h/day for 28 days) in an exposure tube, SG was placed in the exposure tube but not exposed to EMF (1h/day for 28 days). The specific energy absorption rate (SAR) varied between 0.016 (whole body) and 2 W/kg (locally in the head). The CG was not placed into the exposure tube nor was it exposed to EMF during the study period. At the end of the experiment, all of the female rats were sacrificed and the number of Purkinje cells was estimated using a stereological counting technique. Histopathological evaluations were also done on sections of the cerebellum. Results showed that the total number of Purkinje cells in the cerebellum of the EMFG was significantly lower than those of CG ($p < 0.004$) and SG ($p < 0.002$). In addition, there was no significant difference at the 0.05 level between the rats' body and brain weights in the EMFG and CG or SG. Therefore, it is suggested that long duration exposure to 900 MHz EMF leads to decreases of Purkinje cell numbers in the female rat cerebellum.

Tombini M, Pellegrino G, Pasqualetti P, Assenza G, Benvenga A, Fabrizio E, Rossini PM Mobile phone emissions modulate brain excitability in patients with focal epilepsy. *Brain Stimul.* 2012 Aug 9. [Epub ahead of print]

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BACKGROUND: Electromagnetic fields (EMFs) emitted by mobile phones had been shown to increase cortical excitability in healthy subjects following 45 min of continuous exposure on the ipsilateral hemisphere. OBJECTIVE: Using Transcranial Magnetic Stimulation (TMS), the current study assessed the effects of acute exposure to mobile phone EMFs on the cortical excitability in patients with focal epilepsy. METHODS: Ten patients with cryptogenic focal epilepsy originating outside the primary motor area (M1) were studied. Paired-pulse TMS were applied to the M1 of both the hemisphere ipsilateral (IH) and contralateral (CH) to the epileptic focus before and immediately after real/sham exposure to the GSM-EMFs (45 min). The TMS study was carried out in all subjects in three different experimental sessions (IH and CH exposure, sham), 1 week apart, according to a crossover, double-blind and counter-balanced paradigm. RESULTS: The present study clearly demonstrated that an acute and relatively prolonged exposure to GSM-EMFs modulates cortical excitability in patients affected by focal epilepsy; however, in contrast to healthy subjects, these effects were evident only after EMFs exposure over the hemisphere contralateral to the epileptic focus (CH). They were characterized by a significant cortical excitability increase in the exposed hemisphere paired with slight excitability decrease in the other one (IH). Both sham and real EMFs exposure of the IH did not affect brain excitability. CONCLUSION: Present results suggest a significant interaction between the brain excitability changes induced by EMFs and the epileptic focus, which eliminated the excitability enhancing effects of EMFs evident only in the CH.

Perentos N, Croft RJ, McKenzie RJ, Cvetkovic D, Cosic I. The effect of GSM-like ELF radiation on the alpha band of the human resting EEG. Conf Proc IEEE Eng Med Biol Soc. 1:5680-5683, 2008.

Mobile phone handsets such as those operating in the GSM network emit extremely low frequency electromagnetic fields ranging from DC to at least 40 kHz. As a subpart of an extended protocol, the influence of these fields on the human resting EEG has been investigated in a fully counter balanced, double blind, cross-over design study that recruited 72 healthy volunteers. A decrease in the alpha frequency band was observed during the 20 minutes of ELF exposure in the exposed hemisphere only. This result suggests that ELF fields as emitted from GSM handsets during the DTX mode may have an effect on the resting alpha band of the human EEG.

Sokolovic D, Djindjic B, Nikolic J, Bjelakovic G, Pavlovic D, Kocic G, Krstic D, Cvetkovic T, Pavlovic V. Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. J Radiat Res (Tokyo). 49(6):579-586, 2008.

PURPOSE: The aim of the study was to evaluate the intensity of oxidative stress in the brain of animals chronically exposed to mobile phones and potential protective effects of melatonin in reducing oxidative stress and brain injury. MATERIALS AND METHODS: Experiments were performed on Wistar rats exposed to microwave radiation during 20, 40 and 60 days. Four groups were formed: I group (control)- animals treated by saline, intraperitoneally (i.p.) applied daily during follow up, II group (Mel)- rats treated daily

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with melatonin (2 mg kg⁻¹ body weight i.p.), III group (MWs)- microwave exposed rats, IV group (MWs + Mel)- MWs exposed rats treated with melatonin (2 mg kg⁻¹ body weight i.p.). The microwave radiation was produced by a mobile test phone (SAR = 0.043-0.135 W/kg). **RESULTS:** A significant increase in the brain tissue malondialdehyde (MDA) and carbonyl group concentration was registered during exposure. Decreased activity of catalase (CAT) and increased activity of xanthine oxidase (XO) remained after 40 and 60 days of exposure to mobile phones. Melatonin treatment significantly prevented the increase in the MDA content and XO activity in the brain tissue after 40 days of exposure while it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents. **CONCLUSION:** We demonstrated two important findings; that mobile phones caused oxidative damage biochemically by increasing the levels of MDA, carbonyl groups, XO activity and decreasing CAT activity; and that treatment with the melatonin significantly prevented oxidative damage in the brain.

Kesari KK, Meena R, Nirala J, Kumar J, Verma HN. Effect of 3G cell phone exposure with computer controlled 2-D stepper motor on non-thermal activation of the hsp27/p38MAPK stress pathway in rat brain. Cell Biochem Biophys. 68(2):347-358, 2014.

Cell phone radiation exposure and its biological interaction is the present concern of debate. Present study aimed to investigate the effect of 3G cell phone exposure with computer controlled 2-D stepper motor on 45-day-old male Wistar rat brain. Animals were exposed for 2 h a day for 60 days by using mobile phone with angular movement up to zero to 30°. The variation of the motor is restricted to 90° with respect to the horizontal plane, moving at a pre-determined rate of 2° per minute. Immediately after 60 days of exposure, animals were sacrificed and numbers of parameters (DNA double-strand break, micronuclei, caspase 3, apoptosis, DNA fragmentation, expression of stress-responsive genes) were performed. Result shows that microwave radiation emitted from 3G mobile phone significantly induced DNA strand breaks in brain. Meanwhile a significant increase in micronuclei, caspase 3 and apoptosis were also observed in exposed group (P < 0.05). Western blotting result shows that 3G mobile phone exposure causes a transient increase in phosphorylation of hsp27, hsp70, and p38 mitogen-activated protein kinase (p38MAPK), which leads to mitochondrial dysfunction-mediated cytochrome c release and subsequent activation of caspases, involved in the process of radiation-induced apoptotic cell death. Study shows that the oxidative stress is the main factor which activates a variety of cellular signal transduction pathways, among them the hsp27/p38MAPK is the pathway of principle stress response. Results conclude that 3G mobile phone radiations affect the brain function and cause several neurological disorders.

Kesari KK, Kumar S, Behari J. 900-MHz microwave radiation promotes oxidation in rat brain. Electromagn Biol Med. 30(4):219-234, 2011.

Recently, there have been several reports referring to detrimental effects due to radio frequency electromagnetic fields (RF-EMF) exposure. Special attention was given to investigate the effect of mobile phone exposure on the rat brain. Since the integrative

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mechanism of the entire body lies in the brain, it is suggestive to analyze its biochemical aspects. For this, 35-day old Wistar rats were exposed to a mobile phone for 2 h per day for a duration of 45 days where specific absorption rate (SAR) was 0.9 W/Kg. Animals were divided in two groups: sham exposed (n = 6) and exposed group (n = 6). Our observations indicate a significant decrease ($P < 0.05$) in the level of glutathione peroxidase, superoxide dismutase, and an increase in catalase activity. Moreover, protein kinase shows a significant decrease in exposed group ($P < 0.05$) of hippocampus and whole brain. Also, a significant decrease ($P < 0.05$) in the level of pineal melatonin and a significant increase ($P < 0.05$) in creatine kinase and caspase 3 was observed in exposed group of whole brain as compared with sham exposed. Finally, a significant increase in the level of ROS (reactive oxygen species) ($P < 0.05$) was also recorded. The study concludes that a reduction or an increase in antioxidative enzyme activities, protein kinase C, melatonin, caspase 3, and creatine kinase are related to overproduction of reactive oxygen species (ROS) in animals under mobile phone radiation exposure. Our findings on these biomarkers are clear indications of possible health implications.

Fragopoulou AF, Samara A, Antonelou MH, Xanthopoulou A, Papadopoulou A, Vougas K, Koutsogiannopoulou E, Anastasiadou E, Stravopodis DJ, Tsangaris GT, Margaritis LH. Brain proteome response following whole body exposure of mice to mobile phone or wireless DECT base radiation. *Electromagn Biol Med.*31(4):250-274, 2012.

The objective of this study was to investigate the effects of two sources of electromagnetic fields (EMFs) on the proteome of cerebellum, hippocampus, and frontal lobe in Balb/c mice following long-term whole body irradiation. Three equally divided groups of animals (6 animals/group) were used; the first group was exposed to a typical mobile phone, at a SAR level range of 0.17-0.37 W/kg for 3 h daily for 8 months, the second group was exposed to a wireless DECT base (Digital Enhanced Cordless Telecommunications/Telephone) at a SAR level range of 0.012-0.028 W/kg for 8 h/day also for 8 months and the third group comprised the sham-exposed animals. Comparative proteomics analysis revealed that long-term irradiation from both EMF sources altered significantly ($p < 0.05$) the expression of 143 proteins in total (as low as 0.003 fold downregulation up to 114 fold overexpression). Several neural function related proteins (i.e., Glial Fibrillary Acidic Protein (GFAP), Alpha-synuclein, Glia Maturation Factor beta (GMF), and apolipoprotein E (apoE)), heat shock proteins, and cytoskeletal proteins (i.e., Neurofilaments and tropomodulin) are included in this list as well as proteins of the brain metabolism (i.e., Aspartate aminotransferase, Glutamate dehydrogenase) to nearly all brain regions studied. Western blot analysis on selected proteins confirmed the proteomics data. The observed protein expression changes may be related to brain plasticity alterations, indicative of oxidative stress in the nervous system or involved in apoptosis and might potentially explain human health hazards reported so far, such as headaches, sleep disturbance, fatigue, memory deficits, and brain tumor long-term induction under similar exposure conditions.

Beason RC, Semm P. Responses of neurons to an amplitude-modulated microwave

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stimulus. Neurosci Lett 333(3):175-178, 2002.

In this study we investigated the effects of a pulsed radio frequency signal similar to the signal produced by global system for mobile communication telephones (900 MHz carrier, modulated at 217 Hz) on neurons of the avian brain. We found that such stimulation resulted in changes in the amount of neural activity by more than half of the brain cells. Most (76%) of the responding cells increased their rates of firing by an average 3.5-fold. The other responding cells exhibited a decrease in their rates of spontaneous activity Such responses indicate potential effects on humans using hand-held cellular phones.

Ragy MM. Effect of exposure and withdrawal of 900-MHz-electromagnetic waves on brain, kidney and liver oxidative stress and some biochemical parameters in male rats. Electromagn Biol Med. 2014 Apr 8. [Epub ahead of print]

Increasing use of mobile phones in daily life with increasing adverse effects of electromagnetic radiation (EMR), emitted from mobile on some physiological processes, cause many concerns about their effects on human health. Therefore, this work was designed to study the effects of exposure to mobile phone emits 900-MHz EMR on the brain, liver and kidney of male albino rats. Thirty male adult rats were randomly divided into four groups (10 each) as follows: control group (rats without exposure to EMR), exposure group (exposed to 900-MHz EMR for 1 h/d for 60 d) and withdrawal group (exposed to 900-MHz electromagnetic wave for 1 h/d for 60 d then left for 30 d without exposure). EMR emitted from mobile phone led to a significant increase in malondialdehyde (MDA) levels and significant decrease total antioxidant capacity (TAC) levels in brain, liver and kidneys tissues. The sera activity of alanine transaminase (ALT), aspartate aminotransferase (AST), urea, creatinine and corticosterone were significantly increased ($p < 0.05$), while serum catecholamines were insignificantly higher in the exposed rats. These alterations were corrected by withdrawal. In conclusion, electromagnetic field emitting from mobile phone might produce impairments in some biochemicals changes and oxidative stress in brain, liver and renal tissue of albino rats.

Maby E, Le Bouquin Jeanes R, Liegeois-Chauvel C, Gourevitch B, Faucon G. Analysis of auditory evoked potential parameters in the presence of radiofrequency fields using a support vector machines method. Med Biol Eng Comput. 42(4):562-568, 2004.

The paper presents a study of global system for mobile (GSM) phone radiofrequency effects on human cerebral activity. The work was based on the study of auditory evoked potentials (AEPs) recorded from healthy humans and epileptic patients. The protocol allowed the comparison of AEPs recorded with or without exposure to electrical fields. Ten variables measured from AEPs were employed in the design of a supervised support vector machines classifier. The classification performance measured the classifier's ability to discriminate features performed with or without radiofrequency exposure. Most significant features were chosen by a backward sequential selection that ranked the variables according to their pertinence for the discrimination. Finally, the most discriminating features were analysed statistically by a Wilcoxon signed rank test. For both populations, the N100 amplitudes were reduced under the influence of GSM

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radiofrequency (mean attenuation of -0.36 microV for healthy subjects and -0.60 microV for epileptic patients). Healthy subjects showed a N100 latency decrease (-5.23 ms in mean), which could be consistent with mild, localised heating. The auditory cortical activity in humans was modified by GSM phone radiofrequencies, but an effect on brain functionality has not been proven.

Karaca E, Durmaz B, Aktug H, Yildiz T, Guducu C, Irgi M, Koksall MG, Ozkinay F, Gunduz C, Cogulu O. The genotoxic effect of radiofrequency waves on mouse brain. J Neurooncol. 106(1):53-58, 2012.

Concerns about the health effects of radiofrequency (RF) waves have been raised because of the gradual increase in usage of cell phones, and there are scientific questions and debates about the safety of those instruments in daily life. The aim of this study is to evaluate the genotoxic effects of RF waves in an experimental brain cell culture model. Brain cell cultures of the mice were exposed to 10.715 GHz with specific absorption rate (SAR) 0.725 W/kg signals for 6 h in 3 days at 25°C to check for the changes in the micronucleus (MNI) assay and in the expression of 11 proapoptotic and antiapoptotic genes. It was found that MNI rate increased 11-fold and STAT3 expression decreased 7-fold in the cell cultures which were exposed to RF. Cell phones which spread RF may damage DNA and change gene expression in brain cells.

Chen C, Ma Q, Liu C, Deng P, Zhu G, Zhang L, He M, Lu Y, Duan W, Pei L, Li M, Yu Z, Zhou Z. Exposure to 1800 MHz radiofrequency radiation impairs neurite outgrowth of embryonic neural stem cells. Sci Rep. 2014 May 29;4:5103. doi: 10.1038/srep05103.

A radiofrequency electromagnetic field (RF-EMF) of 1800 MHz is widely used in mobile communications. However, the effects of RF-EMFs on cell biology are unclear. Embryonic neural stem cells (eNSCs) play a critical role in brain development. Thus, detecting the effects of RF-EMF on eNSCs is important for exploring the effects of RF-EMF on brain development. Here, we exposed eNSCs to 1800 MHz RF-EMF at specific absorption rate (SAR) values of 1, 2, and 4 W/kg for 1, 2, and 3 days. We found that 1800 MHz RF-EMF exposure did not influence eNSC apoptosis, proliferation, cell cycle or the mRNA expressions of related genes. RF-EMF exposure also did not alter the ratio of eNSC differentiated neurons and astrocytes. However, neurite outgrowth of eNSC differentiated neurons was inhibited after 4 W/kg RF-EMF exposure for 3 days. Additionally, the mRNA and protein expression of the proneural genes Ngn1 and NeuroD, which are crucial for neurite outgrowth, were decreased after RF-EMF exposure. The expression of their inhibitor Hes1 was upregulated by RF-EMF exposure. These results together suggested that 1800 MHz RF-EMF exposure impairs neurite outgrowth of eNSCs. More attention should be given to the potential adverse effects of RF-EMF exposure on brain development.

Bachmann M, Lass J, Kalda J, Säkki M, Tomson R, Tuulik V, Hinrikus H. Integration of differences in EEG analysis reveals changes in human EEG caused by microwave. Conf

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Proc IEEE Eng Med Biol Soc. 1:1597-1600, 2006.

Three different methods in combination with integration of differences in signals were applied for EEG analysis to distinguish changes in EEG caused by microwave: S-parameter, power spectral density and length distribution of low variability periods. The experiments on the effect of modulated low-level microwaves on human EEG were carried out on four different groups of healthy volunteers exposed to 450 MHz microwave radiation modulated with 7 Hz, 14 Hz, 21 Hz, 40 Hz, 70 Hz, 217 or 1000 Hz frequencies. The field power density at the scalp was 0.16 mW/cm². The EEG analysis performed for individuals with three different methods showed that statistically significant changes occur in the EEG rhythms energy and dynamics between 12% and 30% of subjects.

Wang Q, Cao ZJ, Bai XT. [Effect of 900 MHz electromagnetic fields on the expression of GABA receptor of cerebral cortical neurons in postnatal rats] Wei Sheng Yan Jiu. 34(5):546-548, 2005.

OBJECTIVE: To investigate the effects of 900 MHz microwave electromagnetic fields (EMF) on the expression of neurotransmitter GABA receptor of cerebral cortical neurons in postnatal rats. **METHODS:** Neurons were exposed to 900 MHz continuous microwave EMF (SAR = 1.15 - 3.22mW/g) for 2 hours per day in 6 consecutive days and for 12 hours at one time. GABA receptor was chosen to be the biological end. **RESULTS:** Significant changes had been observed in exposed neurons in the expression of GABA receptor. (P < 0.01) . **CONCLUSION:** The expression of GABA receptor of neurons were significantly regulated by 900 MHz microwave, and a power "window" effect was observed in the exposed neurons.

Leung S, Croft RJ, McKenzie RJ, Iskra S, Silber B, Cooper NR, O'Neill B, Cropley V, Diaz-Trujillo A, Hamblin D, Simpson D. Effects of 2G and 3G mobile phones on performance and electrophysiology in adolescents, young adults and older adults. Clin Neurophysiol. 122(11):2203-2216, 2011.

OBJECTIVE: This study examined sensory and cognitive processing in adolescents, young adults and older adults, when exposed to 2nd (2G) and 3rd (3G) generation mobile phone signals. **METHODS:** Tests employed were the auditory 3-stimulus oddball and the N-back. Forty-one 13-15 year olds, forty-two 19-40 year olds and twenty 55-70 year olds were tested using a double-blind cross-over design, where each participant received Sham, 2G and 3G exposures, separated by at least 4 days. **RESULTS:** 3-Stimulus oddball task: Behavioural: accuracy and reaction time of responses to targets were not affected by exposure. Electrophysiological: augmented N1 was found in the 2G condition (independent of age group). N-back task: Behavioural: the combined groups performed less accurately during the 3G exposure (compared to Sham), with post hoc tests finding this effect separately in the adolescents only. Electrophysiological: delayed ERD/ERS responses of the alpha power were found in both 3G and 2G conditions (compared to Sham; independent of age group). **CONCLUSION:** Employing tasks tailored to each individual's ability level, this study provides support for an effect of acute 2G and 3G exposure on human cognitive function. **SIGNIFICANCE:** The subtlety of mobile phone

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effect on cognition in our study suggests that it is important to account for individual differences in future mobile phone research.

Söderqvist F, Hardell L, Carlberg M, Mild KH. Radiofrequency fields, transthyretin, and Alzheimer's disease. *J Alzheimers Dis.* 20(2):599-606, 2010.

Radiofrequency field (RF) exposure provided cognitive benefits in an animal study. In Alzheimer's disease (AD) mice, exposure reduced brain amyloid-beta (Abeta) deposition through decreased aggregation of Abeta and increase in soluble Abeta levels. Based on our studies on humans on RF from wireless phones, we propose that transthyretin (TTR) might explain the findings. In a cross-sectional study on 313 subjects, we used serum TTR as a marker of cerebrospinal fluid TTR. We found a statistically significantly positive beta coefficient for TTR for time since first use of mobile phones and desktop cordless phones combined ($P=0.03$). The electromagnetic field parameters were similar for the phone types. In a provocation study on 41 persons exposed for 30 min to an 890-MHz GSM signal with specific absorption rate of 1.0 Watt/kg to the temporal area of the brain, we found statistically significantly increased serum TTR 60 min after exposure. In our cross-sectional study, use of oral snuff also yielded statistically significantly increased serum TTR concentrations and nicotine has been associated with decreased risk for AD and to upregulate the TTR gene in choroid plexus but not in the liver, another source of serum TTR. TTR sequesters Abeta, thereby preventing the formation of Abeta plaques in the brain. Studies have shown that patients with AD have lowered TTR concentrations in the cerebrospinal fluid and have attributed the onset of AD to insufficient sequestering of Abeta by TTR. We propose that TTR might be involved in the findings of RF exposure benefit in AD mice.

Maby E, Jeannes Rle B, Faucon G. Scalp localization of human auditory cortical activity modified by GSM electromagnetic fields. *Int J Radiat Biol.* 82(7):465-472, 2006.

Purpose: This study attempted to determine whether there is a localized effect of GSM (Global System for Mobile communications) microwaves by studying the Auditory Evoked Potentials (AEP) recorded at the scalp of nine healthy subjects and six epileptic patients. Materials and methods: We determined the influence of GSM RadioFrequency (RF) on parameters characterizing the AEP in time or/and frequency domains. A parameter selection method using SVM (Support Vector Machines)-based criteria allowed us to estimate those most altered by the radiofrequencies. The topography of the parameter modifications was computed to determine the localization of the radiofrequency influence. A statistical test was conducted for selected scalp areas, in order to determine whether there were significant localized alterations due to the RF. Results: The epileptic patients showed a lengthening of the scalp component N100 (100 ms latency) in the frontal area contralateral to the radiation, which may be due to an afferent tract alteration. For the healthy subjects, an amplitude increase of the P200 wave (200 ms latency) was identified in the frontal area. Conclusions: The present study suggests that radiofrequency fields emitted by mobile phones modify the AEP. Nevertheless, no direct link between

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Maskey D, Kim HJ, Kim HG, Kim MJ. Calcium-binding proteins and GFAP immunoreactivity alterations in murine hippocampus after 1 month of exposure to 835MHz radiofrequency at SAR values of 1.6 and 4.0W/kg. Neurosci Lett. 506(2):292-296, 2012.

Abstract. Widespread use of wireless mobile communication has raised concerns of adverse effect to the brain owing to the proximity during use due to the electromagnetic field emitted by mobile phones. Changes in calcium ion concentrations via binding proteins can disturb calcium homeostasis; however, the correlation between calcium-binding protein (CaBP) immunoreactivity (IR) and glial cells has not been determined with different SAR values. Different SAR values [1.6 (E1.6 group) and 4.0 (E4 group) W/kg] were applied to determine the distribution of calbindin D28-k (CB), calretinin (CR), and glial fibrillary acidic protein (GFAP) IR in murine hippocampus. Compared with sham control group, decreased CB and CR IRs, loss of CB and CR immunoreactive cells and increased GFAP IR exhibiting hypertrophic cytoplasmic processes were noted in both experimental groups. E4 group showed a prominent decrement in CB and CR IR than the E1.6 group due to down-regulation of CaBP proteins and neuronal loss. GFAP IR was more prominent in the E4 group than the E1.6 group. Decrement in the CaBPs can affect the calcium-buffering capacity leading to cell death, while increased GFAP IR and changes in astrocyte morphology, may mediate brain injury due to radiofrequency exposure.

Meral I, Mert H, Mert N, Deger Y, Yoruk I, Yetkin A, Keskin S. Effects of 900-MHz electromagnetic field emitted from cellular phone on brain oxidative stress and some vitamin levels of guinea pigs. Brain Res1169:120-124, 2007.

This study was designed to demonstrate the effects of 900-MHz electromagnetic field (EMF) emitted from cellular phone on brain tissue and also blood malondialdehyde (MDA), glutathione (GSH), retinol (vitamin A), vitamin D(3) and tocopherol (vitamin E) levels, and catalase (CAT) enzyme activity of guinea pigs. Fourteen male guinea pigs, weighing 500-800 g were randomly divided into one of two experimental groups: control and treatment (EMF-exposed), each containing seven animals. Animals in treatment group were exposed to 890- to 915-MHz EMF (217-Hz pulse rate, 2-W maximum peak power, SAR 0.95 w/kg) of a cellular phone for 12 h/day (11-h 45-min stand-by and 15-min spiking mode) for 30 days. Control guinea pigs were housed in a separate room without exposing EMF of a cellular phone. Blood samples were collected through a cardiac puncture and brains were removed after decapitation for the biochemical analysis at the end of the 30 days of experimental period. It was found that the MDA level increased ($P<0.05$), GSH level and CAT enzyme activity decreased ($P<0.05$), and vitamins A, E and D(3) levels did not change ($P>0.05$) in the brain tissues of EMF-exposed guinea pigs. In addition, MDA, vitamins A, D(3) and E levels, and CAT enzyme activity increased ($P<0.05$), and GSH level decreased ($P<0.05$) in the blood of EMF-exposed guinea pigs. It was concluded that electromagnetic field emitted from cellular phone might produce oxidative stress in brain tissue of guinea pigs. However, more studies are needed to demonstrate whether these effects are harmful or/and affect the neural functions.

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Mausset-Bonnefont AL, Hirbec H, Bonnefont X, Privat A, Vignon J, de Seze R. Acute exposure to GSM 900-MHz electromagnetic fields induces glial reactivity and biochemical modifications in the rat brain. *Neurobiol Dis.* 17(3):445-454, 2004.

The worldwide proliferation of mobile phones raises the question of the effects of 900-MHz electromagnetic fields (EMF) on the brain. Using a head-only exposure device in the rat, we showed that a 15-min exposure to 900-MHz pulsed microwaves at a high brain-averaged power of 6 W/kg induced a strong glial reaction in the brain. This effect, which suggests neuronal damage, was particularly pronounced in the striatum. Moreover, we observed significant and immediate effects on the K(d) and B(max) values of N-methyl-d-aspartate (NMDA) and GABA(A) receptors as well as on dopamine transporters. Decrease of the amount of NMDA receptors at the postsynaptic membrane is also reported. Although we showed that the rat general locomotor behavior was not significantly altered on the short term, our results provide the first evidence for rapid cellular and molecular alterations in the rat brain after an acute exposure to high power GSM (Global System for Mobile communication) 900-MHz microwaves.

Nittby H, Widegren B, Krogh M, Grafström G, Berlin H, Rehn G, Eberhardt JL, Malmgren L, Persson BRR, Salford L. Exposure to radiation from global system for mobile communications at 1,800 MHz significantly changes gene expression in rat hippocampus and cortex. *Environmentalist* 28(4), 458-465, 2008.

We have earlier shown that radio frequency electromagnetic fields can cause significant leakage of albumin through the blood–brain barrier of exposed rats as compared to non-exposed rats, and also significant neuronal damage in rat brains several weeks after a 2 h exposure to a mobile phone, at 915 MHz with a global system for mobile communications (GSM) frequency modulation, at whole-body specific absorption rate values (SAR) of 200, 20, 2, and 0.2 mW/kg. We have now studied whether 6 h of exposure to the radiation from a GSM mobile test phone at 1,800 MHz (at a whole-body SAR-value of 13 mW/kg, corresponding to a brain SAR-value of 30 mW/kg) has an effect upon the gene expression pattern in rat brain cortex and hippocampus—areas where we have observed albumin leakage from capillaries into neurons and neuronal damage. Microarray analysis of 31,099 rat genes, including splicing variants, was performed in cortex and hippocampus of 8 Fischer 344 rats, 4 animals exposed to global system for mobile communications electromagnetic fields for 6 h in an anechoic chamber, one rat at a time, and 4 controls kept as long in the same anechoic chamber without exposure, also in this case one rat at a time. Gene ontology analysis (using the gene ontology categories biological processes, molecular functions, and cell components) of the differentially expressed genes of the exposed animals versus the control group revealed the following highly significant altered gene categories in both cortex and hippocampus: extracellular region, signal transducer activity, intrinsic to membrane, and integral to membrane. The fact that most of these categories are connected with membrane functions may have a relation to our earlier observation of albumin transport through brain capillaries.

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Söderqvist F, Carlberg M, Hansson Mild K, Hardell L. Exposure to an 890-MHz mobile phone-like signal and serum levels of S100B and transthyretin in volunteers. Toxicol Lett. 189(1):63-66, 2009.

Whether low-intensity non-thermal microwave radiation alters the integrity of the blood-brain barrier has been debated since the late 1970s, yet no experimental study has been carried out on humans. The aim of this study was to test, using peripheral markers, whether exposure to a mobile phone-like signal alters the integrity of the human blood-brain and blood-cerebrospinal fluid barriers. A provocation study was carried out that exposed 41 volunteers to a 30 min GSM 890 MHz signal with an average specific energy absorption rate distribution of 1.0 W/kg in the temporal area of the head as measured over any 1g of contiguous tissue. The outcome was assessed by changes in serum concentrations of two putative markers of brain barrier integrity, S100B and transthyretin. Repeated blood sampling before and after the provocation showed no statistically significant increase in the serum levels of S100B, while for transthyretin a statistically significant increase was seen in the final blood sample 60 min after the end of the provocation as compared to the prior sample taken immediately after provocation (p=0.02). The clinical significance of this finding, if any, is unknown. Further randomized studies with use of additional more brain specific markers are needed.

Schirmacher A, Winters S, Fischer S, Goeke J, Galla H, Kullnick U, Ringelstein EB, Stogbauer F, Electromagnetic fields (1.8 GHz) increase the permeability to sucrose of the blood-brain barrier in vitro. Bioelectromagnetics 21(5):338-345, 2000.

We report an investigation on the influence of high frequency electromagnetic fields (EMF) on the permeability of an in vitro model of the blood-brain barrier (BBB). Our model was a co-culture consisting of rat astrocytes and porcine brain capillary endothelial cells (BCEC). Samples were characterized morphologically by scanning electron microscopy and immunocytochemistry. The BBB phenotype of the BCEC was shown by the presence of zona occludens protein (ZO-1) as a marker for tight junctions and the close contact of the cells together with the absence of intercellular clefts. Permeability measurements using (14)C-sucrose indicated a physiological tightness which correlated with the morphological findings and verified the usefulness of our in vitro model. Samples were exposed to EMF conforming to the GSM1800-standard used in mobile telephones (1.8 GHz). The permeability of the samples was monitored over four days and compared with results of samples that were cultured identically but not exposed to EMF. Exposure to EMF increased permeability for (14)C-sucrose significantly compared to unexposed samples. The underlying pathophysiological mechanism remains to be investigated.

Narayanan SN, Kumar RS, Kedage V, Nalini K, Nayak S, Bhat PG. Evaluation of oxidant stress and antioxidant defense in discrete brain regions of rats exposed to 900 MHz radiation. Bratisl Lek Listy. 115(5):260-266, 2014.

AIM: In the current study, the effects of 900 MHz radio-frequency electromagnetic radiation (RF-EMR) on levels of thiobarbituric acid-reactive substances (TBARS), total

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antioxidants (TA), and glutathione S-transferase (GST) activity in discrete brain regions were studied in adolescent rats. MATERIALS AND METHODS: Thirty-six male Wistar rats (6-8 weeks old) were allotted into three groups (n = 12 in each group). Control group (1) remained undisturbed in their home cage; sham group (2) was exposed to mobile phone in switch off mode for four weeks; RF-EMR-exposed group (3) was exposed to 900 MHz of RF-EMR (1 hr/day with peak power density of 146.60 $\mu\text{W}/\text{cm}^2$) from an activated Global System for Mobile communication (GSM) mobile phone (kept in silent mode; no ring tone and no vibration) for four weeks. On 29th day, behavioral analysis was done. Followed by this, six animals from each group were sacrificed and biochemical parameters were studied in amygdala, hippocampus, frontal cortex, and cerebellum. RESULTS: Altered behavioral performances were found in RF-EMR-exposed rats. Additionally, elevated TBARS level was found with all brain regions studied. RF-EMR exposure significantly decreased TA in the amygdala and cerebellum but its level was not significantly changed in other brain regions. GST activity was significantly decreased in the hippocampus but, its activity was unaltered in other brain regions studied. CONCLUSION: RF-EMR exposure for a month induced oxidative stress in rat brain, but its magnitude was different in different regions studied. RF-EMR-induced oxidative stress could be one of the underlying causes for the behavioral deficits seen in rats after RF-EMR exposure (Fig. 5, Ref. 37).

Narayanan SN, Kumar RS, Potu BK, Nayak S, Bhat PG, Mailankot M. Effect of radio-frequency electromagnetic radiations (RF-EMR) on passive avoidance behaviour and hippocampal morphology in Wistar rats. Ups J Med Sci.115(2):91-96, 2010.

Abstract Introduction. The interaction of mobile phone radio-frequency electromagnetic radiation (RF-EMR) with the brain is a serious concern of our society. Objective. We evaluated the effect of RF-EMR from mobile phones on passive avoidance behaviour and hippocampal morphology in rats. Materials and methods. Healthy male albino Wistar rats were exposed to RF-EMR by giving 50 missed calls (within 1 hour) per day for 4 weeks, keeping a GSM (0.9 GHz/1.8 GHz) mobile phone in vibratory mode (no ring tone) in the cage. After the experimental period, passive avoidance behaviour and hippocampal morphology were studied. Results. Passive avoidance behaviour was significantly affected in mobile phone RF-EMR-exposed rats demonstrated as shorter entrance latency to the dark compartment when compared to the control rats. Marked morphological changes were also observed in the CA(3) region of the hippocampus of the mobile phone-exposed rats in comparison to the control rats. Conclusion. Mobile phone RF-EMR exposure significantly altered the passive avoidance behaviour and hippocampal morphology in rats.

Murbach, M., Neufeld, E., Christopoulou, M., Achermann, P. and Kuster, N. (2014), Modeling of EEG electrode artifacts and thermal ripples in human radiofrequency exposure studies. Bioelectromagnetics. doi: 10.1002/bem.21837.

The effects of radiofrequency (RF) exposure on wake and sleep electroencephalogram (EEG) have been in focus since mobile phone usage became pervasive. It has been hypothesized that effects may be explained by (1) enhanced induced fields due to RF

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coupling with the electrode assembly, (2) the subsequent temperature increase around the electrodes, or (3) RF induced thermal pulsing caused by localized exposure in the head. We evaluated these three hypotheses by means of both numerical and experimental assessments made with appropriate phantoms and anatomical human models. Typical and worst-case electrode placements were examined at 900 and 2140 MHz. Our results indicate that hypothesis 1 can be rejected, as the induced fields cause <20% increase in the 10 g-averaged specific absorption rate (SAR). Simulations with an anatomical model indicate that hypothesis 2 is also not supported, as the realistic worst-case electrode placement results in a maximum skin temperature increase of 0.31 °C while brain temperature elevations remained <0.1 °C. These local short-term temperature elevations are unlikely to change brain physiology during the time period from minutes to several hours after exposure. The maximum observed temperature ripple due to RF pulses is <0.001 °C for GSM-like signals and <0.004 °C for 20-fold higher pulse energy, and offers no support for hypothesis 3. Thus, the mechanism of interaction between RF and changes in the EEG power spectrum remains unknown.

Vorobyov VV, Galchenko AA, Kukushkin NI, Akoev IG, Effects of weak microwave fields amplitude modulated at ELF on EEG of symmetric brain areas in rats.

Bioelectromagnetics 18(4):293-298, 1997.

Averaged electroencephalogram (EEG) frequency spectra were studied in eight unanesthetized and unmyorelaxed adult male rats with chronically implanted carbon electrodes in symmetrical somesthetic areas when a weak (0.1-0.2 mW/cm²) microwave (MW, 945 MHz) field, amplitude-modulated at extremely low frequency (ELF) (4 Hz), was applied. Intermittent (1 min "On," 1 min "Off") field exposure (10-min duration) was used. Hemispheric asymmetry in frequency spectra (averaged data for 10 or 1 min) of an ongoing EEG was characterized by a power decrease in the 1.5-3 Hz range on the left hemisphere and by a power decrease in the 10-14 and 20-30 Hz ranges on the right hemisphere. No differences between control and exposure experiments were shown under these routines of data averaging. Significant elevations of EEG asymmetry in 10-14 Hz range were observed during the first 20 s after four from five onsets of the MW field, when averaged spectra were obtained for every 10 s. Under neither control nor pre- and postexposure conditions was this effect observed. These results are discussed with respect to interaction of MW fields with the EEG generators.

Maskey D, Pradhan J, Aryal B, Lee CM, Choi IY, Park KS, Kim SB, Kim HG, Kim MJ.

Chronic 835 MHz radiofrequency exposure to mice hippocampus alters the distribution of calbindin and GFAP immunoreactivity. Brain Res 1346:237-246, 2010.

Exponential interindividual handling in wireless communication system has raised possible doubts in the biological aspects of radiofrequency (RF) exposure on human brain owing to its close proximity to the mobile phone. In the nervous system, calcium (Ca²⁺) plays a critical role in releasing neurotransmitters, generating action potential and membrane integrity. Alterations in intracellular Ca²⁺ concentration trigger

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aberrant synaptic action or cause neuronal apoptosis, which may exert an influence on the cellular pathology for learning and memory in the hippocampus. Calcium binding proteins like calbindin D28-K (CB) is responsible for the maintaining and controlling Ca(2+) homeostasis. Therefore, in the present study, we investigated the effect of RF exposure on rat hippocampus at 835MHz with low energy (Specific Absorption Rate: SAR=1.6W/kg) for 3months by using both CB and glial fibrillary acidic protein (GFAP) specific antibodies by immunohistochemical method. Decrease in CB immunoreactivity (IR) was noted in exposed (E1.6) group with loss of interneurons and pyramidal cells in CA1 area and loss of granule cells. Also, an overall increase in GFAP IR was observed in the hippocampus of E1.6. By TUNEL assay, apoptotic cells were detected in the CA1, CA3 areas and dentate gyrus of hippocampus, which reflects that chronic RF exposure may affect the cell viability. Additionally, the increase of GFAP IR due to RF exposure could be well suited with the feature of reactive astrogliosis, which is an abnormal increase in the number of astrocytes due to the loss of nearby neurons. Chronic RF exposure to the rat brain suggested that the decrease of CB IR accompanying apoptosis and increase of GFAP IR might be morphological parameters in the hippocampus damages.

Maby E, Jeannes RL, Faucon G, Liegeois-Chauvel C, De Seze R. Effects of GSM signals on auditory evoked responses. *Bioelectromagnetics*. 26(5):341-350, 2005.

The article presents a study of the influence of radio frequency (RF) fields emitted by mobile phones on human cerebral activity. Our work was based on the study of Auditory Evoked Potentials (AEPs) recorded on the scalp of healthy humans and epileptic patients. The protocol allowed us to compare AEPs recorded with or without exposure to RFs. To get a reference, a control session was also introduced. In this study, the correlation coefficients computed between AEPs, as well as the correlation coefficients between spectra of AEPs were investigated to detect a possible difference due to RFs. A difference in the correlation coefficients computed in control and experimental sessions was observed, but it was difficult to deduce the effect of RFs on human health.

Maaroufi K, Had-Aissouni L, Melon C, Sakly M, Abdelmelek H, Poucet B, Save E. Spatial learning, monoamines and oxidative stress in rats exposed to 900MHz electromagnetic field in combination with iron overload. *Behav Brain Res*. 2013 Oct 18. pii: S0166-4328(13)00624-4. doi: 10.1016/j.bbr.2013.10.016. [Epub ahead of print]

The increasing use of mobile phone technology over the last decade raises concerns about the impact of high frequency electromagnetic fields (EMF) on health. More recently, a link between EMF, iron overload in the brain and neurodegenerative disorders including Parkinson's and Alzheimer's diseases has been suggested. Co-exposure to EMF and brain iron overload may have a greater impact on brain tissues and cognitive processes than each treatment by itself. To examine this hypothesis, Long-Evans rats submitted to 900MHz exposure or combined 900MHz EMF and iron overload treatments were tested in various spatial learning tasks (navigation task in the Morris water maze, working memory task in the radial-arm maze, and object exploration task involving spatial and non spatial processing). Biogenic monoamines and metabolites (dopamine, serotonin) and oxidative stress were measured. Rats exposed to EMF were

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impaired in the object exploration task but not in the navigation and working memory tasks. They also showed alterations of monoamine content in several brain areas but mainly in the hippocampus. Rats that received combined treatment did not show greater behavioral and neurochemical deficits than EMF-exposed rats. None of the two treatments produced global oxidative stress. These results show that there is an impact of EMF on the brain and cognitive processes but this impact is revealed only in a task exploiting spontaneous exploratory activity. In contrast, there are no synergistic effects between EMF and a high content of iron in the brain.

Lv B, Su C, Yang L, Xie Y, Wu T. Whole brain EEG synchronization likelihood modulated by long term evolution electromagnetic fields exposure. Conf Proc IEEE Eng Med Biol Soc. 2014:986-989, 2014.

In this paper, we aimed to investigate the possible interactions between human brain and radiofrequency electromagnetic fields (EMF) with electroencephalogram (EEG) technique. Unlike the previous studies which mainly focused on EMF effect on local brain activities, we attempted to evaluate whether the EMF emitted from Long Term Evolution (LTE) devices can modulate the functional connectivity of brain electrical activities. Ten subjects were recruited to participate in a crossover, double-blind exposure experiment which included two sessions (real and sham exposure). In each session, LTE EMF exposure (power on or off) lasted for 30 min and the EEG signals were collected with 32 channels throughout the experiment. Then we applied the synchronization likelihood method to quantify the neural synchronization over the whole brain in different frequency bands and in different EEG record periods. Our results illustrated that the short-term LTE EMF exposure would modulate the synchronization patterns of EEG activation across the whole brain.

Lv B, Chen Z, Wu T, Shao Q, Yan D, Ma L, Lu K, Xie Y. The alteration of spontaneous low frequency oscillations caused by acute electromagnetic fields exposure. Clin Neurophysiol. 2013 Sep 4. pii: S1388-2457(13)00976-0. doi: 10.1016/j.clinph.2013.07.018. [Epub ahead of print]

OBJECTIVE: The motivation of this study is to evaluate the possible alteration of regional resting state brain activity induced by the acute radiofrequency electromagnetic field (RF-EMF) exposure (30min) of Long Term Evolution (LTE) signal. **METHODS:** We designed a controllable near-field LTE RF-EMF exposure environment. Eighteen subjects participated in a double-blind, crossover, randomized and counterbalanced experiment including two sessions (real and sham exposure). The radiation source was close to the right ear. Then the resting state fMRI signals of human brain were collected before and after the exposure in both sessions. We measured the amplitude of low frequency fluctuation (ALFF) and fractional ALFF (fALFF) to characterize the spontaneous brain activity. **RESULTS:** We found the decreased ALFF value around in left superior temporal gyrus, left middle temporal gyrus, right superior temporal gyrus, right medial frontal gyrus and right paracentral lobule after the real exposure. And the decreased fALFF value was also detected in right medial frontal gyrus and right paracentral lobule. **CONCLUSIONS:** The study provided the evidences that 30min LTE RF-EMF exposure modulated the spontaneous low frequency fluctuations in some brain

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regions. SIGNIFICANCE: With resting state fMRI, we found the alteration of spontaneous low frequency fluctuations induced by the acute LTE RF-EMF exposure.

López-Martín E, Bregains J, Relova-Quinteiro JL, Cadarso-Suárez C, Jorge-Barreiro FJ, Ares-Pena FJ. The action of pulse-modulated GSM radiation increases regional changes in brain activity and c-Fos expression in cortical and subcortical areas in a rat model of picrotoxin-induced seizure proneness. J Neurosci Res. 87(6):1484-1499, 2009.

The action of the pulse-modulated GSM radiofrequency of mobile phones has been suggested as a physical phenomenon that might have biological effects on the mammalian central nervous system. In the present study, GSM-exposed picrotoxin-pretreated rats showed differences in clinical and EEG signs, and in c-Fos expression in the brain, with respect to picrotoxin-treated rats exposed to an equivalent dose of unmodulated radiation. Neither radiation treatment caused tissue heating, so thermal effects can be ruled out. The most marked effects of GSM radiation on c-Fos expression in picrotoxin-treated rats were observed in limbic structures, olfactory cortex areas and subcortical areas, the dentate gyrus, and the central lateral nucleus of the thalamic intralaminar nucleus group. Nonpicrotoxin-treated animals exposed to unmodulated radiation showed the highest levels of neuronal c-Fos expression in cortical areas. These results suggest a specific effect of the pulse modulation of GSM radiation on brain activity of a picrotoxin-induced seizure-proneness rat model and indicate that this mobile-phone-type radiation might induce regional changes in previous preexcitability conditions of neuronal activation.

López-Martín E, Bregains J, Relova-Quinteiro JL, Cadarso-Suárez C, Jorge-Barreiro FJ, Ares-Pena FJ. The action of pulse-modulated GSM radiation increases regional changes in brain activity and c-Fos expression in cortical and subcortical areas in a rat model of picrotoxin-induced seizure proneness. J Neurosci Res. 87(6):1484-1499, 2009.

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Lebedeva NN, Sulimov AV, Sulimova OP, Kotrovskaya TI, Gailus T. Cellular phone

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electromagnetic field effects on bioelectric activity of human brain. Crit Rev Biomed Eng 28(1-2):323-337, 2000.

24 volunteers participated in the experiments. The investigation of EEG reactions to cellular phone (EMF frequency 902.4 MHz and intensity 0.06 mW/cm²) was conducted. Two experiments were performed with each subject--cellular phone exposure and Placebo Duration of the experiment was 60 min: 15 min--background; 15 min--EMF exposure or Placebo; 30 min--afterexposure. EEG was recorded in 16 standard leads with "eyes open" and "eyes closed". Special software with non-linear dynamics was developed for EEG analyses. One parameter, multichannel (global) correlation dimension, was calculated. The changes of these parameters can be evidence of brain functional state changes. As a result of EEG record processing, a significant increase of global correlation dimension during the exposure and afterexposure period was discovered, more pronounced in the case of "eyes closed". That can be viewed as the manifestation of cortex activation under phone EMF exposure.

Lass L, Tuulik V, Ferenets CR, Riisalo R, Hinrikus H. Effects of 7 Hz-modulated 450 MHz electromagnetic radiation on human performance in visual memory tasks. Int. J. Rad. Biol. 78: 937-944, 2002.

Abstract: Purpose: The aim was to examine low-level 7 Hz-modulated 450 MHz radiation effects on human performance in visually presented neuropsychological tasks associated with attention and short-term memory. Materials and methods: A homogeneous group of 100 subjects (37 female, 63 male) were randomly assigned to either the exposed (10-20 min, 0.158mW cm⁻²) or the sham-exposed group. A battery of three different tests measured attention and shortterm memory. Task 1 involved alternately selecting black digits from 1 to 25 in ascending order and white digits from 24 to 1 in descending order. The time spent on the task and the number of errors were recorded and analysed. Task 2 involved viewing a picture of 12 objects during 3 s, followed by a list of 24 words. The subject was required to select words representing previously presented objects. In task 3, an array of letters in 10 rows (60 in each row) was presented, and the subject was required to identify all examples of a particular two-letter combination. Results: The results of tasks 1 and 3 showed a significant increase in variances of errors ($p < 0.05$) in the exposed versus the shamexposed group. The results of task 2 indicated a significant decrease in errors ($p < 0.05$) in the exposed group. Conclusions: The data provide additional evidence that acute lowlevel exposure to microwaves modulated at 7 Hz can affect cognitive processes such as attention and short-term memory.

Kramarenko AV, Tan U. Effects of high-frequency electromagnetic fields on human eeg: A brain mapping study. Int J Neurosci. 113(7):1007-1019, 2003.

Cell phones emitting pulsed high-frequency electromagnetic fields (EMF) may affect the human brain, but there are inconsistent results concerning their effects on electroencephalogram (EEG). We used a 16-channel telemetric electroencephalograph (ExpertTM), to record EEG changes during exposure of human skull to EMF emitted by a mobile phone. Spatial distribution of EMF was especially concentrated around the

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ipsilateral eye adjacent to the basal surface of the brain. Traditional EEG was full of noises during operation of a cellular phone. Using a telemetric electroencephalograph (ExpertTM) in awake subjects, all the noise was eliminated, and EEG showed interesting changes: after a period of 10-15 s there was no visible change, the spectrum median frequency increased in areas close to antenna; after 20-40 s, a slow-wave activity (2.5-6.0 Hz) appeared in the contralateral frontal and temporal areas. These slow waves lasting for about one second repeated every 15-20 s at the same recording electrodes. After turning off the mobile phone, slow-wave activity progressively disappeared; local changes such as increased median frequency decreased and disappeared after 15-20 min. We observed similar changes in children, but the slow-waves with higher amplitude appeared earlier in children (10-20 s) than adults, and their frequency was lower (1.0-2.5 Hz) with longer duration and shorter intervals. The results suggested that cellular phones may reversibly influence the human brain, inducing abnormal slow waves in EEG of awake persons.

Krause CM, Sillanmaki L, Koivisto M, Haggqvist A, Saarela C, Revonsuo A, Laine M, Hamalainen H, Effects of electromagnetic field emitted by cellular phones on the EEG during a memory task. Neuroreport 11(4):761-764, 2000.

The effects of electromagnetic fields (EMF) emitted by cellular phones on the ERD/ERS of the 4-6 Hz, 6-8 Hz, 8-10 Hz and 10-12 Hz EEG frequency bands were studied in 16 normal subjects performing an auditory memory task. All subjects performed the memory task both with and without exposure to a digital 902 MHz EMF in counterbalanced order. The exposure to EMF significantly increased EEG power in the 8-10 Hz frequency band only. Nonetheless, the presence of EMF altered the ERD/ERS responses in all studied frequency bands as a function of time and memory task (encoding vs retrieval). Our results suggest that the exposure to EMF does not alter the resting EEG per se but modifies the brain responses significantly during a memory task.

Krause CM, Sillanmaki L, Koivisto M, Haggqvist A, Saarela C, Revonsuo A, Laine M, Hamalainen H, Effects of electromagnetic fields emitted by cellular phones on the electroencephalogram during a visual working memory task. Int J Radiat Biol 76(12):1659-1667, 2000.

PURPOSE: To examine the effects of electromagnetic fields (EMF) emitted by cellular phones on the event-related desynchronization/synchronization (ERD/ERS) responses of the 4-6, 6-8, 8-10 and 10-12Hz EEG frequency bands during cognitive processing.

MATERIALS AND METHODS: Twenty-four subjects performed a visual sequential letter task (n-back task) with three different working memory load conditions: zero, one and two items. All subjects performed the memory task both with and without exposure to a digital 902 MHz EMF in counterbalanced order. **RESULTS:** The presence of EMF altered the ERD/ERS responses in the 6-8 and 8-10 Hz frequency bands but only when examined as a function of memory load and depending also on whether the presented stimulus was a target or not. **CONCLUSIONS:** The results suggest that the exposure to EMF modulates the responses of EEG oscillatory activity approximately 8 Hz specifically during cognitive processes.

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Krause CM, Haarala C, Sillanmaki L, Koivisto M, Alanko K, Revonsuo A, Laine M, Hamalainen H. Effects of electromagnetic field emitted by cellular phones on the EEG during an auditory memory task: a double blind replication study. *Bioelectromagnetics*. 25(1): 33-40, 2004.

The effects of electromagnetic fields (EMF) emitted by cellular phones on the event related desynchronization/synchronization (ERD/ERS) of the 4-6, 6-8, 8-10, and 10-12 Hz electroencephalogram (EEG) frequency bands were studied in 24 normal subjects performing an auditory memory task. This study was a systematic replication of our previous work. In the present double blind study, all subjects performed the memory task both with and without exposure to a digital 902 MHz field in a counterbalanced order. We were not able to replicate the findings from our earlier study. All eight of the significant changes in our earlier study were not significant in the present double blind replication. Also, the effect of EMF on the number of incorrect answers in the memory task was inconsistent. We previously reported no significant effect of EMF exposure on the number of incorrect answers in the memory task, but a significant increase in errors was observed in the present study. We conclude that EMF effects on the EEG and on the performance on memory tasks may be variable and not easily replicable for unknown reasons.

Köktürk S, Yardimoglu M, Celikozlu SD, Dolanbay EG, Cimbiz A. Effect of *Lycopersicon esculentum* extract on apoptosis in the rat cerebellum, following prenatal and postnatal exposure to an electromagnetic field. *Exp Ther Med*. 6(1):52-56, 2013.

The expansion of mobile phone technology has raised concerns regarding the effect of 900-MHz electromagnetic field (EMF) exposure on the central nervous system. At present, the developing human brain is regularly exposed to mobile telephones, pre- and postnatally. Several studies have demonstrated the acute effects of EMF exposure during pre- or postnatal periods; however, the chronic effects of EMF exposure are less understood. Thus, the aim of the present study was to determine the chronic effects of EMF on the pre- and postnatal rat cerebellum. The control group was maintained in the same conditions as the experimental groups, without the exposure to EMF. In the EMF1 group, the rats were exposed to EMF during pre- and postnatal periods (until postnatal day 80). In the EMF2 group, the rats were also exposed to EMF pre- and postnatally; in addition, however, they were provided with a daily oral supplementation of *Lycopersicon esculentum* extract (~2 g/kg). The number of caspase-3-labeled Purkinje neurons and granule cells present in the rats in the control and experimental groups were then counted. The neurodegenerative changes were studied using cresyl violet staining, and these changes were evaluated. In comparison with the control animals, the EMF1 group demonstrated a significant increase in the number of caspase-3-labeled Purkinje neurons and granule cells present in the cerebellum ($P < 0.001$). However, in comparison with the EMF1 group, the EMF2 group exhibited significantly fewer caspase-3-labeled Purkinje neurons and granule cells in the cerebellum. In the EMF1 group, the Purkinje neurons were revealed to have undergone dark neuron degenerative changes. However, the presence of dark Purkinje neurons was reduced in the EMF2 group,

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compared with the EMF1 group. The results indicated that apoptosis and neurodegeneration in rats exposed to EMF during pre- and postnatal periods may be reduced with *Lycopersicon esculentum* extract therapy.

Krause CM, Pesonen M, Haarala Bjornberg C, Hamalainen H. Effects of pulsed and continuous wave 902 MHz mobile phone exposure on brain oscillatory activity during cognitive processing. *Bioelectromagnetics*.28(4):296-308, 2007.

The aim of the current double-blind studies was to partially replicate the studies by Krause et al. [2000ab, 2004] and to further investigate the possible effects of electromagnetic fields (EMF) emitted by mobile phones (MP) on the event-related desynchronisation/synchronisation (ERD/ERS) EEG (electroencephalogram) responses during cognitive processing. Two groups, both consisting of 36 male participants, were recruited. One group performed an auditory memory task and the other performed a visual working memory task in six exposure conditions: SHAM (no EMF), CW (continuous wave EMF) and PM (pulse modulated EMF) during both left- and right-side exposure, while the EEG was recorded. In line with our previous studies, we observed that the exposure to EMF had modest effects on brain oscillatory responses in the alpha frequency range (approximately 8-12 Hz) and had no effects on the behavioural measures. The effects on the EEG were, however, varying, unsystematic and inconsistent with previous reports. We conclude that the effects of EMF on brain oscillatory responses may be subtle, variable and difficult to replicate for unknown reasons.

Imge EB, Kiliçoğlu B, Devrim E, Cetin R, Durak I. Effects of mobile phone use on brain tissue from the rat and a possible protective role of vitamin C - a preliminary study. *Int J Radiat Biol*.86(12):1044-1049, 2010.

Purpose: To evaluate effects of mobile phone use on brain tissue and a possible protective role of vitamin C. Materials and methods: Forty female rats were divided into four groups randomly (Control, mobile phone, mobile phone plus vitamin C and, vitamin C alone). The mobile phone group was exposed to a mobile phone signal (900 MHz), the mobile phone plus vitamin C group was exposed to a mobile phone signal (900 MHz) and treated with vitamin C administered orally (per os). The vitamin C group was also treated with vitamin C per os for four weeks. Then, the animals were sacrificed and brain tissues were dissected to be used in the analyses of malondialdehyde (MDA), antioxidant potential (AOP), superoxide dismutase, catalase (CAT), glutathione peroxidase (GSH-Px), xanthine oxidase, adenosine deaminase (ADA) and 5'nucleotidase (5'-NT). Results: Mobile phone use caused an inhibition in 5'-NT and CAT activities as compared to the control group. GSH-Px activity and the MDA level were also found to be reduced in the mobile phone group but not significantly. Vitamin C caused a significant increase in the activity of GSH-Px and non-significant increase in the activities of 5'-NT, ADA and CAT enzymes. Conclusion: Our results suggest that vitamin C may play a protective role against detrimental effects of mobile phone radiation in brain tissue.

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Hountala CD, Maganioti AE, Papageorgiou CC, Nanou ED, Kyprianou MA, Tsiafakis VG, Rabavilas AD, Capsalis CN. The spectral power coherence of the EEG under different EMF conditions. *Neurosci Lett.* 441(2):188-192, 2008.

The present study introduces the concept of spectral power coherence (SPC), which reflects the pattern of coordination of the four basic EEG bands (delta, theta, alpha, and beta) at a specific location of the brain. The SPC was calculated for the pre-stimulus EEG signal during an auditory memory task under different electromagnetic field (EMF) conditions (900 MHz and 1800 MHz). The results showed that delta rhythm is less consequential in the overall cooperation between the bands than the higher frequency theta, alpha and beta rhythms. Additionally, it has been shown that the radiation effect on SPC is different for the two genders. In the absence of radiation males exhibit higher overall SPC than females. These differences disappear in the presence of 900 MHz and are reversed in the presence of 1800 MHz.

Ilhan A, Gurel A, Armutcu F, Kamisli S, Iraz M, Akyol O, Ozen S. Ginkgo biloba prevents mobile phone-induced oxidative stress in rat brain. *Clin Chim Acta.* 340(1-2): 153-162, 2004.

BACKGROUND: The widespread use of mobile phones (MP) in recent years has raised the research activities in many countries to determine the consequences of exposure to the low-intensity electromagnetic radiation (EMR) of mobile phones. Since several experimental studies suggest a role of reactive oxygen species (ROS) in EMR-induced oxidative damage in tissues, in this study, we investigated the effect of Ginkgo biloba (Gb) on MP-induced oxidative damage in brain tissue of rats. METHODS: Rats (EMR+) were exposed to 900 MHz EMR from MP for 7 days (1 h/day). In the EMR+Gb groups, rats were exposed to EMR and pretreated with Gb. Control and Gb-administrated groups were produced by turning off the mobile phone while the animals were in the same exposure conditions. Subsequently, oxidative stress markers and pathological changes in brain tissue were examined for each groups. RESULTS: Oxidative damage was evident by the: (i) increase in malondialdehyde (MDA) and nitric oxide (NO) levels in brain tissue, (ii) decrease in brain superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities and (iii) increase in brain xanthine oxidase (XO) and adenosine deaminase (ADA) activities. These alterations were prevented by Gb treatment. Furthermore, Gb prevented the MP-induced cellular injury in brain tissue histopathologically. CONCLUSION: Reactive oxygen species may play a role in the mechanism that has been proposed to explain the biological side effects of MP, and Gb prevents the MP-induced oxidative stress to preserve antioxidant enzymes activity in brain tissue.

Ingole IV, Ghosh SK. Effect of exposure to radio frequency radiation emitted by cell phone on the developing dorsal root ganglion of chick embryo: a light microscopic study. *Nepal Med Coll J.* 14(4):337-341, 2012.

With an ever increasing number of cell phone users since late twenty first century, magnitude of the problem of exposure to radiation emitted by cell phone is self evident. Extensive research had been devoted to incriminate or absolve it as a health hazard.

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Radiofrequency radiation emitted by cell phone had been stated to be a potent carcinogen, cytotoxic, genotoxic, mutagenic and neurobehavioral teratogen. Its effect on the brain had been a subject of extensive research evidently due to its proximity to the user's brain. While considering the biological effects of radiofrequency radiation, its intensity, frequency and the duration of exposure are important determinants. Nevertheless the results of these different studies have not been unequivocal. Considering the contradictory reports, the present work was undertaken to study the effect of such an exposure on the developing neural tissue of chick embryo. The processes of cell division and differentiation are fundamental to the development of any living being and are a sensitive index of any insult sustained at this stage. Neurons of dorsal root ganglion were selected for the present study as these ganglia were fully differentiated as early as fourth day of embryonic life. By varying duration of exposure, the embryos were exposed to different doses of radiation, sacrificed at different periods of incubation and subjected to histological processing. On light microscopic study it was observed that developing neurons of dorsal root ganglion suffered a damage which was dose dependent and persisted in spite of giving the exposure-free period between two exposures.

Haarala C, Aalto S, Hautzel H, Julkunen L, Rinne JO, Laine M, Krause B, Hamalainen H. Effects of a 902 MHz mobile phone on cerebral blood flow in humans: a PET study. Neuroreport. 14(16):2019-2023, 2003.

SUMMARY: Fourteen healthy right-handed subjects were scanned using PET with a [15O]water tracer during exposure to electromagnetic field (EMF) emitted by a mobile phone and a sham-exposure under double-blind conditions. During scanning, the subjects performed a visual working memory task. Exposure to an active mobile phone produced a relative decrease in regional cerebral blood flow (rCBF) bilaterally in the auditory cortex but no rCBF changes were observed in the area of maximum EMF. It is possible that these remote findings were caused by the EMF emitted by the active mobile phone. A more likely interpretation of the present findings were a result of an auditory signal from the active mobile phone. Therefore, it is not reasoned to attribute this finding to the EMF emitted by the phone. Further study on human rCBF during exposure to EMF of a mobile phone is needed.

Hamblin DL, Wood AW, Croft RJ, Stough C. Examining the effects of electromagnetic fields emitted by GSM mobile phones on human event-related potentials and performance during an auditory task. Clin Neurophysiol. 115(1):171-178, 2004.

OBJECTIVE: Due to the widespread use of mobile phones (MP), it is important to determine whether they affect human physiology. The aim of this study was to explore the sensitivity of auditory event-related potentials to electromagnetic emissions. METHODS: Twelve participants attended two sessions, 1 week apart. Participants performed an auditory oddball task while they were exposed to an active MP during one session and sham exposure during the other. Each condition lasted 1 h and order was counterbalanced. N100 and P200 latencies and amplitudes were analysed for non-target waveforms, and N200 and P300 latencies and amplitudes were analysed for target

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waveforms. RESULTS: In real relative to sham exposure N100 amplitude and latency to non-targets were reduced, with the reduction larger over midline and right hemisphere sites. P300 latency to targets was delayed in the real exposure condition, however as this difference was greatest at left frontal and left central sites the interpretation of this result is unclear. Reaction time increased in the real relative to sham condition. No difference in accuracy was found. CONCLUSIONS: The results suggest that MP exposure may affect neural activity, particularly in proximity to the phone, however caution should be applied due to the small sample size.

Gandhi OP, Lazzi G, Tinniswood A, Yu QS, Comparison of numerical and experimental methods for determination of SAR and radiation patterns of handheld wireless telephones. Bioelectromagnetics Suppl 4:93-101, 1999.

Some recent developments in both the numerical and experimental methods for determination of SARs and radiation patterns of handheld wireless telephones are described, with emphasis on comparison of results using the two methods. For numerical calculations, it was possible to use the Pro-Engineer CAD Files of cellular telephones for a realistic description of the device. Also, we used the expanding grid formulation of the finite-difference time-domain (FDTD) method for finer-resolution representation of the coupled region, including the antenna, and an increasingly coarser representation of the more-distant, less-coupled region. Together with the truncation of the model of the head, this procedure led to a saving of computer memory needed for SAR calculations by a factor of over 20. Automated SAR and radiation pattern measurement systems were used to validate both the calculated 1-g SARs and radiation patterns for several telephones, including some research test samples, using a variety of antennas. Even though widely different peak 1-g SARs were obtained, ranging from 0.13 to 5.41 W/kg, agreement between the calculated and the measured data for these telephones, five each at 835 and 1900 MHz, was excellent and generally within +/-20% (+/-1 dB). An important observation was that for a maximum radiated power of 600 mW at 800/900 MHz, which may be used for telephones using AMPS technology, the peak 1-g SARs can be higher than 1.6 W/kg unless antennas are carefully designed and placed further away from the head.

Frey AH, Headaches from cellular telephones: are they real and what are the implications? Environ Health Perspect 106(3):101-103, 1998.

There have been numerous recent reports of headaches occurring in association with the use of hand-held cellular telephones. Are these reported headaches real? Are they due to emissions from telephones? There is reason to believe that the answer is "yes" to both questions. There are several lines of evidence to support this conclusion. First, headaches as a consequence of exposure to low intensity microwaves were reported in the literature 30 years ago. These were observed during the course of microwave hearing research before there were cellular telephones. Second, the blood-brain barrier appears to be involved in headaches, and low intensity microwave energy exposure affects the barrier. Third, the dopamine-opiate systems of the brain appear to be involved in headaches, and low intensity electromagnetic energy exposure affects those

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systems. In all three lines of research, the microwave energy used was approximately the same—in frequencies, modulations, and incident energies—as those emitted by present day cellular telephones. Could the current reports of headaches be the canary in the coal mine, warning of biologically significant effects?

Freude, G, Ullsperger, P, Eggert, S, Ruppe, I, Microwaves emitted by cellular telephones affect human slow brain potentials. Eur J Appl Physiol 81(1-2):18-27, 2000.

The influence of electromagnetic fields (EMF) emitted by cellular telephones on preparatory slow brain potentials (SP) was studied in two experiments, about 6 months apart. In the first experiment, a significant decrease of SP was found during exposure to EMF in a complex visual monitoring task (VMT). This effect was replicated in the second experiment. In addition to the VMT, EMF effects on SP were analysed in two further, less demanding tasks: in a simple finger movement task to elicit a Bereitschaftspotential (BP) and in a two-stimulus task to elicit a contingent negative variation (CNV). In comparison to the VMT, no significant main EMF effects were found in BP and CNV tasks. The results accounted for a selective EMF effect on particular aspects of human information processing, but did not indicate any influence on human performance, well-being and health.

Freude, G, Ullsperger, P, Eggert, S, Ruppe, I, Effects of microwaves emitted by cellular phones on human slow brain potentials. Bioelectromagnetics 19(6):384-387, 1998.

The influence of electromagnetic fields (EMF) emitted by cellular phones on preparatory slow brain potentials (SP) was studied in two different experimental tasks: In the first, healthy male human subjects had to perform simple self-paced finger movements to elicit a Bereitschaftspotential; in the second, they performed a complex and cognitive demanding visual monitoring task (VMT). Both tasks were performed with and without EMF exposure in counterbalanced order. Whereas subjects' performance did not differ between the EMF exposure conditions, SP parameters were influenced by EMF in the VMT: EMF exposure effected a significant decrease of SPs at central and temporo-parieto-occipital brain regions, but not at the frontal one. In the simple finger movement task, EMF did not affect the Bereitschaftspotential.

Finnie JW, Blumbergs PC, Manavis J, Utteridge TD, Gebiski V, Davies RA, Vernon-Roberts B, Kuchel TR. Effect of long-term mobile communication microwave exposure on vascular permeability in mouse brain. Pathology 34(4):344-347, 2002.

AIMS: To study the effect of long-term exposure to global system for mobile communication (GSM) radiofrequency fields on vascular permeability in murine brains. METHODS: Using a purpose-designed exposure system at 900 MHz, mice were given a 60-minute far-field, whole body exposure on each of 5 days per week for 104 weeks at specific absorption rates (SAR) of 0.25, 1.0, 2.0 and 4.0 W/kg. Control mice were sham-exposed or permitted free movement in a cage to evaluate any stress-related effects. Albumin immunohistochemistry was used to detect increased vascular permeability and the efficacy of the vascular tracer was confirmed with a positive control group exposed to a clostridial toxin known to increase vascular permeability in the brain. RESULTS: In all

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exposed and control groups, albumin extravasation was minimal, often leptomeningeal, and was deemed insignificant as a maximum of three capillaries or venules in a given brain showed leakage from the very many blood vessels present in the three coronal brain sections. CONCLUSIONS: These results suggest that prolonged exposure to mobile telephone-type radiation produces negligible disruption to blood-brain barrier integrity at the light microscope level using endogenous albumin as a vascular tracer.

Ferreri F, Curcio G, Pasqualetti P, De Gennaro L, Fini R, Rossini PM. Mobile phone emissions and human brain excitability. *Ann Neurol*.60(2):188-196, 2006.

OBJECTIVE: To test-via Transcranial Magnetic Stimulation (TMS)-the excitability of each brain hemisphere after 'real' or 'sham' exposure to the electromagnetic field (EMF) generated by a mobile phone operating in the Global System for Mobile Communication (GSM). METHODS: Fifteen male volunteers attended two experimental sessions, one week apart, in a cross-over, double-blind paradigm. In one session the signal was turned ON (EMF-on, real exposure), in the other it was turned OFF (EMF-off, sham exposure), for 45 minutes. Motor Evoked Potentials (MEPs) were recorded using a paired-pulse paradigm (testing intracortical excitability with 1 to 17 ms interstimulus intervals), both before and at different times after exposure to the EMF. Short Intracortical Inhibition (SICI) and Facilitation (ICF) curves were evaluated both on the exposed and non-exposed hemispheres. Tympanic temperature was collected during each session. RESULTS: The intracortical excitability curve becomes significantly modified during real exposure, with SICI being reduced and ICF enhanced in the acutely exposed brain hemisphere as compared to the contralateral, non-exposed hemisphere or to sham exposure. Tympanic temperature showed no significant main effect or interactions. INTERPRETATION: These results demonstrate that GSM-EMFs modify brain excitability. Possible implications and applications are discussed.

Fayos-Fernandez J, Arranz-Faz C, Martinez-Gonzalez AM, Sanchez-Hernandez D. Effect of pierced metallic objects on sar distributions at 900 MHz. *Bioelectromagnetics*. 27(5):337-353, 2006.

. A study of the interaction between mobile phone antennas and a human head in the presence of different types of metallic objects, attached and pierced to the compressed ear, is presented in this article. Computed and measured results have been performed by considering a quasi-half-wavelength dipole as the radiating source and measurements with the DASY4 dosimetric assessment system. Two different human head models have been implemented: a homogeneously shaped sphere and a three-level head model with four different kinds of tissue. Antenna input impedance, reflection coefficient, radiation patterns, SAR distribution, absorbed power, and peak SAR values have been computed and measured for diverse scenarios, electromagnetic simulators, and organs. Despite the measuring accuracy limitations of the study, both simulated and measured results suggest that special attention has to be paid to peak SAR averaged values when wearing metallic objects close to the radiation source, since some increment of peak SAR averaged values is expected.

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Faucon G, Le Bouquin Jeannes R, Maby E. Short-term effects of GSM mobiles phones on spectral components of the human electroencephalogram. Conf Proc IEEE Eng Med Biol Soc. 1(1):3751-3754, 2006.

The aim of the study was to investigate whether the GSM (global system for mobile) signals affect the electrical activity of the human brain. Nine healthy subjects and six temporal epileptic patients were exposed to radiofrequencies emitted by a GSM mobile phone signals. Electroencephalographic (EEG) signals were recorded using surface electrodes with and without radiofrequency. In order to obtain a reference, a control session was also carried out. The spectral attributes of the EEG signals recorded by surface electrodes were analyzed. The significant decrease of spectral correlation coefficients under radiofrequency influence showed that the GSM signal altered the spectral arrangement of the EEG activity for healthy subjects as well as epileptic patients. For the healthy subjects, the EEG spectral energy decreased on the studied frequency band [0-40 Hz] and more precisely on occipital electrodes for the alpha-band. For the epileptic patients, these modifications were demonstrated by an increase of the power spectral density of the EEG signal. Nevertheless, these biological effects on the EEG are not sufficient to put forward some electrophysiological hypothesis.

Eulitz, C, Ullsperger, P, Freude, G, Elbert ,T, Mobile phones modulate response patterns of human brain activity. Neuroreport 9(14):3229-3232, 1998.

Mobile phones emit a pulsed high-frequency electromagnetic field (PEMF) which may penetrate the scalp and the skull. Increasingly, there is an interest in the interaction of this pulsed microwave radiation with the human brain. Our investigations show that these electromagnetic fields alter distinct aspects of the brain's electrical response to acoustic stimuli. More precisely, our results demonstrate that aspects of the induced but not the evoked brain activity during PEMF exposure can be different from those not influenced by PEMF radiation. This effect appears in higher frequency bands when subjects process task-relevant target stimuli but was not present for irrelevant standard stimuli. As the induced brain activity in higher frequency bands has been proposed to be a correlate of coherent high-frequency neuronal activity, PEMF exposure may provide means to systematically alter the pattern fluctuations in neural mass activity.

Eberhardt JL, Persson BR, Brun AE, Salford LG, Malmgren LO. Blood-brain barrier permeability and nerve cell damage in rat brain 14 and 28 days after exposure to microwaves from GSM mobile phones. Electromagn Biol Med. 27(3):215-229, 2008.

We investigated the effects of global system for mobile communication (GSM) microwave exposure on the permeability of the blood-brain barrier and signs of neuronal damage in rats using a real GSM programmable mobile phone in the 900 MHz band. Ninety-six non-anaesthetized rats were either exposed to microwaves or sham exposed in TEM-cells for 2 h at specific absorption rates of average whole-body Specific Absorption Rates (SAR) of 0.12, 1.2, 12, or 120 mW/kg. The rats were sacrificed after a recovery time of either 14 or 28 d, following exposure and the extravasation of albumin, its uptake into neurons, and occurrence of damaged neurons was assessed. Albumin

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extravasation and also its uptake into neurons was seen to be enhanced after 14 d (Kruskal Wallis test: $p = 0.02$ and 0.002 , respectively), but not after a 28 d recovery period. The occurrence of dark neurons in the rat brains, on the other hand, was enhanced later, after 28 d ($p = 0.02$). Furthermore, in the 28-d brain samples, neuronal albumin uptake was significantly correlated to occurrence of damaged neurons (Spearman $r = 0.41$; $p < 0.01$).

de Tommaso M, Rossi P, Falsaperla R, Francesco VD, Santoro R, Federici A. Mobile Phones exposure induces changes of Contingent Negative Variation in humans. *Neurosci Lett.*464(2):79-83, 2009.

Event related potentials have been largely employed to test effects of GSM emissions on human brain. The aim of the present study, was the evaluation of initial Contingent Negative Variation (iCNV) changes, induced by 900MHz GSM exposure, in a double blind design in healthy volunteers, subjected to a threefold experimental condition, EXPOSED (A), a real GSM phone emitting electromagnetic power, SHAM (B), a real phone where the electromagnetic power was dissipated on an internal load and OFF (C), a phone completely switched off. Ten healthy right-handed volunteers were evaluated. The CNV was recorded during a 10minutes time interval in each of the three experimental conditions A, B, and C, in order to assess the iCNV amplitude and habituation. The iCNV amplitude decreased and habituation increased during both A and B conditions, compared with condition C. This effect was diffuse over the scalp, and there was no significant prevalence of iCNV amplitude reduction on the left side, where the phones were located. Mobile Phones exposures A and B seemed to act on brain electrical activity, reducing the arousal and expectation of warning stimulus. This evidence, limited by the low number of subjects investigated, could be explained in terms of an effect induced by both the GSM signal and the Extremely Low Frequency magnetic field produced by battery and internal circuits.

Dasdag S, Akdag MZ, Ulukaya E, Uzunlar AK, Ocak AR. Effect of mobile phone exposure on apoptotic glial cells and status of oxidative stress in rat brain. *Electromagn Biol Med.* 28(4):342-354, 2009.

The aim of this study was to investigate the effects of mobile phone exposure on glial cells in brain. The study carried out on 31 Wistar Albino adult male rats. The rat heads in a carousel exposed to 900 MHz microwave. For the study group (n:14), rats exposed to the radiation 2 h per day (7 days in a week) for 10 months. For the sham group (n:7), rats were placed into the carousel and the same procedure was applied except that the generator was turned off. For the cage control (n:10), nothing applied to rats in this group. In this study, rats were euthanized after 10 months of exposure periods and brains were removed. Brain tissues were immunohistochemically stained for the active (cleaved) caspase-3, which is a well-known apoptosis marker, and p53. The expression of the proteins was evaluated by a semi-quantitative scoring system. However, total antioxidative capacity (TAC), catalase, total oxidant status (TOS), and oxidative stress index were measured in rat brain. Final score for apoptosis in the exposed group was significantly lower than the sham ($p < 0.001$) and the cage control groups ($p < 0.01$). p53

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was not significantly changed by the exposure ($p > 0.05$). The total antioxidant capacity and catalase in the experimental group was found higher than that in the sham group ($p < 0.001$, $p < 0.05$). In terms of the TOS and oxidative stress index, there was no statistically significant difference between exposure and sham groups ($p > 0.05$). In conclusion, the final score for apoptosis, total antioxidant capacity and catalase in rat brain might be altered by 900 MHz radiation produced by a generator to represent exposure of global systems for mobile communication (GSM) cellular phones.

Croft RJ, Hamblin DL, Spong J, Wood AW, McKenzie RJ, Stough C. The effect of mobile phone electromagnetic fields on the alpha rhythm of human electroencephalogram. *Bioelectromagnetics*.29(1):1-10,2008.

Mobile phones (MP) emit low-level electromagnetic fields that have been reported to affect neural function in humans; however, demonstrations of such effects have not been conclusive. The purpose of the present study was to test one of the strongest findings in the literature; that of increased "alpha" power in response to MP-type radiation. Healthy participants (N = 120) were tested using a double-blind counterbalanced crossover design, with each receiving a 30-min Active and a 30-min Sham Exposure 1 week apart, while electroencephalogram (EEG) data were recorded. Resting alpha power (8-12 Hz) was then derived as a function of time, for periods both during and following exposure. Non-parametric analyses were employed as data could not be normalized. Previous reports of an overall alpha power enhancement during the MP exposure were confirmed (relative to Sham), with this effect larger at ipsilateral than contralateral sites over posterior regions. No overall change to alpha power was observed following exposure cessation; however, there was less alpha power contralateral to the exposure source during this period (relative to ipsilateral). Employing a strong methodology, the current findings support previous research that has reported an effect of MP exposure on EEG alpha power.

Chia SE, Chia HP, Tan JS, Prevalence of headache among handheld cellular telephone users in singapore: A community study. *Environ Health Perspect* 108(11):1059-1062, 2000.

We carried out a cross-sectional community study in Singapore to determine the prevalence of specific central nervous system (CNS) symptoms among hand-held cellular telephone (HP) users compared to nonusers and to study the association of risk factors and CNS symptoms among HP users. A total of 808 men and women between 12 and 70 years of age, who lived in one community, were selected using one-stage cluster random sampling and responses to a structured questionnaire. The prevalence of HP users was 44.8%. Headache was the most prevalent symptom among HP users compared to non-HP users, with an adjusted prevalence rate ratio of 1.31 [95% confidence interval, 1.00-1.70]. There is a significant increase in the prevalence of headache with increasing duration of usage (in minutes per day). Prevalence of headache was reduced by more than 20% among those who used hand-free equipment for their cellular telephones as compared to those who never use the equipment. The use of HPs is not associated with a significant increase of CNS symptoms other than

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headache.

Celikozlu SD, Ozyurt MS, Cimbiz A, Yardimoglu MY, Cayci MK, Ozay Y. The effects of long-term exposure of magnetic field via 900-MHz GSM radiation on some biochemical parameters and brain histology in rats. *Electromagn Biol Med.* 31(4):344-355, 2012.

The aim of this study is to determine the effects of magnetic field via cell phones on some blood parameters and neurons in the brain of rats. Animals have been classified into three groups: control, Magnetic Field (MF), and F2 groups. Throughout this study, cell phones were placed on the wall of the cages. Rats were exposed to the effects of cell phones during prenatal and postnatal periods until they were 80 days old. During the study, the exposure procedure of rats was that the phone was in standby mode for a whole day and in talking mode for 30 min per day. The waves of cell phones caused an increased blood glucose level from 96.52 ± 5.64 mg/dl to 132.14 ± 5.93 mg/dl and an increased serum protein level from 131.14 ± 6.19 mg/dl to 319.29 ± 6.73 mg/dl compared to control. Statistically, significant differences wasn't observed in the blood cholesterol concentration between the groups compared to the control. Weekly weight gain decreased in all groups compared to the control. MF exposure decreased pyramidal neuron numbers 51.15% and increased ischemic neuron numbers 73% at cortex region of brain. In addition, vascular dilatations have increased clearly in group F2. Whereas the procedure of MF did not have any effects on hippocampal pyramidal cell numbers, magnetic fields increased the amount of ischemic neurons three-fold compared to the control. In conclusion, MF affected some biochemical parameters, especially the cortex region of the brain.

Carrubba S, Frilot C 2nd, Chesson AL Jr, Marino AA. Mobile-phone pulse triggers evoked potentials. *Neurosci Lett.* 469(1):164-168, 2010.

If mobile-phone electromagnetic fields (EMFs) are hazardous, as suggested in the literature, processes or mechanisms must exist that allow the body to detect the fields. We hypothesized that the low-frequency pulses produced by mobile phones (217Hz) were detected by sensory transduction, as evidenced by the ability of the pulses to trigger evoked potentials (EPs). Electroencephalograms (EEGs) were recorded from six standard locations in 20 volunteers and analyzed to detect brain potentials triggered by a pulse of the type produced by mobile phones. Evoked potentials having the expected latency were found in 90% of the volunteers, as assessed using a nonlinear method of EEG analysis. Evoked potentials were not detected when the EEG was analyzed using time averaging. The possibility of systematic error was excluded by sham-exposure analyses. The results implied that mobile-phones trigger EP at the rate of 217Hz during ordinary phone use. Chronic production of the changes in brain activity might be pertinent

Carballo-Quintás M, Martínez-Silva I, Cadarso-Suárez C, Alvarez-Figueiras M, Ares-Pena FJ, López-Martín E. A study of neurotoxic biomarkers, c-fos and GFAP after acute

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exposure to GSM radiation at 900 MHz in the picrotoxin model of rat brains.

Neurotoxicology. 32(4):478-494, 2011.

The acute effects of microwave exposure from the Global System for Mobile Communication (GSM) were studied in rats, using 900MHz radiation at an intensity similar to mobile phone emissions. Acute subconvulsive doses of picrotoxin were then administered to the rats and an experimental model of seizure-proneness was created from the data. Seventy-two adult male Sprague-Dawley rats underwent immunochemical testing of relevant anatomical areas to measure induction of the c-fos neuronal marker after 90min and 24h, and of the glial fibrillary acidic protein (GFAP) 72h after acute exposure to a 900MHz electromagnetic field (EMF). The experimental set-up facilitated measurement of absorbed power, from which the average specific absorption rate was calculated using the finite-difference time-domain (FDTD) 2h after exposure to EMF radiation at 1.45W/kg in picrotoxin-treated rats and 1.38W/kg in untreated rats. Ninety minutes after radiation high levels of c-fos expression were recorded in the neocortex and paleocortex along with low hippocampus activation in picrotoxin treated animals. Most brain areas, except the limbic cortical region, showed important increases in neuronal activation 24h after picrotoxin and radiation. Three days after picrotoxin treatment, radiation effects were still apparent in the neocortex, dentate gyrus and CA3, but a significant decrease in activity was noted in the piriform and entorhinal cortex. During this time, glial reactivity increased with every seizure in irradiated, picrotoxin-treated brain regions. Our results reveal that c-fos and glial markers were triggered by the combined stress of non-thermal irradiation and the toxic effect of picrotoxin on cerebral tissues.

Brillaud E, Piotrowski A, de Seze R. Effect of an acute 900MHz GSM exposure on glia in the rat brain: A time-dependent study. Toxicology.238(1):23-33,2007.

Because of the increasing use of mobile phones, the possible risks of radio frequency electromagnetic fields adverse effects on the human brain has to be evaluated. In this work we measured GFAP expression, to evaluate glial evolution 2, 3, 6 and 10 days after a single GSM exposure (15min, brain averaged SAR=6W/kg, 900MHz signal) in the rat brain. A statistically significant increase of GFAP stained surface area was observed 2 days after exposure in the frontal cortex and the caudate putamen. A smaller statistically significant increase was noted 3 days after exposure in the same areas and in the cerebellum cortex. Our results confirm the Mausset-Bonnefont et al. study [Mausset-Bonnefont, A.L., Hirbec, H., Bonnefont, X., Privat, A., Vignon, J., de Seze, R., 2004. Acute exposure to GSM 900MHz electromagnetic fields induces glial reactivity and biochemical modifications in the rat brain. Neurobiol. Dis. 17, 445-454], showing the existence of glial reactivity after a 15min GSM acute exposure at a brain averaged SAR of 6W/kg. We conclude to a temporary effect, probably due to a hypertrophy of glial cells, with a temporal and a spatial modulation of the effect. Whether this effect could be harmful remains to be studied.

Bortkiewicz A, Gadzicka E, Szymczak W, Zmysłony M. Changes in tympanic temperature during the exposure to electromagnetic fields emitted by mobile phone.

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Int J Occup Med Environ Health. 25(2): 145-150, 2012.

OBJECTIVE: Mobile phones generate microwave radiation which is absorbed by exposed tissue and converted into heat. It may cause detrimental health effects. The aim of the experiment was to check if exposure to EMF emitted by mobile phone influenced the tympanic temperature. **MATERIAL AND METHODS:** Human volunteer study was performed on ten healthy young men, aged 22.1 ± 4.7 years, examined three times: 1. on a day with 2×60 min of no exposure (sham day), 2. on a day with continuous, 60 min exposure and 60 min of no exposure, 3. on a day with intermittent exposure (4×15 min "on" and 4×15 min "off"). Exposure was generated by mobile phone (frequency 900 MHz, SAR 1.23 W/kg). The study was double-blind, performed under controlled conditions (at 24°C and 70% humidity). The tympanic temperature ($T(\text{ty})$) was monitored every 10 sec by a thermistor probe placed close to the aural canal membrane in the ear opposite the one in contact with mobile phone (contralateral position). Multivariate repeated-measures analysis of variance was used to calculate the results. **RESULTS:** The mean $T(\text{ty})$ in the whole group during continuous exposure was significantly higher than during sham exposure ($p = 0.0001$). During intermittent exposure the temperature was lower than during sham day (difference was up to 0.11°C). Within an hour after continuous exposure, $T(\text{ty})$ was higher by 0.03°C and after intermittent exposure $T(\text{ty})$ was lower by 0.18°C in comparison with sham day. Two hours after exposure $T(\text{ty})$ was significantly lower ($p = 0.0001$) than after sham exposure (0.06°C and 0.26°C respectively). The trends in $T(\text{ty})$ during experiment differed significantly in relation to exposure conditions ($p < 0.05$). **CONCLUSIONS:** The results of this analysis indicate that the physiological response to EMF exposure from mobile phone was mostly related to type of exposure (continuous or intermittent).

Bilgici B, Akar A, Avci B, Tuncel OK. Effect of 900 MHz radiofrequency radiation on oxidative stress In rat brain and serum. Electromagn Biol Med. 32(1):20-29, 2013.

The increasing use of mobile telephones raises the question of possible adverse effects of the electromagnetic fields (EMF) that these phones produce. In this study, we examined the oxidative stress in the brain tissue and serum of rats that resulted from exposure to a 900-MHz EMF at a whole body average specific absorption rate (SAR) of 1.08 W/kg for 1 h/day for 3 weeks. We also examined the antioxidant effect of garlic powder (500 mg/kg/day) given orally to EMF-exposed rats. We found that malondialdehyde (MDA) ($p < 0.001$) and advanced oxidation protein product (AOPP) ($p < 0.05$) increased in rat brain tissue exposed to the EMF and that garlic reduced these effects ($p < 0.05$). There was no significant difference in the nitric oxide (NO) levels in the brain. Paraoxonase (PON) was not detected in the brain. There was a significant increase in the levels of NO ($p < 0.001$) detected in the serum after EMF exposure, and garlic intake did not affect this increase in NO. Our results suggest that there is a significant increase in brain lipid and protein oxidation after electromagnetic radiation (EMR) exposure and that garlic has a protective effect against this oxidative stress.

Bachmann M, Rubljova J, Lass J, Tomson R, Tuulik V, Hinrikus H. Adaptation of human brain bioelectrical activity to low-level microwave. Conf Proc IEEE Eng Med Biol Soc. 2007:4747-4750, 2007.

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The experiments of adaptation of the human brain bioelectrical activity were carried out on a group of 14 healthy volunteers exposed to 450 MHz microwave radiation modulated at 40 Hz frequencies. The field power density at the scalp was 0.16 mW/cm². Results of the study indicate that adaptation effect of human brain to low-level microwave exposure is evident. The initial increase of EEG power was compensated and even overcompensated. The adaptation phenomena were obvious in EEG alpha and beta rhythms.

Barcal J, Cendelín J, Vozech F, Zalud V. Effect of whole-body exposure to high-frequency electromagnetic field on the brain electrogeny in neurodefective and healthy mice. Prague Med Rep. 106(1):91-100, 2005.

A direct registration of brain cortical and hippocampal activity during a high-frequency electromagnetic field (HF EMF) exposure was performed. All experimental procedures were done under urethane anaesthesia (20%, 2 g/kg i.p.) in Lurcher mutant mice, wild type (healthy littermates) were used as controls. Experimental animals were exposed to the HF EMF with frequency corresponding to cellular phones. Our method is based on the use of gel electrodes (silicon tubes or glass microcapillaries filled with agar) where the connection with classical electrodes is located out of HF EMF space. ECoG evaluation showed a distinct shift to lower frequency components but clear effect has been observed only in wild type (healthy) mice whereas in Lurcher mutant mice only gentle differences between frequency spectra were found. Measurement of hippocampal rhythmicity showed gentle changes with increase of higher frequencies (i.e. opposite effect than in cortex) and changes in theta oscillations registered from a dentate gyrus and CA1 area in both types of animals (healthy and mutant). These findings support the idea about possible influencing the central nervous system by HF EMF exposure and support also some recent results about possible health risks resulting from cellular phones use.

Barcal J, Vozech F. Effect of whole-body exposure to high-frequency electromagnetic field on the brain cortical and hippocampal activity in mouse experimental model. NeuroQuantology 5:292-302, 2007.

Evaluation of the direct registration of brain cortical and hippocampal activity during a high-frequency electromagnetic field (HF-EMF) exposure was performed. Experimental procedures were done under general anesthesia (urethane, 20%, 2g/kg i.p.) in Lurcher mutant mice, wild type (healthy littermates) were used as controls. Animals were exposed to the HF-EMF with frequency corresponding to cellular phones (900 MHz). We used of gel electrodes (silicon tubes or glass microcapillary filled with agar) where the connection with classical electrodes was located out of HF-EMF space. ECoG evaluation showed a distinct shift to lower frequency components but clear effect has been observed only in wild type (healthy) mice whereas in Lurcher mutant mice only gentle differences between frequency spectra were found. Measurement of hippocampal rhythmicity showed gentle changes with increase of higher frequencies (i.e. opposite effect than in cortex) and changes in theta oscillations registered from a dentate gyrus and CA1 area in both types of animals (healthy and mutant). These findings support an

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idea about possible influencing the central nervous system by HF-EMF exposure and support also some recent results about possible health risks resulting from cellular phones use.

Bas O, Odaci E, Kaplan S, Acer N, Ucok K, Colakoglu S. 900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in the adult female rat. Brain Res. 1265:178-185, 2009.

The effects of electromagnetic fields (EMFs) emitted by mobile phones on humans hold special interest due to their use in close proximity to the brain. The current study investigated the number of pyramidal cells in the cornu ammonis (CA) of the 16-week-old female rat hippocampus following postnatal exposure to a 900 megahertz (MHz) EMF. In this study were three groups of 6 rats: control (Cont), sham exposed (Sham), and EMF exposed (EMF). EMF group rats were exposed to 900 MHz EMF (1 h/day for 28 days) in an exposure tube. Sham group was placed in the exposure tube but not exposed to EMF (1 h/day for 28 days). Cont group was not placed into the exposure tube nor were they exposed to EMF during the study period. In EMF group rats, the specific energy absorption rate (SAR) varied between 0.016 (whole body) and 2 W/kg (locally in the head). All of the rats were sacrificed at the end of the experiment and the number of pyramidal cells in the CA was estimated using the optical fractionator technique. Histopathological evaluations were made on sections of the CA region of the hippocampus. Results showed that postnatal EMF exposure caused a significant decrease of the pyramidal cell number in the CA of the EMF group (P<0.05). Additionally, cell loss can be seen in the CA region of EMF group even at qualitative observation. These results may encourage researchers to evaluate the chronic effects of 900 MHz EMF on teenagers' brains.

Behari J, Kunjilwar KK, and Pyne S, Interaction of low level modulated RF radiation with Na⁺-K⁺-ATPase. Bioelectrochem Bioenerg 47:247-252, 1998.

The effect of low-level amplitude modulated radiofrequency radiation were studied on Na⁺-K⁺-ATPase activity in the brain of developing male Wistar rats of age 23 days (body weight 55-60 g). They were exposed to carrier wave (CW) frequency 147 MHz and its sub-harmonic frequencies 73.5 and 36.75 MHz amplitude modulated (AM) at 16 and 76 Hz for 30-35 days (3 h day⁻¹, Power density 1.47 mW cm⁻², average specific absorption rate 9.65-6.11 W kg⁻¹). We observed a statistically significant increase in Na⁺-K⁺-ATPase activity in chronically exposed rats compared to the control ones. The increase in Na⁺-K⁺-ATPase activity was around 19-20% in the rats exposed to CW frequencies AM at 16 Hz compared to the controls, whereas the increase in Na⁺-K⁺-ATPase activity was around 15-16% in rats exposed to the same set of CW frequencies but AM at 76 Hz. Though there was a difference in Na⁺-K⁺-ATPase activities (3-4%) in the two groups but the difference was found to be statistically insignificant. Within the group of rats exposed to CW frequencies amplitude modulated at 16 and 76 Hz, respectively, the effect on Na⁺-K⁺-ATPase activity was found to be independent of the magnitude of CW frequencies. An additional single short duration (20-60 min) exposure of membranes in vitro from different exposed group to the above field did not show any significant

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alteration on Na⁺-K⁺-ATPase activity. It is concluded that a low level effect of amplitude modulated radiation produces statistically significant effect on Na⁺-K⁺-ATPase activity but is insensitive to the carrier wave frequencies under investigation.

Zhou H, Su Z, Ning J, Wang C, Xie X, Qu D, Wu K, Zhang X, Pan J, Yang G. EFFECTS OF FREQUENCY, IRRADIATION GEOMETRY AND POLARISATION ON COMPUTATION OF SAR IN HUMAN BRAIN. Radiat Prot Dosimetry. 2014 Jan 6. [Epub ahead of print]

The power absorbed by the human brain has possible implications in the study of the central nervous system-related biological effects of electromagnetic fields. In order to determine the specific absorption rate (SAR) of radio frequency (RF) waves in the human brain, and to investigate the effects of geometry and polarisation on SAR value, the finite-difference time-domain method was applied for the SAR computation. An anatomically realistic model scaled to a height of 1.70 m and a mass of 63 kg was selected, which included 14 million voxels segmented into 39 tissue types. The results suggested that high SAR values were found in the brain, i.e. ~250 MHz for vertical polarisation and 900-1200 MHz both for vertical and horizontal polarisation, which may be the result of head resonance at these frequencies.

Mausset A, de Seze R, Montpeyroux F, Privat A. Effects of radiofrequency exposure on the GABAergic system in the rat cerebellum: clues from semi-quantitative immunohistochemistry. Brain Res 912(1):33-46, 2001.

The widespread use of cellular phones raises the problem of interaction of electromagnetic fields with the central nervous system (CNS). In order to measure these effects on neurotransmitter content in the CNS, we developed a protocol of neurotransmitter detection based on immunohistochemistry and image analysis. Gamma-vinyl-GABA (GVG), an inhibitor of the GABA-transaminase was injected in rats to increase GABA concentration in the CNS. The cellular GABA contents were then revealed by immunohistochemistry and semi-quantified by image analysis thanks to three parameters: optical density (O.D.), staining area, and number of positive cells. The increase in cerebellar GABA content induced by GVG 1200 mg/kg was reflected in these three parameters in the molecular and the granular layers. Therefore, control of immunohistochemistry parameters, together with appropriate image analysis, allowed both the location and the detection of variations in cellular neurotransmitter content. This protocol was used to investigate the effects of exposure to 900 MHz radiofrequencies on cerebellar GABA content. Both pulsed emission with a specific absorption rate (SAR) of 4 W/kg and continuous emission with high SAR (32 W/kg) were tested. We observed a selective diminution of the stained processes area in the Purkinje cell layer after exposure to pulsed radiofrequency and, in addition, a decrease in O.D. in the three cell layers after exposure to continuous waves. Whether this effect is, at least partly, due to a local heating of the tissues is not known. Overall, it appears that high energetic radiofrequency exposure induces a diminution in cellular GABA content in the cerebellum.

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Croft RJ, Leung S, McKenzie RJ, Loughran SP, Iskra S, Hamblin DL, Cooper NR. Effects of 2G and 3G mobile phones on human alpha rhythms: Resting EEG in adolescents, young adults, and the elderly. *Bioelectromagnetics*. 31(6):434-444, 2010.

The present study was conducted to determine whether adolescents and/or the elderly are more sensitive to mobile phone (MP)-related bioeffects than young adults, and to determine this for both 2nd generation (2G) GSM, and 3rd generation (3G) W-CDMA exposures. To test this, resting alpha activity (8-12 Hz band of the electroencephalogram) was assessed because numerous studies have now reported it to be enhanced by MP exposure. Forty-one 13-15 year olds, forty-two 19-40 year olds, and twenty 55-70 year olds were tested using a double-blind crossover design, where each participant received Sham, 2G and 3G exposures, separated by at least 4 days. Alpha activity, during exposure relative to baseline, was recorded and compared between conditions. Consistent with previous research, the young adults' alpha was greater in the 2G compared to Sham condition, however, no effect was seen in the adolescent or the elderly groups, and no effect of 3G exposures was found in any group. The results provide further support for an effect of 2G exposures on resting alpha activity in young adults, but fail to support a similar enhancement in adolescents or the elderly, or in any age group as a function of 3G exposure.

Central Nervous System Effects

Xu S, Zhou Z, Zhang L, Yu Z, Zhang W, Wang Y, Wang X, Li M, Chen Y, Chen C, He M, Zhang G, Zhong M. Exposure to 1800 MHz radiofrequency radiation induces oxidative damage to mitochondrial DNA in primary cultured neurons. *Brain Res*. 1311:189-196. 2010.

Increasing evidence indicates that oxidative stress may be involved in the adverse effects of radiofrequency (RF) radiation on the brain. Because mitochondrial DNA (mtDNA) defects are closely associated with various nervous system diseases and mtDNA is highly susceptible to oxidative stress, the purpose of this study was to determine whether radiofrequency radiation can cause oxidative damage to mtDNA. In this study, we exposed primary cultured cortical neurons to pulsed RF electromagnetic fields at a frequency of 1800 MHz modulated by 217 Hz at an average specific absorption rate (SAR) of 2 W/kg. At 24h after exposure, we found that RF radiation induced a significant increase in the levels of 8-hydroxyguanine (8-OHdG), a common biomarker of DNA oxidative damage, in the mitochondria of neurons. Consistent with this finding, the copy number of mtDNA and the levels of mitochondrial RNA (mtRNA) transcripts showed an obvious reduction after RF exposure. Each of these mtDNA disturbances could be reversed by pretreatment with melatonin, which is known to be an efficient in the brain. Together, these results suggested that 1800 MHz RF radiation could cause oxidative damage to mtDNA in primary cultured neurons. Oxidative damage to mtDNA may account for the neurotoxicity of RF radiation in the brain.

Pakhomov AG, [Non-thermal microwave effect on nerve fiber function]. *Biofizika*

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38(2):367-371, 1993. [Article in Russian]

Effects of microwave radiation (915 MHz, PW, peak SAR 20-30 W/g, pulse duration 1 mcs, 50.000 and 25.000 p.p.s.) were investigated in isolated frog nerve cord preparation. Nerve VHF heating didn't exceed 2.2 degrees C due to intense Ringer's solution perfusion. It was established that nerve irradiation simultaneously with its stimulation lead to significant decrease of action potential amplitude and peak latency. Since the equal conventional heating of the nerve caused the opposite changes (amplitude increase), the results obtained argue for non-thermal mechanism of microwave action.

Schüz J, Waldemar G, Olsen JH, Johansen C. Risks for central nervous system diseases among mobile phone subscribers: a Danish retrospective cohort study. PLoS One. 4(2):e4389, 2009

The aim of this study was to investigate a possible link between cellular telephone use and risks for various diseases of the central nervous system (CNS). We conducted a large nationwide cohort study of 420 095 persons whose first cellular telephone subscription was between 1982 and 1995, who were followed through 2003 for hospital contacts for a diagnosis of a CNS disorder. Standardized hospitalization ratios (SHRs) were derived by dividing the number of hospital contacts in the cohort by the number expected in the Danish population. The SHRs were increased by 10-20% for migraine and vertigo. No associations were seen for amyotrophic lateral sclerosis, multiple sclerosis or epilepsy in women. SHRs decreased by 30-40% were observed for dementia (Alzheimer disease, vascular and other dementia), Parkinson disease and epilepsy among men. In analyses restricted to subscribers of 10 years or more, the SHRs remained similarly increased for migraine and vertigo and similarly decreased for Alzheimer disease and other dementia and epilepsy (in men); the other SHRs were close to unity. In conclusion, the excesses of migraine and vertigo observed in this first study on cellular telephones and CNS disease deserve further attention. An interplay of a healthy cohort effect and reversed causation bias due to prodromal symptoms impedes detection of a possible association with dementia and Parkinson disease. Identification of the factors that result in a healthy cohort might be of interest for elucidation of the etiology of these diseases.

Hardell L, Söderqvist F, Carlberg M, Zetterberg H, Mild KH. Exposure to wireless phone emissions and serum beta-trace protein. Int J Mol Med. 26(2):301-306, 2010.

The lipocalin type of prostaglandin D synthase or beta-trace protein is synthesized in the choroid plexus, lepto-meninges and oligodendrocytes of the central nervous system and is secreted into the cerebrospinal fluid. beta-trace protein is the key enzyme in the synthesis of prostaglandin D2, an endogenous sleep-promoting neurohormone in the brain. Electromagnetic fields (EMF) in the radio frequency (RF) range have in some studies been associated with disturbed sleep. We studied the concentration of beta-trace protein in blood in relation to emissions from wireless phones. This study included 62 persons aged 18-30 years. The concentration of beta-trace protein decreased with increasing number of years of use of a wireless phone yielding a negative beta coefficient = -0.32, 95% confidence interval -0.60 to -0.04. Also cumulative use in hours

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gave a negative beta coefficient, although not statistically significant. Of the 62 persons, 40 participated in an experimental study with 30 min exposure to an 890-MHz GSM signal. No statistically significant change of beta-trace protein was found. In a similar study of the remaining 22 participants with no exposure, beta-trace protein increased significantly over time, probably due to a relaxed situation. EMF emissions may down-regulate the synthesis of beta-trace protein. This mechanism might be involved in sleep disturbances reported in persons exposed to RF fields. The results must be interpreted with caution since use of mobile and cordless phones were self-reported. Awareness of exposure condition in the experimental study may have influenced beta-trace protein concentrations.

Hamann W, Abou-Sherif S, Thompson S, Hall S. Pulsed radiofrequency applied to dorsal root ganglia causes a selective increase in ATF3 in small neurons. *Eur J Pain.* 10(2):171-176, 2006.

BACKGROUND: This is a "proof of concept study" to test the hypothesis that pulsed radiofrequency, PRF, produces cell stress at the primary afferent level without signs of overt thermal damage. We assumed that cell stress would result in impairment of normal function, and used the expression of activating transcription factor 3, ATF3, as an indicator of cellular "stress". **METHODS:** PRF (20ms of 500-kHz RF pulses, delivered at a rate of 2Hz; maximum temperature 42 degrees C) was delivered either to the sciatic nerve of adult rats in mid thigh, or to the L4 anterior primary ramus just distal to the intervertebral foramen. Controls were sham-operated or L4 axotomised. All tissues were examined 14 days after surgery. The percentage of CGRP- or ATF3-positive DRG neuronal somata was calculated using image analysis software (SigmaScan Pro 4). **RESULTS:** ATF3 expression was upregulated in L4 DRG neuronal cell bodies, irrespective of their size, after axotomy. It was also upregulated significantly ($p < 0.002$) and selectively, in small and medium calibre L4 DRG neurons, when PRF was applied close to the DRG just distal to the intervertebral foramen. PRF did not produce any obvious cellular changes in the nerve or L4 DRG neurons when applied to the sciatic nerve in mid-thigh. **CONCLUSION:** PRF has a biological effect, unlikely to be related to overt thermal damage. It appears to be selective in that it targets the group of neurons whose axons are the small diameter C and Adelta nociceptive fibres.

Bak M, Dudarewicz A, Zmyślony M, Sliwinska-Kowalska M. Effects of GSM signals during exposure to event related potentials (ERPs). *Int J Occup Med Environ Health.* 23(2):191-199, 2010.

OBJECTIVES: The primary aim of this work was to assess the effect of electromagnetic field (EMF) from the GSM mobile phone system on human brain function. The assessment was based on the assay of event related potentials (ERPs). **MATERIAL AND METHODS:** The study group consisted of 15 volunteers, including 7 men and 8 women. The test protocol comprised determination of P300 wave in each volunteer during exposure to the EMF. To eliminate possible effects of the applied test procedure on the final result, the test was repeated without EMF exposure. P300 latency, amplitude, and latency of the N1, N2, P2 waves were analysed. **RESULTS:** The statistical analysis

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revealed an effect of EMF on P300 amplitude. In the experiment with EMF exposure, lower P300 amplitudes were observed only at the time in which the volunteers were exposed to EMF; when the exposure was discontinued, the values of the amplitude were the same as those observed before EMF application. No such change was observed when the experiment was repeated with sham exposure, which may be considered as an indirect proof that lower P300 amplitude values were due to EMF exposure. No statistically significant changes were noted in the latencies of the N1, N2, P2 waves that precede the P300 wave, nor in the latency of the P300 itself.

CONCLUSIONS: The results suggest that exposure to GSM EMF exerts some effects on CNS, including effects on long latency ERPs.

Moretti D, Garenne A, Haro E, Poullétier de Gannes F, Lagroye I, Lévêque P, Veyret B, Lewis N. In-vitro exposure of neuronal networks to the GSM-1800 signal.

Bioelectromagnetics. 2013 Aug 1. doi: 10.1002/bem.21805. [Epub ahead of print]

The central nervous system is the most likely target of mobile telephony radiofrequency (RF) field exposure in terms of biological effects. Several electroencephalography (EEG) studies have reported variations in the alpha-band power spectrum during and/or after RF exposure, in resting EEG and during sleep. In this context, the observation of the spontaneous electrical activity of neuronal networks under RF exposure can be an efficient tool to detect the occurrence of low-level RF effects on the nervous system. Our research group has developed a dedicated experimental setup in the GHz range for the simultaneous exposure of neuronal networks and monitoring of electrical activity. A transverse electromagnetic (TEM) cell was used to expose the neuronal networks to GSM-1800 signals at a SAR level of 3.2 W/kg. Recording of the neuronal electrical activity and detection of the extracellular spikes and bursts under exposure were performed using microelectrode arrays (MEAs). This work provides the proof of feasibility and preliminary results of the integrated investigation regarding exposure setup, culture of the neuronal network, recording of the electrical activity, and analysis of the signals obtained under RF exposure. In this pilot study on 16 cultures, there was a 30% reversible decrease in firing rate (FR) and bursting rate (BR) during a 3 min exposure to RF. Additional experiments are needed to further characterize this effect.

Xu S, Ning W, Xu Z, Zhou S, Chiang H, Luo J. Chronic exposure to GSM 1800-MHz microwaves reduces excitatory synaptic activity in cultured hippocampal neurons. *Neurosci Lett.*398(3):253-257,2006.

The world wide proliferation of mobile phones raises the concern about the health effects of 1800-MHz microwaves on the brain. The present study assesses the effects of microwave exposure on the function of cultured hippocampal neurons of rats using whole cell patch-clamp analysis combined with immunocytochemistry. We showed that chronic exposure (15min per day for 8 days) to Global System for Mobile Communication (GSM) 1800-MHz microwaves at specific absorption rate (SAR) of 2.4W/kg induced a selective decrease in the amplitude of alpha-amino-3-hydroxy-5-methyl-4-soxazole propionic acid (AMPA) miniature excitatory postsynaptic currents (mEPSCs), whereas the frequency of AMPA mEPSCs and the amplitude of N-methyl-d-

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aspartate (NMDA) mEPSCs did not change. Furthermore, the GSM microwave treatment decreased the expression of postsynaptic density 95 (PSD95) in cultured neurons. Our results indicated that 2.4W/kg GSM 1800-MHz microwaves may reduce excitatory synaptic activity and the number of excitatory synapses in cultured rat hippocampal neurons.

Barteri M, Pala A, Rotella S. Structural and kinetic effects of mobile phone microwaves on acetylcholinesterase activity. *Biophys Chem.* 113(3):245-253, 2005.

The present study provides evidence that "in vitro" simple exposure of an aqueous solution of electric eel acetylcholinesterase (EeAChE; EC 3.1.1.7.) to cellular phone emission alters its enzymatic activity. This paper demonstrates, by combining different experimental techniques, that radio frequency (RF) radiations irreversibly affect the structural and biochemical characteristics of an important CNS enzyme. These results were obtained by using a commercial cellular phone to reproduce the reality of the human exposition. This experimental procedure provided surprising effects collected practically without experimental errors because they were obtained comparing native and irradiated sample of the same enzyme solution. Although these results cannot be used to conclude whether exposure to RF during the use of cellular phone can lead to any hazardous health effect, they may be a significant first step towards further verification of these effects on other "ex vivo" or "in vivo" biological systems.

Acar GO, Yener HM, Savrun FK, Kalkan T, Bayrak I, Enver O. Thermal effects of mobile phones on facial nerves and surrounding soft tissue. *Laryngoscope.* 119(3):559-562, 2009.

OBJECTIVE: To investigate the possible thermal effects of microwaves from mobile phones on **facial nerves (FN)** and surrounding soft tissue. STUDY DESIGN:: A prospective study. METHODS: We studied FN conduction rate and compound muscle action potentials (CMAP) on 12 rabbits before exposure to radiofrequency radiation (RFR) emitted from a mobile phone. Also, the temperature change in the soft tissues around the FN was investigated by a four channel Luxtron fiber optic system. A mobile phone with 1900 MHz frequency was placed over the ipsilateral ear of the rabbit for 25 minutes, and FN and surrounding tissues were exposed to a 1.5 watts pulse modulated (217 packets/s) electromagnetic field. During exposure to RFR, immediately after turning off the mobile phone, and 25 minutes after the exposure temperature change in the surrounding tissue of the FN was recorded and compared to preexposure values. Additionally, another recording regarding the FN functions was done and the data were compared to preexposure values. RESULTS: The average temperature of the surrounding soft tissues was 0.39 K higher than the preexposure values during the exposure and immediately after turning off the mobile phone, and decreased to normal levels 25 minutes after the exposure, which was statistically significant. The amplitudes of FN CMAP after radiofrequency radiation exposure were significantly smaller than the preexposure amplitudes and the amplitudes were normal in the 25 minute measurement. CONCLUSION: The RFR emitted from a mobile phone can cause temporary FN dysfunction that can be due to temporary temperature increase in the

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soft tissue around the FN.

Ersan Odacı, Ayşe İkinci, Mehmet Yıldırım, Haydar Kaya, Metehan Akça, Hatice Hancı, Osman Fikret Sönmez, Ali Aslan, Mukadder Okuyan, Orhan Baş The Effects of 900 Megahertz Electromagnetic Field Applied in the Prenatal Period on Spinal Cord Morphology and Motor Behavior in Female Rat Pups. NeuroQuantology 11:573-581, 2013.

This study investigated the effect of a 900 megahertz (MHz) electromagnetic field (EMF) applied in the prenatal period on the spinal cord and motor behavior of female rat pups. Beginning of the study, female Sprague Dawley rats (180–250 g) were left to mate with male rats. Rats identified as pregnant were then divided into control (n=3) and EMF groups (n=3). The EMF group was exposed to 1-h 900 MHz EMF daily between days 13 and 21 of pregnancy. At 21 days old, rat pups were removed from their mothers and divided into two newborn rat groups, control (n=13) and EMF (n=10). The rotarod test was applied to the rat pups to assess motor functions and the open field test to evaluate locomotor activity. On day 32 of the study, the rat pups were decapitated, and the spinal cord in the upper thoracic region was removed. Following routine histological tests, they were stained with Cresyl fast violet. Rotarod test results revealed a significant increase in EMF group rat pups' motor functions ($p=0.037$). However, no difference was observed in the open field test results ($p>0.05$). In the EMF group' rat pups, we observed pathological changes in the spinal cord. On the basis of our results, 900 MHz EMF applied in the prenatal period affected spinal cord development. This effect was observed in the form of pathological changes in the spinal cord of rat pups, and it may be that these pathological changes led to an increase in rat pups' motor activities.

Lu Y, He M, Zhang Y, Xu S, Zhang L, He Y, Chen C, Liu C, Pi H, Yu Z, Zhou Z. Differential Pro-Inflammatory Responses of Astrocytes and Microglia Involve STAT3 Activation in Response to 1800 MHz Radiofrequency Fields. PLoS One. 2014 Oct 2;9(9):e108318. doi: 10.1371/journal.pone.0108318.

Microglia and astrocytes play important role in maintaining the homeostasis of central nervous system (CNS). Several CNS impacts have been postulated to be associated with radiofrequency (RF) electromagnetic fields exposure. Given the important role of inflammation in neural physiopathologic processes, we investigated the pro-inflammatory responses of microglia and astrocytes and the involved mechanism in response to RF fields. Microglial N9 and astroglial C8-D1A cells were exposed to 1800 MHz RF for different time with or without pretreatment with STAT3 inhibitor. Microglia and astrocytes were activated by RF exposure indicated by up-regulated CD11b and glial fibrillary acidic protein (GFAP). However, RF exposure induced differential pro-inflammatory responses in astrocytes and microglia, characterized by different expression and release profiles of IL-1 β , TNF- α , IL-6, PGE2, nitric oxide (NO), inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2). Moreover, the RF exposure activated STAT3 in microglia but not in astrocytes. Furthermore, the STAT3 inhibitor Stattic ameliorated the RF-induced release of pro-inflammatory cytokines in microglia but not in astrocytes. Our results demonstrated that RF exposure differentially induced

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pro-inflammatory responses in microglia and astrocytes, which involved differential activation of STAT3 in microglia and astrocytes. Our data provide novel insights into the potential mechanisms of the reported CNS impacts associated with mobile phone use and present STAT3 as a promising target to protect humans against increasing RF exposure.

Zuo H, Lin T, Wang D, Peng R, Wang S, Gao Y, Xu X, Zhao L, Wang S, Su Z. RKIP Regulates Neural Cell Apoptosis Induced by Exposure to Microwave Radiation Partly Through the MEK/ERK/CREB Pathway. Mol Neurobiol. 2014 Aug 10. [Epub ahead of print]

In the present study, we investigated whether Raf-1 kinase inhibitory protein (RKIP) is important for neural cell apoptosis induced by microwave exposure and explored the role of MEK/ERK/CREB pathway regulated by RKIP in the apoptosis. Differentiated PC12 cells were exposed to continuous microwave radiation at 2.856 GHz for 5 min with average power density of 30 mW/cm². RKIP sense and anti-sense recombinant plasmids were constructed and transfected into PC12 cells, respectively. Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling (TUNEL) staining and caspase-3 activity assay were used to detect cell apoptosis. The results showed that RKIP was downregulated after microwave exposure while the MEK/ERK/CREB signaling pathway was activated excessively. Moreover, the ratio of Bcl-2/Bax decreased, activity of caspase-3 increased, and thus apoptotic DNA fragmentation increased. RKIP overexpression significantly inhibited the phosphorylation of MEK, ERK, and CREB, while RKIP downregulation had the reverse effect. Furthermore, U0126 was found to antagonize the changes caused by RKIP downregulation after exposure to radiation. In conclusion, RKIP plays an important role in the neural cell apoptosis induced by microwave radiation, and the regulation of cell apoptosis by RKIP is partly through the MEK/ERK/CREB pathway. This suggests that RKIP may act as a key regulator of neuronal damage caused by microwave radiation. Extremely Low-Frequency Electromagnetic Fields Cause G1 Phase Arrest through the Activation of the ATM-Chk2-p21 Pathway

Ivanova Vlu, Martynova OV, Aleinik SV, Limarenko AV. [Effect of modified SHF and acoustic stimulation on spectral characteristics of the electroencephalograms of the cat brain] Biofizika. 45(5):935-940, 2000. [Article in Russian]

The effect of modulated electromagnetic fields on the spectral parameters of bioelectric brain activity in awake cats was studied by registering the electroencephalogram from the skin surface in the vertex area using carbon electrodes. In the normal electroencephalogram, spectral components in the range above 20 Hz predominated. It was shown that, upon irradiation with electromagnetic field (basic frequency 980 MHz, power density 30-50 microW/cm²), spectral components in the range of 12-18 Hz begin to prevail. A similarity in the redistribution of the power of spectral components upon both acoustic and modulated electromagnetic influences was revealed. The results suggest that there is a a common neurophysiological mechanism by which modulated electromagnetic radiation and acoustic stimulation affect the electrical activity of the brain. This ia consistent with the assumption that the effect of the electromagnetic field

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on the central nervous system is mediated through the acoustic sensory system.

Verma M, Dutta SK. Microwave induced alteration in the neuron specific enolase gene expression. Cancer Biochem Biophys. 13(4):239-244, 1993.

Exposure of pNGE7, a recombinant clone containing the coding and regulatory sequences for the expression of neuron specific enolase gene, cells to electromagnetic radiations (915 MHz, 16 Hz AM, SAR 0.05 mW/kg) resulted in the elevation of neuron specific enolase (NSE), a diagnostic marker for neuron and lung cancer. Using ion-exchange chromatography we separated the neuron specific enolase activity from the non-neuronal enolase (NNE) activity and observed an alteration in the expression of neuron specific enolase and non-neuronal enolase. The clinical applications of the present studies have been discussed.

Khudnitskii, SS, Moshkarev, EA, Fomenko, TV, [On the evaluation of the influence of cellular phones on their users]. [Article in Russian] Med Tr Prom Ekol (9):20-24, 1999.

The authors studied influence of ultrahigh frequency radiation caused by cellular phones on functional state of central nervous, cardiovascular systems and local temperature changes in cellular phones users. The head area near the phone antenna appeared to be under the most intensive heating. Ultrahigh frequency radiation induces significant changes in local temperature and in physiologic parameters of central nervous and cardiovascular systems.

Liu ML, Wen JQ, Fan YB. Potential protection of green tea polyphenols against 1800 MHz electromagnetic radiation-induced injury on rat cortical neurons. Neurotox Res. 20(3):270-276, 2011.

Radiofrequency electromagnetic fields (EMF) are harmful to public health, but the certain anti-irradiation mechanism is not clear yet. The present study was performed to investigate the possible protective effects of green tea polyphenols against electromagnetic radiation-induced injury in the cultured rat cortical neurons. In this study, green tea polyphenols were used in the cultured cortical neurons exposed to 1800 MHz EMFs by the mobile phone. We found that the mobile phone irradiation for 24 h induced marked neuronal cell death in the MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl-tetrazolium bromide) and TUNEL (TdT mediated biotin-dUTP nicked-end labeling) assay, and protective effects of green tea polyphenols on the injured cortical neurons were demonstrated by testing the content of Bcl-2 Associated X protein (Bax) in the immunoprecipitation assay and Western blot assay. In our study results, the mobile phone irradiation-induced increases in the content of active Bax were inhibited significantly by green tea polyphenols, while the contents of total Bax had no marked changes after the treatment of green tea polyphenols. Our results suggested a neuroprotective effect of green tea polyphenols against the mobile phone irradiation-induced injury on the cultured rat cortical neurons.

Ivaschuk OI, Jones RA, Ishida-Jones T, Haggren W, Adey WR, Phillips JL, Exposure of nerve growth factor-treated PC12 rat pheochromocytoma cells to a modulated

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radiofrequency field at 836.55 MHz: effects on c-jun and c-fos expression. Bioelectromagnetics 18(3):223-229, 1997.

Rat PC12 pheochromocytoma cells have been treated with nerve growth factor And then exposed to athermal levels of a packet-modulated radiofrequency field At 836.55 MHz. This signal was produced by a prototype time-domain multiple-access (TDMA) transmitter that conforms to the North American digital cellular telephone standard. Three slot average power densities were used: 0.09, 0.9, and 9 mW/cm². Exposures were for 20, 40, and 60 min and included an intermittent exposure regimen (20 min on/20 min off), resulting in total incubation times of 20, 60, and 100 min, respectively. Concurrent controls were sham exposed. After extracting total cellular RNA, Northern blot analysis was used to assess the expression of the immediate early genes, c-fos and c-jun, in all cell populations. No change in c-fos transcript levels were detected after 20 min exposure at each field intensity (20 min was the only time period at which c-fos message could be detected consistently). Transcript levels for c-jun were altered only after 20 min exposure to 9 mW/cm² (average 38% decrease).

Joubert V, Bourthoumieu S, Leveque P, Yardin C. Apoptosis is Induced by Radiofrequency Fields through the Caspase-Independent Mitochondrial Pathway in Cortical Neurons. Radiat Res. 169(1):38-45, 2008.

In the present study, we investigated whether continuous-wave (CW) radiofrequency (RF) fields induce neuron apoptosis in vitro. Rat primary neuronal cultures were exposed to a CW 900 MHz RF field with a specific absorption rate (SAR) of 2 W/kg for 24 h. During exposure, an increase of 2 degrees C was measured in the medium; control experiments with neurons exposed to 39 degrees C were then performed. Apoptosis was assessed by condensation of nuclei with 4',6-diamino-2-phenylindole (DAPI) staining observed with an epifluorescence microscope and fragmentation of DNA with TdT-mediated dUTP nick-end labeling (TUNEL) analyzed by flow cytometry. A statistically significant difference in the rate of apoptosis was found in the RF-field-exposed neurons compared to the sham-, 37 degrees C- and 39 degrees C-exposed neurons either 0 or 24 h after exposure using both methods. To assess whether the observed apoptosis was caspase-dependent or -independent, assays measuring caspase 3 activity and apoptosis-inducing factor (AIF) labeling were performed. No increase in the caspase 3 activity was found, whereas the percentage of AIF-positive nuclei in RF-field-exposed neurons was increased by three- to sevenfold compared to other conditions. Our results show that, under the experimental conditions used, exposure of primary rat neurons to CW RF fields may induce a caspase-independent pathway to apoptosis that involves AIF.

Seaman RL, Phelix CF. Acute effects of pulsed microwaves and 3-nitropropionic acid on neuronal ultrastructure in the rat caudate-putamen. Bioelectromagnetics. 26(2):82-101, 2005.

Ultrastructure of the medium sized "spiny" neuron in rat dorsal-lateral caudate-putamen was assessed after administration of 3-nitropropionic acid (3-NP) and exposure to pulsed microwaves. Sprague-Dawley male rats were given two daily intraperitoneal doses of 0 or 10 mg/kg 3-NP and 1.5 h after each dose were exposed to

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microwave radiation at a whole body averaged specific absorption rate (SAR) of 0 (sham exposure), 0.6, or 6 W/kg for 30 min. Microwave exposure consisted of 1.25 GHz radiation delivered as 5.9 μ s pulses with repetition frequency 10 Hz. Tissue samples taken 2-3 h after the second sham or microwave exposure showed no injury with light microscope methods. Blinded qualitative assessment of ultrastructure of randomly selected neurons from the same samples did reveal differences. Subsequent detailed, quantitative measurements showed that, when followed by sham exposure, administration of 3-NP significantly increased endoplasmic reticulum (ER) intracisternal width, ER area density, and nuclear envelope thickness. Microwave exposure at 6 W/kg alone also significantly increased these measures. Exposure of 3-NP treated animals at 6 W/kg significantly increased effects of 3-NP on ultrastructure. Although exposure at 0.6 W/kg alone did not affect ultrastructure measures, exposure of 3-NP treated animals at 0.6 W/kg reduced the effects of 3-NP. We concluded that 3-NP changed neuronal ultrastructure and that the microwave exposures used here changed neuronal ultrastructure in ways that depended on microwave SAR and neuron metabolic status. The apparent cancellation of 3-NP induced changes by exposure to pulsed microwaves at 0.6 W/kg indicated the possibility that such exposure can protect against the effects of mitochondrial toxins on the nervous system.

Zhou H, Su Z, Ning J, Wang C, Xie X, Qu D, Wu K, Zhang X, Pan J, Yang G. EFFECTS OF FREQUENCY, IRRADIATION GEOMETRY AND POLARISATION ON COMPUTATION OF SAR IN HUMAN BRAIN. Radiat Prot Dosimetry. 2014 Jan 6. [Epub ahead of print]

The power absorbed by the human brain has possible implications in the study of the central nervous system-related biological effects of electromagnetic fields. In order to determine the specific absorption rate (SAR) of radio frequency (RF) waves in the human brain, and to investigate the effects of geometry and polarisation on SAR value, the finite-difference time-domain method was applied for the SAR computation. An anatomically realistic model scaled to a height of 1.70 m and a mass of 63 kg was selected, which included 14 million voxels segmented into 39 tissue types. The results suggested that high SAR values were found in the brain, i.e. ~250 MHz for vertical polarisation and 900-1200 MHz both for vertical and horizontal polarisation, which may be the result of head resonance at these frequencies.

Hao D, Yang L, Chen S, Tong J, Tian Y, Su B, Wu S, Zeng Y. Effects of long-term electromagnetic field exposure on spatial learning and memory in rats. Neurol Sci. 2012 Feb 24. [Epub ahead of print]

With the development of communications industry, mobile phone plays an important role in daily life. Whether or not the electromagnetic radiation emitted by mobile phone causes any adverse effects on brain function has become of a great concern. This paper investigated the effect of electromagnetic field on spatial learning and memory in rats. 32 trained Wistar rats were divided into two groups: exposure group and control group. The exposure group was exposed to 916 MHz, 10w/m² mobile phone electromagnetic field (EMF) 6 h a day, 5 days a week, 10 weeks. The completion time, number of total errors and the neuron discharge signals were recorded while the rats were searching for

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food in an eight-arm radial maze at every weekend. The neuron signals of one exposed rat and one control rat in the maze were obtained by the implanted microelectrode arrays in their hippocampal regions. It can be seen that during the weeks 4-5 of the experiment, the average completion time and error rate of the exposure group were longer and larger than that of control group ($p < 0.05$). During the weeks 1-3 and 6-9, they were close to each other. The hippocampal neurons showed irregular firing patterns and more spikes with shorter interspike interval during the whole experiment period. It indicates that the 916 MHz EMF influence learning and memory in rats to some extent in a period during exposure, and the rats can adapt to long-term EMF exposure.

Esen F, Esen H Effect of electromagnetic fields emitted by cellular phones on the latency of evoked electrodermal activity. *Int J Neurosci.* 116(3):321-329, 2006.

The widespread use of cellular phones raises the question of their possible adverse biological effects, especially on the central nervous system (CNS). Therefore, the authors examined the effect of electromagnetic fields emitted by cellular phones (CPEMFs) on the evoked neuronal activity of CNS relating to generation and representation of electrodermal activity (EDA), an index of sympathetic nervous system activity. EDA (skin resistance response; SRR) latency was lengthened approximately 200 ms with CPEMFs exposure irrespective of the head site next to mobile phone used. Hemispheric asymmetry of EDA-2 pathway, which is represented by shorter SRR latency in the right hand of the right hand responders, was also distorted with CPEMFs. Because the CNS regions including EDA-2 are also involved in tasks of motor timing and time estimation, delayed response in this neuronal network due to CPEMFs exposure may increase the response time of mobile phone users. Therefore, the findings point to the potential risks of mobile phones on the function of CNS and consequently, possible increase in the risk of phone-related driving hazards.

Calabrò E, Condello S, Currò M, Ferlazzo N, Caccamo D, Magazù S, Ientile R. Modulation of heat shock protein response in SH-SY5Y by mobile phone microwaves. *World J Biol Chem.* 3(2):34-40, 2012.

AIM: To investigate putative biological damage caused by GSM mobile phone frequencies by assessing electromagnetic fields during mobile phone working. METHODS: Neuron-like cells, obtained by retinoic-acid-induced differentiation of human neuroblastoma SH-SY5Y cells, were exposed for 2 h and 4 h to microwaves at 1800 MHz frequency bands. RESULTS: Cell stress response was evaluated by MTT assay as well as changes in the heat shock protein expression (Hsp20, Hsp27 and Hsp70) and caspase-3 activity levels, as biomarkers of apoptotic pathway. Under our experimental conditions, neither cell viability nor Hsp27 expression nor caspase-3 activity was significantly changed. Interestingly, a significant decrease in Hsp20 expression was observed at both times of exposure, whereas Hsp70 levels were significantly increased only after 4 h exposure. CONCLUSION: The modulation of the expression of Hsps in neuronal cells can be an early response to radiofrequency microwaves.

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Partsvania B, Sulaberidze T, Shoshiashvili L, Modebadze Z. Acute effect of exposure of mollusk single neuron to 900-MHz mobile phone radiation. Electromagn Biol Med. 30(3):170-179, 2011.

The goal of the present work was to explore the influence of commercially available cell phone irradiation on the single neuron excitability and memory processes. A Transverse Electromagnetic Cell (TEM Cell) was used to expose single neurons of mollusk to the electromagnetic field. Finite-Difference Time-Domain (FDTD) method was used for modeling the TEM Cell and the electromagnetic field interactions with living nerve ganglion and neurons. Neuron electrophysiology was investigated using standard microelectrode technique. The specific absorption rate (SAR) deposited into the single neuron was calculated to be 0.63 W/kg with a temperature increment of 0.1°C. After acute exposure, average firing threshold of the action potentials was not changed. However, the average latent period was significantly decreased. This indicates that together with latent period the threshold and the time of habituation might be altered during exposure. However, these alterations are transient and only latent period remains on the changed level.

Hearing Effects

Panda NK, Modi R, Munjal S, Virk RS. Auditory changes in mobile users: is evidence forthcoming? Otolaryngol Head Neck Surg. 144(4):581-585, 2011.

OBJECTIVE: Genuine concerns are being raised as to the potential health risks posed by electromagnetic frequency exposure secondary to mobile phone usage. This study was undertaken to assess and compare potential changes in hearing function at the level of the inner ear and central auditory pathway due to chronic exposure to electromagnetic waves from both global system for mobile communications (GSM) and code division multiple access (CDMA) mobile phone usage. DESIGN: Cohort study. SETTING: Tertiary referral center. SUBJECTS AND METHODS: One hundred twenty-five subjects who were long-term mobile phone users (more than 1 year; 63 GSM and 62 CDMA) and 58 controls who had never used mobile phones underwent audiological investigations including pure tone audiometry (250-12 kHz), tympanometry, distortion product otoacoustic emissions (DPOAE), auditory brain responses (ABR), and middle latency responses (MLRs). The changes in various parameters were studied in mobile-using and non-mobile-using ears of both GSM and CDMA subjects and corresponding ears of the controls to ascertain the effects of electromagnetic exposure. RESULTS: GSM and CDMA users were found to be at a significantly higher risk of having DPOAE absent as compared with controls ($P < .05$). They were found to have higher speech frequency thresholds and lower MLR wave and Na and Pa amplitudes. More than 3 years of mobile phone usage emerged as a risk factor ($P < .05$). The damage done was bilateral, with the quantum of damage being the same for both GSM and CDMA. CONCLUSION: Long-term and intensive GSM and CDMA mobile phone use may cause damage to cochlea as well as the auditory cortex.

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Panda NK, Jain R, Bakshi J, Munjal S. Audiologic disturbances in long-term mobile phone users. J Otolaryngol Head Neck Surg. 39(1):5-11, 2010.

Abstract. INTRODUCTION:There is general concern regarding the possible hazardous health effects of exposure to radiofrequency electromagnetic radiation emitted from mobile phones. This study aimed to assess the effects of chronic exposure to electromagnetic waves emitted from Global System for Mobile Communication (GSM) mobile phones on auditory functions.MATERIAL AND METHODS:A retrospective, cross-sectional, randomized, case control study was carried out in a tertiary care hospital. One hundred twelve subjects who were long-term mobile phone users (more than 1 year) and 50 controls who had never used a mobile phone underwent a battery of audiologic investigations including pure-tone audiometry (both speech and high frequency), tympanometry, distortion product otoacoustic emissions, auditory brain responses, and middle latency responses. Changes in the various parameters were studied in the mobile phone- and non-mobile phone-using ears of subjects and corresponding ears of the controls to ascertain the effects of electromagnetic exposure.RESULTS:There was no significant difference between users and controls for any of the audiologic parameters. However, trends for audiologic abnormalities were seen within the users. High-frequency loss and absent distortion product otoacoustic emissions were observed with an increase in the duration of mobile phone use, excessive use of mobile phones, and age more than 30 years. Additionally, users with some complaints during mobile phone use demonstrated absent distortion product otoacoustic emissions and abnormalities in auditory brainstem response.CONCLUSION:Long-term and intensive mobile phone use may cause inner ear damage. A large sample size would be required to reach definitive conclusions.

Oktay MF, Dasdag S. Effects of intensive and moderate cellular phone use on hearing function. Electromagn Biol Med. 25(1):13-21, 2006.

The purpose of this study is to investigate the effects of radiation emitted by mobile phones on the hearing of users. The study was carried out on three groups: 1) 20 men who have used a cellular phone frequently and spoken approximately 2 h per day for four years; 2) 20 men who have used a cellular phone for 10-20 min per day for four years; and 3) 20 healthy men who have never used a cellular phone (the control group). Brainstem evoked response audiometric (BERA) and pure tone audiometric (PTA) methods were used to measure the effects of exposure on hearing function of the subjects. In BERA measurements, I-III, III-V, and I-V interpeak latencies were evaluated. Interpeak latency of subjects in two experimental groups was compared to that of subjects in the control group. The BERA results showed no differences among the groups ($p > 0.05$).In PTA measurements, detection thresholds at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz frequencies were measured in all three groups. No differences were observed between moderate mobile phone users (10-20 min. per day) and control subjects. However, detection thresholds in those who talked approximately 2 h per day were found to be higher than those in either moderate users or control subjects. Differences at 4000 Hz for both bone and air conduction for right ears, and 500 Hz, and 4000 Hz bone and air conduction for left ears were significant for mean hearing

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threshold. This study shows that a higher degree of hearing loss is associated with long-term exposure to electromagnetic (EM) field generated by cellular phones.

Meo SA, Al-Drees AM. Mobile phone related-hazards and subjective hearing and vision symptoms in the Saudi population. Int J Occup Med Environ Health. 18(1):53-57, 2005

OBJECTIVES: Over the past decade utilization of mobile phones has dramatically increased. They are now an essential part of business, commerce, and communication, however, their use may lead to health problems. Therefore, the present study was designed to investigate a link between the use of mobile phones and hearing and vision symptoms in the Saudi population and also to contribute to the increase in social awareness of health problems associated with the use of these devices. MATERIALS AND METHODS: A total of 873 (57.04% of males and 39.86% of females) subjects using mobile phones were invited to participate in the presented study. A structured questionnaire was distributed among them to collect a detailed medical history. The Chi-square test was employed to observe the relationship between duration of calls and hearing and vision complaints. RESULTS: The present study showed an association between the use of mobile phones and hearing and vision complaints. About 34.59% of problems were related with impaired hearing, ear ache and/or warmth on the ear, and 5.04% of complaints with the decreased and/or blurred vision. CONCLUSIONS: It is concluded that the use of mobile phone is a health risk factor, and thus it is suggested that excessive use of mobile phones should be avoided and social awareness increased through health promotion activities, such as group discussions or public presentations and via electronic and printed media sources.

Velayutham P, Govindasamy GK, Raman R, Prepageran N, Ng KH. High-frequency hearing loss among mobile phone users. Indian J Otolaryngol Head Neck Surg. 66(Suppl 1):169-172, 2014.

The objective of this study is to assess high frequency hearing (above 8 kHz) loss among prolonged mobile phone users in a tertiary Referral Center. Prospective single blinded study. This is the first study that used high-frequency audiometry. The wide usage of mobile phone is so profound that we were unable to find enough non-users as a control group. Therefore we compared the non-dominant ear to the dominant ear using audiometric measurements. The study was a blinded study wherein the audiologist did not know which was the dominant ear. A total of 100 subjects were studied. Of the subjects studied 53% were males and 47% females. Mean age was 27. The left ear was dominant in 63%, 22% were dominant in the right ear and 15% did not have a preference. This study showed that there is significant loss in the dominant ear compared to the non-dominant ear ($P < 0.05$). Chronic usage mobile phone revealed high frequency hearing loss in the dominant ear (mobile phone used) compared to the non dominant ear.

Seckin E, Suren Basar F, Atmaca S, Kaymaz FF, Suzer A, Akar A, Sunan E, Koyuncu M. The effect of radiofrequency radiation generated by a Global System for Mobile

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Communications source on cochlear development in a rat model. J Laryngol Otol. 2014 May 1:1-6. [Epub ahead of print]

Objective: This study aimed to determine the effect of radiofrequency radiation generated by 900 and 1800 MHz Global System for Mobile Communications sources on cochlear development in the rat model. Methods: Eight pregnant albino Wistar rats were divided into three groups: control, 900 MHz and 1800 MHz. The latter two groups of pregnant rats were exposed to radiofrequency radiation for 1 hour per day starting on the 12th day of pregnancy until delivery. The rats in the control, 900 MHz and 1800 MHz groups gave birth to 24, 31 and 26 newborn rats respectively. Newborn rats in the 900 MHz and 1800 MHz groups were exposed to radiofrequency radiation for 1 hour per day for 21 days after delivery. Hearing evaluations of newborn rats were carried out using distortion product otoacoustic emissions testing. Eight newborn rats were randomly selected from each group for electron microscopic evaluation. Results: Distortion product otoacoustic emission tests revealed no significant difference among the groups, but electron microscopic evaluation revealed significant differences among the groups with regard to the number of normal, apoptotic and necrotic cells. Conclusion: The findings indicated cellular structural damage in the cochlea caused by radiofrequency radiation exposure during cochlear development in the rat model.

Kerekhanjanarong V, Supiyaphun P, Naratricocon J, Laungpitackchumpon P. The effect of mobile phone to audiologic system. J Med Assoc Thai.88 Suppl 4:S231-234, 2005.

Mobile phones have come into widespread use. There are a lot of possible adverse effect to health. Use of mobile phone generate potentially harmful radiofrequency electromagnetic field (EMF) particularly for the hearing aspect. 98 subjects underwent hearing evaluations at Department of Otolaryngology, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University. 31 males and 67females, mean age was 30.48 +/- 9.51 years old, all subjects were investigated the hearing level by audiometry, tympanometry, otoacoustic emission (OAE) and auditory brain stem evoked response (ABR). The average of using time were 32.54 +/- 27.64 months, 57 subjects usually used the right side and 41 the left side. Average time of use per day was 26.31 +/- 30.91 minutes (range from 3 to 180 mins). When the authors compared the audiogram, both pure tone and speech audiometry, between the dominant and nondominant side, it indicated that there is no significant different. When the authors focused on the 8 subjects that used the mobile phone more than 60 mins per day. It indicated that the hearing threshold of the dominant ears was worse than the nondominant ears.

Khullar S1, Sood A2, Sood S3. Auditory Brainstem Responses and EMFs Generated by Mobile Phones. Indian J Otolaryngol Head Neck Surg. 65(Suppl 3):645-649, 2013.

There has been a manifold increase in the number of mobile phone users throughout the world with the current number of users exceeding 2 billion. However this advancement in technology like many others is accompanied by a progressive increase in the frequency and intensity of electromagnetic waves without consideration of the health consequences. The aim of our study was to advance our understanding of the

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potential adverse effects of GSM mobile phones on auditory brainstem responses (ABRs). 60 subjects were selected for the study and divided into three groups of 20 each based on their usage of mobile phones. Their ABRs were recorded and analysed for latency of waves I-V as well as interpeak latencies I-III, I-V and III-V (in ms). Results revealed no significant difference in the ABR parameters between group A (control group) and group B (subjects using mobile phones for maximum 30 min/day for 5 years). However the latency of waves was significantly prolonged in group C (subjects using mobile phones for 10 years for a maximum of 30 min/day) as compared to the control group. Based on our findings we concluded that long term exposure to mobile phones may affect conduction in the peripheral portion of the auditory pathway. However more research needs to be done to study the long term effects of mobile phones particularly of newer technologies like smart phones and 3G.

Kellenyi, L, Thuroczy, G, Faludy, B, Lenard, L, Effects of mobile GSM radiotelephone exposure on the auditory brainstem response (ABR). Neurobiology 7:79-81, 1999.

A 15-min exposure to GSM phone radiation caused an increase in auditory brainstem response in the exposed side of human subjects. Subjects also showed a hearing deficiency in the high frequency range (20 dB hearing deficiency from 2 KHz to 10 KHz).

Kaprana AE, Chimona TS, Papadakis CE, Velegrakis SG, Vardiambasis IO, Adamidis G, Velegrakis GA. Auditory brainstem response changes during exposure to GSM-900 radiation: An experimental study. Audiol Neurootol. 16(4):270-276, 2011.

Abstract. The objective of the present study was to investigate the possible electrophysiological time-related changes in auditory pathway during mobile phone electromagnetic field exposure. Thirty healthy rabbits were enrolled in an experimental study of exposure to GSM-900 radiation for 60 min and auditory brainstem responses (ABRs) were recorded at regular time-intervals during exposure. The study subjects were radiated via an adjustable power and frequency radio transmitter for GSM-900 mobile phone emission simulation, designed and manufactured according to the needs of the experiment. The mean absolute latency of waves III-V showed a statistically significant delay ($p < 0.05$) after 60, 45 and 15 min of exposure to electromagnetic radiation of 900 MHz, respectively. Interwave latency I-III was found to be prolonged after 60 min of radiation exposure in correspondence to wave III absolute latency delay. Interwave latencies I-V and III-V were found with a statistically significant delay ($p < 0.05$) after 30 min of radiation. No statistically significant delay was found for the same ABR parameters in recordings from the ear contralateral to the radiation source at 60 min radiation exposure compared with baseline ABR. The ABR measurements returned to baseline recordings 24 h after the exposure to electromagnetic radiation of 900 MHz. The prolongation of interval latencies I-V and III-V indicates that exposure to electromagnetic fields emitted by mobile phone can affect the normal electrophysiological activity of the auditory system, and these findings fit the pattern of general responses to a stressor.

Hutter HP, Moshammer H, Wallner P, Cartellieri M, Denk-Linnert DM, Katzinger M, Ehrenberger K, Kundi M. Tinnitus and mobile phone use. Occup Environ Med.

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67(12):804-808, 2010.

Objectives The mechanisms that produce tinnitus are not fully understood. While tinnitus can be associated with diseases and disorders of the ear, retrocochlear diseases and vascular pathologies, there are few known risk factors for tinnitus apart from these conditions. There is anecdotal evidence of a link between mobile phone use and tinnitus, but so far there have been no systematic investigations into this possible association. **Methods** 100 consecutive patients presenting with tinnitus were enrolled in an individually matched case-control study. For each case a control subject was randomly selected from visiting outpatients matched for sex and age. The patient's history was obtained and clinical examinations were conducted to exclude patients with known underlying causes of tinnitus. Mobile phone use was assessed based on the Interphone Study protocol. ORs were computed by conditional logistic regression with years of education and living in an urban area as covariates. **Results** Mobile phone use up to the index date (onset of tinnitus) on the same side as the tinnitus did not have significantly elevated ORs for regular use and intensity or for cumulative hours of use. The risk estimate was significantly elevated for prolonged use (≥ 4 years) of a mobile phone (OR 1.95; CI 1.00 to 3.80). **Conclusions** Mobile phone use should be included in future investigations as a potential risk factor for developing tinnitus.

Cox RA, Luxton LM, Cerebral symptoms from mobile telephones. Occup Environ Med 57(6):431, 2000. (letter to the editor)

Mobile phones affect the inner ear in 5-8% of users leading to dizziness, disorientation, nausea, headache and transient confusion.

Alsanosi AA, Al-Momani MO, Hagr AA, Almomani FM, Shami IM, Al-Habeeb SF. The acute auditory effects of exposure for 60 minutes to mobile`s electromagnetic field. Saudi Med J. 34(2):142-146, 2013.

OBJECTIVE: To assess the immediate consequences of 60 minutes exposure to mobile phones on hearing function by determining changes in distortion product otoacoustic emission (DPOAE) and hearing threshold levels (HTLs). **METHODS:** This prospective control clinical trial study was carried out at the Ear, Nose and Throat Department, King Abdulaziz University Hospital, Riyadh, Kingdom of Saudi Arabia from July 2009 to July 2011. The data collected included age, symptoms experienced after exposure, and HTLs and DPOAE were recorded before, and immediately after 60 minutes of exposure to the same model of mobile phone. **RESULTS:** Heat/pain was the most commonly reported symptom. In the test-ears, significant shift ($p < 0.05$) was noticed in HTLs at 1000 and 2000 Hz but not at other frequencies, while non test-ears did not reveal significant shift in HTLs. Additionally, test-ears revealed significant differences ($p < 0.05$) in DPOAE at 1000 Hz, 1400 Hz, 2000 Hz, and at the average of all frequencies, while non test-ears did not show significant differences. **CONCLUSION:** Sixty minutes of close exposure to electromagnetic fields emitted by a mobile phone had an immediate effect on HTL assessed by pure-tone audiogram and inner ear (assessed by DPOAE) in young human subjects. It also caused a number of other otologic symptoms.

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Mandalà M, Colletti V, Sacchetto L, Manganotti P, Ramat S, Marcocci A, Colletti L. Effect of Bluetooth headset and mobile phone electromagnetic fields on the human auditory nerve. *Laryngoscope*. 2013 Apr 25. doi: 10.1002/lary.24103. [Epub ahead of print]

OBJECTIVES/HYPOTHESIS: The possibility that long-term mobile phone use increases the incidence of astrocytoma, glioma and acoustic neuroma has been investigated in several studies. Recently, our group showed that direct exposure (in a surgical setting) to cell phone electromagnetic fields (EMFs) induces deterioration of auditory evoked cochlear nerve compound action potential (CNAP) in humans. To verify whether the use of Bluetooth devices reduces these effects, we conducted the present study with the same experimental protocol. STUDY DESIGN: Randomized trial. METHODS: Twelve patients underwent retrosigmoid vestibular neurectomy to treat definite unilateral Ménière's disease while being monitored with acoustically evoked CNAPs to assess direct mobile phone exposure or alternatively the EMF effects of Bluetooth headsets. RESULTS: We found no short-term effects of Bluetooth EMFs on the auditory nervous structures, whereas direct mobile phone EMF exposure confirmed a significant decrease in CNAPs amplitude and an increase in latency in all subjects. CONCLUSIONS: The outcomes of the present study show that, contrary to the finding that the latency and amplitude of CNAPs are very sensitive to EMFs produced by the tested mobile phone, the EMFs produced by a common Bluetooth device do not induce any significant change in cochlear nerve activity. The conditions of exposure, therefore, differ from those of everyday life, in which various biological tissues may reduce the EMF affecting the cochlear nerve. Nevertheless, these novel findings may have important safety implications.

Grisanti G, Parlapiano C, Tamburello CC, Tine G, Zanforlin L. Cellular phone effects on otoacoustic emissions. *IEEE MTT-S Digest 2: 771-774, 1998.*

A study on bioelectromagnetic effects induced by the use of TACS phones, evidencing a variation of the natural response of the auditory system is presented. This study was performed applying a method based on the registration of the evoked otoacoustic emissions (transient and distortion products). The experimental results show that modulated electromagnetic fields modify the distortion products in about all the examined subjects.

Garcia Callejo FJ, Garcia Callejo F, Pena Santamaria J, Alonso Castaneira I, Sebastian Gil E, Marco Algarra J. [Hearing level and intensive use of mobile phones] *Acta Otorrinolaringol Esp*. 56(5):187-191, 2005. [Article in Spanish]

INTRODUCTION: Wide studies and substantial controversies build on utilization of actual mobile phones and appearance of systemic disorders or even tumours, but there is no knowledge about an eventual involvement on early hearing loss. PATIENTS AND METHODS: In a group of three hundred and twenty-three healthy and normoacoustic volunteers who were usual costumers of mobile phones an audiometric evaluation was made at the beginning of its use and three years later, inquiring about the periods of time

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per day and year employed on direct contacts with phone. A healthy and normoacoustic control group of non users was studied too. RESULTS: Cases carried out 24.3 +/- 8.2 active contacts, reaching 50.4 +/- 27.8 days of mobile phone employment in three years. Audiometric curve was similar in cases and controls at the beginning of the study. After this follow-up, cases showed an increase on hearing threshold between 1 and 5 dB HL more than controls in speech tones ($p < 0.001$). Moreover, there was a trend to correlate time of phone use to hearing impairment, but this finding did not result statistically significative. CONCLUSIONS: Frequent management of mobile phones in a middle period of time allows to detect a mild hearing loss, but the cause of this disorder keeps unclear.

Fritze K, Wiessner C, Kuster N, Sommer C, Gass P, Hermann DM, Kiessling M, Hossmann KA, Effect of global system for mobile communication microwave exposure on the genomic response of the rat brain. Neuroscience 81(3):627-639, 1997.

The acute effect of global system for mobile communication (GSM) microwave exposure on the genomic response of the central nervous system was studied in rats by measuring changes in the messenger RNAs of hsp70, the transcription factor genes c-fos and c-jun and the glial structural gene GFAP using in situ hybridization histochemistry. Protein products of transcription factors, stress proteins and marker proteins of astroglial and microglial activation were assessed by immunocytochemistry. Cell proliferation was evaluated by bromodeoxyuridine incorporation. A special GSM radiofrequency test set, connected to a commercial cellular phone operating in the discontinuous transmission mode, was used to simulate GSM exposure. The study was conducted at time averaged and brain averaged specific absorption rates of 0.3 W/kg (GSM exposure), 1.5 W/kg (GSM exposure) and 7.5 W/kg (continuous wave exposure), respectively. Immediately after exposure, in situ hybridization revealed slight induction of hsp70 messenger RNA in the cerebellum and hippocampus after 7.5 W/kg exposure, but not at lower intensities. A slightly increased expression of c-fos messenger RNA was observed in the cerebellum, neocortex and piriform cortex of all groups subjected to immobilization, but no differences were found amongst different exposure conditions. C-jun and GFAP messenger RNAs did not increase in any of the experimental groups. 24 h after exposure, immunocytochemical analysis of FOS and JUN proteins (c-FOS, FOS B, c-JUN JUN B, JUN D), of HSP70 or of KROX-20 and -24 did not reveal any alterations. Seven days after exposure, neither increased cell proliferation nor altered expression of astroglial and microglial marker proteins were observed. In conclusion, acute high intensity microwave exposure of immobilized rats may induce some minor stress response but does not result in lasting adaptive or reactive changes of the brain.

Colletti V, Mandalà M, Manganotti P, Ramat S, Sacchetto L, Colletti L. Intraoperative observation of changes in cochlear nerve action potentials during exposure to electromagnetic fields generated by mobile phones. J Neurol Neurosurg Psychiatry.82(7):766-71, 2010

Background The rapid spread of devices generating electromagnetic fields (EMF) has raised concerns as to the possible effects of this technology on humans. The auditory system is the neural organ most frequently and directly exposed to electromagnetic

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activity owing to the daily use of mobile phones. In recent publications, a possible correlation between mobile phone usage and central nervous system tumours has been detected. Very recently a deterioration in otoacoustic emissions and in the auditory middle latency responses after intensive and long-term magnetic field exposure in humans has been demonstrated. Methods To determine with objective observations if exposure to mobile phone EMF affects acoustically evoked cochlear nerve compound action potentials, seven patients suffering from Ménière's disease and undergoing retrosigmoid vestibular neurectomy were exposed to the effects of mobile phone placed over the craniotomy for 5 min. Results All patients showed a substantial decrease in amplitude and a significant increase in latency of cochlear nerve compound action potentials during the 5 min of exposure to EMF. These changes lasted for a period of around 5 min after exposure. Discussion The possibility that EMF can produce relatively long-lasting effects on cochlear nerve conduction is discussed and analysed in light of contrasting previous literature obtained under non-surgical conditions. Limitations of this novel approach, including the effects of the anaesthetics, craniotomy and surgical procedure, are presented in detail.

Budak GG, Muluk NB, Budak B, Oztürk GG, Apan A, Seyhan N. Effects of intrauterine and extrauterine exposure to GSM-like radiofrequency on distortion product otoacoustic emissions in infant male rabbits. *Int J Pediatr Otorhinolaryngol.* 73(3):391-399, 2009.

OBJECTIVES: The aim of this study was to investigate the potential hazardous effects of intrauterine (IU) and/or extrauterine (EU) exposure to 1800 MHz Global System for Mobile Communications-like (GSM-like) radiofrequency (RF) on the cochlear functions of infant rabbits by measuring distortion product otoacoustic emission (DPOAE) response amplitudes. **METHODS:** Thirty-six white infant male New Zealand rabbits each 1-month-old were included in the study. The animals were randomly divided into four groups. Nine infant rabbits (Group 1) were not exposed to 1800 MHz GSM-like RF (Control-C). Nine infant rabbits (Group 2) were exposed to 1800 MHz GSM-like RF, 15 min daily for 14 days after they reached 1-month of age (extrauterine-EU). Nine infant rabbits (Group 3) were exposed to 1800 MHz GSM-like RF, 15 min daily for 7 days in the intrauterine period (between 15th and 22nd days of the gestational period) (intrauterine-IU). Nine infant rabbits (Group 4) were exposed to 1800 MHz GSM-like RF, 15 min daily for 7 days in the intrauterine period (between 15th and 22nd days of the gestational period) and 15 min daily for 14 days after they reached to 1-month of age (IU+EU). The cochlear functions were assessed by DPOAEs at 1.0-8.0 kHz. **RESULTS:** At 1.5 kHz, the mean DPOAE amplitude of Group 3 was higher than that of the controls and Group 2; and the mean DPOAE value of Group 4 was higher than that of the controls and Group 2. At 2.0 kHz, the mean DPOAE amplitude of Group 4 was higher than that of Group 2. At 3.0 kHz, the mean DPOAE amplitude of Group 4 was higher than that of the controls and Group 2. At 4.0 kHz, the mean DPOAE amplitude of Group 2 was lower than that of the controls, while the mean value of Group 4 was higher than the mean value of the controls and Group 2. At 6.0 kHz, the mean DPOAE amplitude of Group 2 was lower than that of the control group; however, the mean value of Group 4 was

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higher than that of Group 2. At 1.0 and 8.0 kHz, no significant differences were found among the four groups. CONCLUSION: Prolonged exposure and hyperthermia related to the power density of applied RF, increasing the temperature in the ear canal, may affect DPOAE amplitudes. Harmful effects of RF are mainly observed as a decrease in DPOAE amplitudes at 4.0-6.0 kHz during extrauterine exposure in infancy. During the intrauterine period, the water content of the middle and inner ear and amnion fluid may play a protective role. Therefore, children must be protected from RF exposure. The use of mobile phones at short distances from the ear of the infants should be avoided because of the lower thickness of the anatomical structure in infancy.

Tahvanainen K, Nino J, Halonen P, Kuusela T, Alanko T, Laitinen T, Lansimies E, Hietanen M, Lindholm H. Effects of cellular phone use on ear canal temperature measured by NTC thermistors. Clin Physiol Funct Imaging. 27(3):162-172, 2007.

The earlier studies using phantom models and human subjects concerning warming effects during cellular phone use have been controversial, partly because radiofrequency (RF) exposures have been variable. In this randomized, double-blind, placebo-controlled crossover trial, 30 healthy subjects were submitted to 900 MHz (2W) and 1800 MHz (1W) cellular phone RF exposure, and to sham exposure in separate study sessions. Temperature signals were recorded continuously in both ear canals before, during and after the 35-min RF exposure and the 35-min sham exposure sessions. Temperature was measured by using small-sized NTC thermistors placed in the ear canals through disposable ear plugs. The mean temperature changes were determined during a set cardiovascular autonomic function studies: during a 5-min controlled breathing test, during a 5-min spontaneous breathing test, during 7-min head-up tilting, 1-min before, during and after two consecutive Valsalva manoeuvres and during a deep breathing test. Temperatures in the exposed ear were significantly higher during RF exposures compared with sham exposure in both 900 and 1800 MHz studies with maximum differences of 1.2 +/- 0.5 degrees C (900 MHz exposure) and 1.3 +/- 0.7 degrees C (1800 MHz exposure). Temperatures in the RF-exposed ear were also significantly higher during the postexposure period compared with post-sham exposure period with maximum differences of 0.6 +/- 0.3 degrees C for 900 MHz and 0.5 +/- 0.5 degrees C for 1800 MHz. The results of this study suggest that RF exposure to a cellular phone, either using 900 or 1800 MHz with their maximal allowed antenna powers, increases the temperature in the ear canal. The reason for the ear canal temperature rising is a consequence of mobile phone battery warming during maximal antenna power use. The earlier published articles do not indicate that temperature rising in the ear canal has any significant contribution from the RF fields emitted from mobile phones.

Budak GG, Muluk NB, Budak B, Oztürk GG, Apan A, Seyhan N. Effects of GSM-like radiofrequency on distortion product otoacoustic emissions of rabbits: comparison of infants versus adults. Int J Pediatr Otorhinolaryngol. 73(8):1143-1147, 2009.

OBJECTIVES: The aim of this study is to investigate the potential hazardous effects of 1800 MHz Global System for Mobile Communications-like (GSM-like) Radiofrequency

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(RF) exposure on the cochlear functions of female infant and adult rabbits by measuring Distortion Product Otoacoustic Emission (DPOAE) response amplitudes. METHODS: Eighteen each one-month-old New Zealand White female rabbits and eighteen each 13-month-old adult rabbits were included into the study. They were randomly divided into four groups. Nine infant rabbits (Group 1) were not exposed to 1800 MHz GSM-like RF (Infant Control, C-In). Nine infant rabbits (Group 2) were exposed to 1800 MHz GSM-like RF, 15 min daily for 7 days after they reached one-month of age (Infant RF, RF-In). Nine adult rabbits were not exposed to 1800 MHz GSM-like RF, 15 min daily for 7 (Adult Control, C-Ad). Nine adult rabbits were exposed to 1800 MHz GSM-like RF, 15 min daily for 7 days (Adult RF, RF-Ad). Cochlear functions were assessed by DPOAEs at 1.0-8.0 kHz. RESULTS: At 1.0-2.0 and 6.0 kHz, the mean DPOAE values of Group 2 were significantly higher than that of Group 1. At 3.0-8.0 kHz, the mean DPOAE values of Group 4 were significantly lower than that of Group 1. At 6.0-8.0 kHz, the mean DPOAE values of Group 2 were significantly higher than that of Group 3. At 1.0-8.0 kHz, the mean DPOAE values of Group 4 were significantly lower than that of Group 2. At 1.0-8.0 kHz, the mean DPOAE values of Group 4 were significantly lower than that of Group 3. CONCLUSION: Harmful effects of GSM-like 1800 MHz RF exposure was detected more in the adult female rabbits than infant female rabbits by DPOAE measurement. Prolonged exposure and hyperthermia related to the power density of applied RFR, increasing the temperature in the ear canal, may decrease the DPOAE amplitudes. Water containing medium in the middle ear of infant rabbits may play the protective role from the RF damage.

Budak GG, Muluk NB, Oztürk GG, Budak B, Apan A, Seyhan N, Sanli C. Effects of GSM-like radiofrequency on distortion product otoacoustic emissions in pregnant adult rabbits. Clin Invest Med. 32(2):E112-116, 2009.

OBJECTIVES: To determine the effects of 1800 MHz GSM-like Radiofrequency (RFR) on the cochlear functions of pregnant adult rabbits by Distortion Product Otoacoustic Emissions (DPOAEs). METHODS: Eighteen 13-month-old pregnant and eighteen 13-month-old non-pregnant New Zealand White rabbits were studied. They were randomly divided into four groups. Nine pregnant rabbits (Group 2) and nine non-pregnant rabbits (Group 4) were exposed to 1800 MHz GSM-like RFR 15 min daily for 7 days. Nine pregnant (Group 1) and nine non-pregnant rabbits (Group 3) were not exposed to GSM like RFR. Cochlear functions were assessed by DPOAEs at 1.0-8.0 kHz. RESULTS: In all pregnant groups except 2.0 kHz, DPOAE amplitudes were not different in Group 2 and Group 1. In Group 4, DPOAE amplitudes at 1.0-4.0 kHz (-1.68 dB SPL at 1.0 kHz, 3.05 dB SPL at 1.5 kHz, 2.96 dB SPL at 2.0 kHz, 1.30 dB SPL at 3.0 kHz and 12.22 dB SPL at 4.0 kHz) were lower than Group 3 (8.67 dB SPL at 1.0 kHz, 17.67 dB SPL at 1.5 kHz, 26.10 dB SPL at 2.0 kHz, 18.10 dB SPL at 3.0 kHz and 35.13 dB SPL at 4.0 kHz) ($P < 0.0125$). In the pregnant group, harmful effects of GSM-like RFR were less than in the non-pregnant group. CONCLUSION: GSM-like RFR caused decreases in DPOAE amplitudes mainly in non-pregnant adult rabbits. Prolonged exposure may affect the DPOAE amplitude. Recommendations are given to prevent the potential hazardous effects of RF in humans.

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Al-Dousary SH Mobile phone induced sensorineural hearing loss. Saudi Med J. 28(8):1283-1286, 2007.

The increased use of mobile phones worldwide has focused interest on the biological effects and possible health outcomes of exposure to radiofrequency fields from mobile phones, and their base stations. Various reports suggest that mobile phone use can cause health problems like fatigue, headache, dizziness, tension, and sleep disturbances; however, only limited research data is available in medical literature regarding interaction between electromagnetic fields emitted by mobile phones and auditory function; and the possible impact on hearing. We report a case of sensorineural hearing loss due to Global System for Mobile Communications mobile phone use, in a 42-year-old male.

Effects on Eyes

Yu Y, Yao K. Non-thermal cellular effects of lowpower microwave radiation on the lens and lens epithelial cells. J Int Med Res. 38(3):729-736, 2010.

Because of the increased use of modern radiofrequency devices, public concern about the possible health effects of exposure to microwave radiation has arisen in many countries. It is well established that high-power microwave radiation can induce cataracts via its thermal effects. It remains unclear whether low-power microwave radiation, especially at levels below the current exposure limits, is cataractogenic. This review summarizes studies on the biological effects of low-power microwave radiation on lens and lens epithelial cells (LECs). It has been reported that exposure affects lens transparency, alters cell proliferation and apoptosis, inhibits gap junctional intercellular communication, and induces genetic instability and stress responses in LECs. These results raise the question of whether the ambient microwave environment can induce non-thermal effects in the lens and whether such effects have potential health consequences. Further in vivo studies on the effects on the lens of exposure to low-power microwave radiation are needed.

Balik HH, Turgut-Balik D, Balikci K, Ozcan IC. Some ocular symptoms and sensations experienced by long term users of mobile phones. Pathol Biol (Paris). 53(2):88-91, 2005.

In this study, a survey was conducted to investigate the possible effects of long term usage of mobile phone (MP) on eyes. The studied symptoms are blurring of vision, redness on the eyes, vision disturbance, secretion of the eyes, inflammation in the eyes and lacrimation of the eyes. There is no effect on redness on the eyes and vision disturbance, but some statistical evidences are found that MP may cause blurring of vision, secretion of the eyes, inflammation in the eyes and lacrimation of the eyes. These results suggest an awareness of the symptoms and sensations.

Yu Y, Yao K, Wu W, Wang K, Chen G, Lu D. Effects of exposure to 1.8 GHz

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radiofrequency field on the expression of Hsps and phosphorylation of MAPKs in human lens epithelial cells. *Cell Res.* 18(12):1233-1235, 2008.

(No abstract available) Last sentence of discussion:

“Our results suggest that exposure to RF of wireless communications can induce expression of Hsp27 and Hsp70 and the activation of ERK1/2 and JNK1/2 in human LECs. The induction of Hsp27 and Hsp70, by a non-thermal stress, together with the activation of signal transduction pathways, provides reliable and sensitive biomarkers that could serve as the basis for improved mobile phone safety guidelines.”

Dovrat A, Berenson R, Bormusov E, Lahav A, Lustman T, Sharon N, Schachter L. Localized effects of microwave radiation on the intact eye lens in culture conditions. *Bioelectromagnetics.* 26(5):398-405, 2005.

A novel experimental system was used to investigate the localized effects of microwave radiation on bovine eye lenses in culture for over 2 weeks. Using this setup, we found clear evidence that this radiation has a significant impact on the eye lens. At the macroscopic level, it is demonstrated that exposure to a few mW at 1 GHz for over 36 h affects the optical function of the lens. Most importantly, self-recovery occurs if the exposure is interrupted. At the microscopic level, close examination of the lens indicates that the interaction mechanism is completely different from the mechanism-causing cataract via temperature increase. Contrary to the latter's effect, that is particularly pronounced in the vicinity of the sutures and it is assumed to be a result of local friction between the edges of the fibers consisting the lens. Even if macroscopically the lens has recovered from the irradiation, microscopically the indicators of radiation impact remain.

Lu L, Xu H, Wang X, Guo G. Increased nitric oxide synthase activity is essential for electromagnetic-pulse-induced blood-retinal barrier breakdown in vivo. *Brain Res.* 1264:104-10, 2009.

PURPOSE: To examine whether electromagnetic pulses (EMPs) affected the permeability of the blood-retinal barrier (BRB), gene expression of occludin and activity of nitric oxide synthase (NOS). **METHODS:** Sprague-Dawley (SD) rats were used and randomized into EMP and control groups. Retinas were removed immediately, and 2 h or 24 h after EMP radiation. BRB permeability was analyzed by transmission electron microscopy and Evans Blue staining. Retinal NOS activity and concentrations of nitrite and nitrate were measured. Occludin mRNA and protein levels were detected by RT-PCR and Western blotting. **RESULTS:** Exposure of SD rats to EMP resulted in increased BRB permeability, with the greatest decrease in occludin at 24 h. Moreover, this permeability defect was also correlated with significant increases in the formation of NO and induction of NOS activity in SD rats. Furthermore, we found that treatment with NOS inhibitor N-nitro-L-arginine methyl ester (L-NAME) blocked BRB breakdown and prevented the increase in NO formation and induction of NOS activity, as well as the decrease in occluding expression. **CONCLUSION:** Taken together, these results support the view that NOS-dependent NO production is an important factor that contributes to EMP-induced BRB dysfunction, and suggests that NOS induction may play an important

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role in BRB breakdown.

Teerapot Wessapan, Phadungsak Rattanadecho. Specific absorption rate and temperature increase in the human eye due to electromagnetic fields exposure at different frequencies. International Journal of Heat and Mass Transfer, 64:426-435, September 2013.

This study presents a numerical analysis of the specific absorption rate (SAR) and the heat transfer in a heterogeneous human eye model exposed to electromagnetic (EM) fields of 900 and 1800 MHz. In this study, the effect of operating frequency on the SAR and temperature distributions in the eye was systematically investigated. The SAR value and the temperature distribution in various tissues in the eye during exposure to EM fields were obtained by numerical simulation of EM wave propagation and a heat transfer model was then developed based on the natural convection and porous media theories. The study highlights two transport phenomena: heat and mass transfer in the eye during exposure to EM fields at different frequencies. This study indicated that when the eye exposed to EM fields at the frequencies of 900 and 1800 MHz, the highest SAR values at two chosen frequencies was in the cornea, and the highest temperature at the frequency of 900 MHz was in the anterior chamber while the highest for the frequency of 1800 MHz was in the vitreous. The temperature distribution in the eye induced by EM fields was not directly related to the SAR distribution due to the effect of the interaction among the dielectric properties, thermal properties, blood perfusion, and penetration depth of the EM power. Moreover, this study also showed that the exposure time had an influence on the temperature increase in the eye.

Teerapot Wessapan, Phadungsak Rattanadecho. Influence of ambient temperature on heat transfer in the human eye during exposure to electromagnetic fields at 900 MHz. International Journal of Heat and Mass Transfer 70: 378-388, 2014.

The topic of temperature increase in human tissue when exposed to EM fields, particularly those radiated to the eye, has been of interest for many years. This study presents a numerical analysis of the specific absorption rate (SAR) and the heat transfer in a heterogeneous two-dimensional human eye model exposed to TM-mode of electromagnetic (EM) fields of 900 MHz at various power densities. In this study, the effects of ambient temperature and power density on the temperature distributions and fluid flow in the eye during exposure to electromagnetic fields were systematically investigated. The electric field, SAR, temperature distribution and fluid flow in various tissues in the eye during exposure to EM fields were obtained by numerical simulation of EM wave propagation and a heat transfer model. The heat transfer model was then developed based on the porous media theories. The study highlights heat transfer and fluid flow in the eye during exposure to EM fields at different ambient temperatures. This study indicated that when the eye exposed to EM fields at the frequency of 900 MHz, the highest electric field intensity and SAR values at the chosen frequency was in the cornea. At the highest power density of 100 mW/cm^2 , the absorbed EM energy is converted to heat causes a further increase of $3 \text{ }^\circ\text{C}$ in corneal temperature in cases of

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hot, moderate and cold ambient temperatures. The result shows important information related to a complex interaction between ambient temperature, fluid flow and temperature distribution in the eye during exposure to electromagnetic fields. Moreover, this study also showed that the power density had a strong influence on the temperature increase and fluid flow in the eye.

Balci M, Devrim E, Durak I. Effects of mobile phones on oxidant/antioxidant balance in cornea and lens of rats. *Curr Eye Res.* 32(1):21-25, 2007.

Purpose: To investigate the effects of mobile-phone-emitted radiation on the oxidant/antioxidant balance in corneal and lens tissues and to observe any protective effects of vitamin C in this setting. Methods: Forty female albino Wistar rats were assigned to one of four groups containing 10 rats each. One group received a standardized daily dose of mobile phone radiation for 4 weeks. The second group received this same treatment along with a daily oral dose of vitamin C (250 mg/kg). The third group received this dose of vitamin C alone, while the fourth group received standard laboratory care and served as a control. In corneal and lens tissues, malondialdehyde (MDA) levels and activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) were measured with spectrophotometric methods. Results: In corneal tissue, MDA level and CAT activity significantly increased in the mobile phone group compared with the mobile phone plus vitamin C group and the control group ($p < 0.05$), whereas SOD activity was significantly decreased ($p < 0.05$). In the lens tissues, only the MDA level significantly increased in the mobile phone group relative to mobile phone plus vitamin C group and the control groups ($p < 0.05$). In lens tissue, significant differences were not found between the groups in terms of SOD, GSH-Px, or CAT ($p > 0.05$). Conclusions: The results of this study suggest that mobile telephone radiation leads to oxidative stress in corneal and lens tissues and that antioxidants such as vitamin C can help to prevent these effects

Lixia S, Yao K, Kaijun W, Deqiang L, Huajun H, Xiangwei G, Baohong W, Wei Z, Jianling L, Wei W. Effects of 1.8GHz radiofrequency field on DNA damage and expression of heat shock protein 70 in human lens epithelial cells. *Mutat Res.*602(1-2):135-142, 2006.

To investigate the DNA damage, expression of heat shock protein 70 (Hsp70) and cell proliferation of human lens epithelial cells (hLEC) after exposure to the 1.8GHz radiofrequency field (RF) of a global system for mobile communications (GSM). An Xc-1800 RF exposure system was used to employ a GSM signal at 1.8GHz (217Hz amplitude-modulated) with the output power in the specific absorption rate (SAR) of 1, 2 and 3W/kg. After 2h exposure to RF, the DNA damage of hLEC was accessed by comet assay at five different incubation times: 0, 30, 60, 120 and 240min, respectively. Western blot and RT-PCR were used to determine the expression of Hsp70 in hLECs after RF exposure. The proliferation rate of cells was evaluated by bromodeoxyuridine incorporation on days 0, 1 and 4 after exposure. The results show that the difference of DNA-breaks between the exposed and sham-exposed (control) groups induced by 1 and 2W/kg

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irradiation were not significant at any incubation time point ($P>0.05$). The DNA damage caused by 3W/kg irradiation was significantly increased at the times of 0 and 30min after exposure ($P<0.05$), a phenomenon that could not be seen at the time points of 60, 120 or 240min ($P>0.05$). Detectable mRNA as well as protein expression of Hsp70 was found in all groups. Exposure at SARs of 2 and 3W/kg for 2h exhibited significantly increased Hsp70 protein expression ($P<0.05$), while no change in Hsp70 mRNA expression could be found in any of the groups ($P>0.05$). No difference of the cell proliferation rate between the sham-exposed and exposed cells was found at any exposure dose tested ($P>0.05$). The results indicate that exposure to non-thermal dosages of RF for wireless communications can induce no or repairable DNA damage and the increased Hsp70 protein expression in hLECs occurred without change in the cell proliferation rate. The non-thermal stress response of Hsp70 protein increase to RF exposure might be involved in protecting hLEC from DNA damage and maintaining the cellular capacity for proliferation.

Gasmelseed A. Electromagnetic energy absorption patterns in subjects with common visual disorders. *Electromagn Biol Med.* 30(3):136-145, 2011.

This article describes the analysis of electromagnetic energy absorption properties of models of the human eye with common visual disorders. The investigation addresses two types of visual disorders, namely hyperopia (or farsightedness) and myopia (or nearsightedness). Calculations were carried out using plane multilayered method with common wireless communication frequencies of 900, 1800, and 2450 MHz. The effect of wireless radiation on the eye is studied by calculation of the specific absorption rate (SAR) in three different eye models. The results of the simulations confirmed the anticipated and more complex relationship between absorption and structural variations of the eye at these frequencies.

Ozguner F, Bardak Y, Comlekci S. Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: A comparative study. *Mol Cell Biochem.* 282(1-2):83-88, 2006.

There are numerous reports on the effects of electromagnetic radiation (EMR) in various cellular systems. Melatonin and caffeic acid phenethyl ester (CAPE), a component of honeybee propolis, were recently found to be potent free radical scavengers and antioxidants. Mechanisms of adverse effects of EMR indicate that reactive oxygen species may play a role in the biological effects of this radiation. The present study was carried out to compare the efficacy of the protective effects of melatonin and CAPE against retinal oxidative stress due to long-term exposure to 900 MHz EMR emitting mobile phones. Melatonin and CAPE were administered daily for 60 days to the rats prior to their EMR exposure during our study. Nitric oxide (NO, an oxidant product) levels and malondialdehyde (MDA, an index of lipid peroxidation), were used as markers of retinal oxidative stress in rats following to use of EMR. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate the changes of antioxidant status in retinal tissue. Retinal levels of NO and MDA increased in EMR exposed rats while both melatonin and

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CAPE caused a significant reduction in the levels of NO and MDA. Likewise, retinal SOD, GSH-Px and CAT activities decreased in EMR exposed animals while melatonin and CAPE caused a significant increase in the activities of these antioxidant enzymes. Treatment of EMR exposed rats with melatonin or CAPE increased the activities of SOD, GSH-Px and CAT to higher levels than those of control rats. In conclusion, melatonin and CAPE reduce retinal oxidative stress after long-term exposure to 900 MHz emitting mobile phone. Nevertheless, there was no statistically significant difference between the efficacies of these two antioxidants against to EMR induced oxidative stress in rat retina. The difference was in only GSH-Px activity in rat retina. Melatonin stimulated the retinal GSH-Px activity more efficiently than CAPE did.

Children Health and Cell Phone Use

Wang PW, Liu TL, Ko CH, Lin HC, Huang MF, Yeh YC, Yen CF. Association between Problematic Cellular Phone Use and Suicide: The Moderating Effect of Family Function and Depression. *Compr Psychiatry*. 2013 Oct 19. pii: S0010-440X(13)00282-4. doi: 10.1016/j.comppsy.2013.09.006. [Epub ahead of print]

BACKGROUND: Suicidal ideation and attempt among adolescents are risk factors for eventual completed suicide. Cellular phone use (CPU) has markedly changed the everyday lives of adolescents. Issues about how cellular phone use relates to adolescent mental health, such as suicidal ideation and attempts, are important because of the high rate of cellular phone usage among children in that age group. This study explored the association between problematic CPU and suicidal ideation and attempts among adolescents and investigated how family function and depression influence the association between problematic CPU and suicidal ideation and attempts. METHODS: A total of 5051 (2872 girls and 2179 boys) adolescents who owned at least one cellular phone completed the research questionnaires. We collected data on participants' CPU and suicidal behavior (ideation and attempts) during the past month as well as information on family function and history of depression. RESULTS: Five hundred thirty-two adolescents (10.54%) had problematic CPU. The rates of suicidal ideation were 23.50% and 11.76% in adolescents with problematic CPU and without problematic CPU, respectively. The rates of suicidal attempts in both groups were 13.70% and 5.45%, respectively. Family function, but not depression, had a moderating effect on the association between problematic CPU and suicidal ideation and attempt. CONCLUSION: This study highlights the association between problematic CPU and suicidal ideation as well as attempts and indicates that good family function may have a more significant role on reducing the risks of suicidal ideation and attempts in adolescents with problematic CPU than in those without problematic CPU.

Leena K, Tomi L, Arja RR. Intensity of mobile phone use and health compromising behaviours-how is information and communication technology connected to health-related lifestyle in adolescence? *J Adolesc*. 28(1):35-47, 2005.

The association of mobile phone use with health compromising behaviours (smoking, snuffing, alcohol) was studied in a survey comprising a representative sample of 14-16-

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year-olds ([Formula: see text]) in 2001. Mobile phone was used by 89% of respondents and by 13% for at least 1h daily. The intensity of use was positively associated with health compromising behaviours. The associations remained, although somewhat reduced, after including weekly spending money in the models. This study concludes that, at least in the present developmental level of communication technologies, intensive mobile phone use seems to be part of the same health-related lifestyle as health compromising behaviours.

Redmayne M, Smith E, Abramson MJ. Adolescent in-school cellphone habits: a census of rules, survey of their effectiveness, and fertility implications. Reprod Toxicol. 32(3):354-359, 2011.

We explored school cellphone rules and adolescent exposure to cellphone microwave emissions during school with a census and survey, respectively. The data were used to assess health and policy implications through a review of papers assessing reproductive bio-effects after exposure to cellphone emissions, this being most relevant to students' exposure. All schools banned private use of cellphones in class. However, 43% of student participants admitted breaking this rule. A high-exposure group of risk-takers was identified for whom prohibited in-school use was positively associated with high texting rates, carrying the phone switched-on >10h/day, and in-pocket use. The fertility literature is inconclusive, but increasingly points towards significant time- and dose-dependent deleterious effects from cellphone exposure on sperm. Genotoxic effects have been demonstrated from 'non-thermal' exposures, but not consistently. There is sufficient evidence and expert opinion to warrant an enforced school policy removing cellphones from students during the day.

Redmayne M. New Zealand adolescents' cellphone and cordless phone user-habits: are they at increased risk of brain tumours already? A cross-sectional study. Environ Health. 12(1):5, 2013.

BACKGROUND: Cellphone and cordless phone use is very prevalent among early adolescents, but the extent and types of use is not well documented. This paper explores how, and to what extent, New Zealand adolescents are typically using and exposed to active cellphones and cordless phones, and considers implications of this in relation to brain tumour risk, with reference to current research findings. **METHODS:** This cross-sectional study recruited 373 Year 7 and 8 school students with a mean age of 12.3 years (range 10.3-13.7 years) from the Wellington region of New Zealand. Participants completed a questionnaire and measured their normal body-to-phone texting distances. Main exposure-metrics included self-reported time spent with an active cellphone close to the body, estimated time and number of calls on both phone types, estimated and actual extent of SMS text-messaging, cellphone functions used and people texted. Statistical analyses used Pearson Chi2 tests and Pearson's correlation coefficient (r). Analyses were undertaken using SPSS version 19.0. **RESULTS:** Both cellphones and cordless phones were used by approximately 90% of students. A third of participants had already used a cordless phone for ≥ 7 years. In 4 years from the survey to mid-2013, the cordless phone use of 6% of participants would equal that of the

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highest Interphone decile (≥ 1640 hours), at the surveyed rate of use. High cellphone use was related to cellphone location at night, being woken regularly, and being tired at school. More than a third of parents thought cellphones carried a moderate-to-high health risk for their child. **CONCLUSIONS:** While cellphones were very popular for entertainment and social interaction via texting, cordless phones were most popular for calls. If their use continued at the reported rate, many would be at increased risk of specific brain tumours by their mid-teens, based on findings of the Interphone and Hardell-group studies.

Redmayne M, Smith E, and Abramson MJ. The relationship between adolescents' well-being and their wireless phone use: a cross-sectional study. Environmental Health 12(1):90, 2013.

Background. The exposure of young people to radiofrequency electromagnetic fields (RF-EMFs) has increased rapidly in recent years with their increased use of cellphones and use of cordless phones and WiFi. We sought to ascertain associations between New Zealand early-adolescents' subjective well-being and self-reported use of, or exposure to, wireless telephone and internet technology. Methods. In this cross-sectional survey, participants completed questionnaires in class about their cellphone and cordless phone use, their self-reported well-being, and possible confounding information such as whether they had had influenza recently or had a television in the bedroom. Parental questionnaires provided data on whether they had WiFi at home and cordless phone ownership and model. Data were analysed with Ordinal Logistic Regression adjusting for common confounders. Odds ratios (OR) and 95% confidence intervals were calculated. Results. The number and duration of cellphone and cordless phone calls were associated with increased risk of headaches (>6 cellphone calls over 10 minutes weekly, adjusted OR 2.4, CI 1.2-4.8; >15 minutes cordless use daily adjusted OR 1.74, CI 1.1-2.9). Texting and extended use of wireless phones was related to having a painful 'texting' thumb). Using a wired cellphone headset was associated with tinnitus (adjusted OR 1.8, CI 1.0-3.3), while wireless headsets were associated with headache (adjusted OR 2.2, CI 1.1-4.5), feeling down/depressed (adjusted OR 2.0, CI 1.1-3.8), and waking in the night (adjusted OR 2.4, CI 1.2-4.8). Several cordless phone frequencies bands were related to tinnitus, feeling down/depressed and sleepiness at school, while the last of these was also related to modulation. Waking nightly was less likely for those with WiFi at home (adjusted OR 0.7, CI 0.4-0.99). Being woken at night by a cellphone was strongly related to tiredness at school (OR 4.1, CI 2.2-7.7). Conclusions. There were more statistically significant associations (36%) than could be expected by chance (5%). Several were dose-dependent relationships. To safeguard young people's well-being, we suggest limiting their use of cellphones and cordless phones to less than 15 minutes daily, and employing a speaker-phone device for longer daily use. We recommend parental measures are taken to prevent young people being woken by their cellphones.

Pedersen W. [Mobile phones, web chat, and sex among Norwegian adolescents]

Tidsskr Nor Laegeforen. 124(13-14):1756-1759, 2004. [article in Norwegian]

BACKGROUND: We investigated the associations between new interactive technology

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for communication, such as web chat or mobile phones, and sexual behaviour among Norwegian adolescents. **MATERIALS AND METHODS:** A representative sample of adolescents (age 13-18, N = 10,926) filled in a questionnaire during school hours; the response rate was 92%. **RESULTS:** Most adolescents have access to communication technology, but how much they use it varies. In particular with regard to mobile phones, a strong association to sexual behaviour was found. Among those who did not use the new technology, less than 10% reported having had intercourse while two out of three of the most active users reported intercourse. The associations remained significant when controls were made for age and a range of contextual, family, peer and individual factors. **INTERPRETATION:** Norwegian adolescents have changed their sexual behaviour over the last decade. The introduction and widespread use of new communication technology is one of the most salient changes over the same period. The findings suggest that this technology may in fact be of importance to teenagers' sexual socialisation.

Thomas S, Heinrich S, von Kries R, Radon K. Exposure to radio-frequency electromagnetic fields and behavioural problems in Bavarian children and adolescents. Eur J Epidemiol. 25(2):135-141, 2010.

Only few studies have so far investigated possible health effects of radio-frequency electromagnetic fields (RF EMF) in children and adolescents, although experts discuss a potential higher vulnerability to such fields. We aimed to investigate a possible association between measured exposure to RF EMF fields and behavioural problems in children and adolescents. 1,498 children and 1,524 adolescents were randomly selected from the population registries of four Bavarian (South of Germany) cities. During an Interview data on participants' mental health, socio-demographic characteristics and potential confounders were collected. Mental health behaviour was assessed using the German version of the Strengths and Difficulties Questionnaire (SDQ). Using a personal dosimeter, we obtained radio-frequency EMF exposure profiles over 24 h. Exposure levels over waking hours were expressed as mean percentage of the reference level. Overall, exposure to radiofrequency electromagnetic fields was far below the reference level. Seven percent of the children and 5% of the adolescents showed an abnormal mental behaviour. In the multiple logistic regression analyses measured exposure to RF fields in the highest quartile was associated to overall behavioural problems for adolescents (OR 2.2; 95% CI 1.1-4.5) but not for children (1.3; 0.7-2.6). These results are mainly driven by one subscale, as the results showed an association between exposure and conduct problems for adolescents (3.7; 1.6-8.4) and children (2.9; 1.4-5.9). As this is one of the first studies that investigated an association between exposure to mobile telecommunication networks and mental health behaviour more studies using personal dosimetry are warranted to confirm these findings.

Thomas S, Benke G, Dimitriadis C, Inyang I, Sim MR, Wolfe R, Croft RJ, Abramson MJ. Use of mobile phones and changes in cognitive function in adolescents. Occup Environ Med.67(12):861-866, 2010.

Background Several studies have investigated the impact of mobile phone exposure on

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cognitive function in adults. However, children and adolescents are of special interest due to their developing nervous systems. Methods Data were derived from the Australian Mobile Radiofrequency Phone Exposed Users' Study (MoRPhEUS) which comprised a baseline examination of year 7 students during 2005/2006 and a 1-year follow-up. Sociodemographic and exposure data were collected with a questionnaire. Cognitive functions were assessed with a computerised test battery and the Stroop Color-Word test. Results 236 students participated in both examinations. The proportion of mobile phone owners and the number of voice calls and short message services (SMS) per week increased from baseline to follow-up. Participants with more voice calls and SMS at baseline showed less reductions in response times over the 1-year period in various computerised tasks. Furthermore, those with increased voice calls and SMS exposure over the 1-year period showed changes in response time in a simple reaction and a working memory task. No associations were seen between mobile phone exposure and the Stroop test. Conclusions We have observed that some changes in cognitive function, particularly in response time rather than accuracy, occurred with a latency period of 1 year and that some changes were associated with increased exposure. However, the increased exposure was mainly applied to those who had fewer voice calls and SMS at baseline, suggesting that these changes over time may relate to statistical regression to the mean, and not be the effect of mobile phone exposure.

Sudan M, Kheifets L, Arah O, Olsen J, Zeltzer L. Prenatal and Postnatal Cell Phone Exposures and Headaches in Children. *Open Pediatr Med Journal*. 6(2012):46-52, 2012.

OBJECTIVE: Children today are exposed to cell phones early in life, and may be at the greatest risk if exposure is harmful to health. We investigated associations between cell phone exposures and headaches in children. STUDY DESIGN: The Danish National Birth Cohort enrolled pregnant women between 1996 and 2002. When their children reached age seven years, mothers completed a questionnaire regarding the child's health, behaviors, and exposures. We used multivariable adjusted models to relate prenatal only, postnatal only, or both prenatal and postnatal cell phone exposure to whether the child had migraines and headache-related symptoms. RESULTS: Our analyses included data from 52,680 children. Children with cell phone exposure had higher odds of migraines and headache-related symptoms than children with no exposure. The odds ratio for migraines was 1.30 (95% confidence interval: 1.01-1.68) and for headache-related symptoms was 1.32 (95% confidence interval: 1.23-1.40) for children with both prenatal and postnatal exposure. CONCLUSIONS: In this study, cell phone exposures were associated with headaches in children, but the associations may not be causal given the potential for uncontrolled confounding and misclassification in observational studies such as this. However, given the widespread use of cell phones, if a causal effect exists it would have great public health impact.

Sudan M, Kheifets L, Arah OA, Olsen J. Cell phone exposures and hearing loss in children in the Danish National Birth Cohort. *Paediatr Perinat Epidemiol*. 27(3):247-257, 2013.

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BACKGROUND: Children today are exposed to cell phones early in life, and may be the most vulnerable if exposure is harmful to health. We investigated the association between cell phone use and hearing loss in children. METHODS: The Danish National Birth Cohort (DNBC) enrolled pregnant women between 1996 and 2002. Detailed interviews were conducted during gestation, and when the children were 6 months, 18 months and 7 years of age. We used multivariable-adjusted logistic regression, marginal structural models (MSM) with inverse-probability weighting, and doubly robust estimation (DRE) to relate hearing loss at age 18 months to cell phone use at age 7 years, and to investigate cell phone use reported at age 7 in relation to hearing loss at age 7. RESULTS: Our analyses included data from 52 680 children. We observed weak associations between cell phone use and hearing loss at age 7, with odds ratios and 95% confidence intervals from the traditional logistic regression, MSM and DRE models being 1.21 [95% confidence interval [CI] 0.99, 1.46], 1.23 [95% CI 1.01, 1.49] and 1.22 [95% CI 1.00, 1.49], respectively. CONCLUSIONS: Our findings could have been affected by various biases and are not sufficient to conclude that cell phone exposures have an effect on hearing. This is the first large-scale epidemiologic study to investigate this potentially important association among children, and replication of these findings is needed.

Krause CM, Bjornberg CH, Pesonen M, Hulten A, Liesivuori T, Koivisto M, Revonsuo A, Laine M, Hamalainen H. Mobile phone effects on children's event-related oscillatory EEG during an auditory memory task. *Int J Radiat Biol.* 82(6):443-450, 2006.

Purpose: To assess the effects of electromagnetic fields (EMF) emitted by mobile phones (MP) on the 1 - 20 Hz event-related brain oscillatory EEG (electroencephalogram) responses in children performing an auditory memory task (encoding and recognition). Materials and methods: EEG data were gathered while 15 subjects (age 10 - 14 years) performed an auditory memory task both with and without exposure to a digital 902 MHz MP in counterbalanced order. Results: During memory encoding, the active MP modulated the event-related desynchronization/synchronization (ERD/ERS) responses in the approximately 4 - 8 Hz EEG frequencies. During recognition, the active MP transformed these brain oscillatory responses in the approximately 4 - 8 Hz and approximately 15 Hz frequencies. Conclusions: The current findings suggest that EMF emitted by mobile phones has effects on brain oscillatory responses during cognitive processing in children.

Kamibeppu K, Sugiura H. Impact of the mobile phone on junior high-school students' friendships in the Tokyo metropolitan area. *Cyberpsychol Behav.* 8(2):121-130, 2005.

The proportion of having keitai (Japanese mobile phone) has increased rapidly in young children. To research how junior high school students use their own keitai and to examine the impact of using it on their psychology, especially on their friendship, we recruited 651 students, grade 8, from five public junior high schools in the Tokyo metropolitan area. Each student participant completed a questionnaire that we had created. The response rates were 88.8% (n = 578) for participants. The proportion of having their own keitai was 49.3% (n = 285) and that of not having it was 50.7% (n = 293). We found that they used it much more frequently for e-mail than as a phone.

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Most of them exchanged e-mails between schoolmates, and more than a half of them exchanged e-mails more than 10 times a day. Sociable students estimated that their own keitai was useful for their friendship. But they experienced some insecurity or started staying up late at night engaged in e-mail exchanges, and they thought that they could not live without their own keitai. Our findings suggest that keitai having an e-mail function play a big part in the junior high-school students' daily life, and its impact on students' friendships, psychology, or health should be discussed among students to prevent keitai addiction.

Soderqvist F, Carlberg M, Hardell L. Use of wireless telephones and self-reported health symptoms: a population-based study among Swedish adolescents aged 15-19 years. Environ Health. 7(1):18, 2008.

ABSTRACT: BACKGROUND: Despite the last years of rapid increase in use of wireless phones little data on the use of these devices has been systematically assessed among young persons. The aim of this descriptive cross-sectional study was to assess use of wireless phones and to study such use in relation to explanatory factors and self-reported health symptoms. METHODS: A postal questionnaire comprising 8 pages of 27 questions with 75 items in total was sent to 2000 Swedish adolescents aged 15-19 years and selected from the population registry using a stratified sampling scheme. RESULTS: The questionnaire was answered by 63.5 % of the study subjects. Most participants reported access to a mobile phone (99.6%) and use increased with age; 55.6% of the 15-year-olds and 82.2% of the 19-year-olds were regular users. Girls generally reported more frequent use than boys. Use of wired hands-free equipment 'anytime' was reported by 17.4%. Cordless phones were used by 81.9%, and 67.3% were regular users. Watching TV increased the odds ratio for use of wireless phones, adjusted for age and gender. Some of the most frequently reported health complaints were tiredness, stress, headache, anxiety, concentration difficulties and sleep disturbances. Regular users of wireless phones had health symptoms more often and reported poorer perceived health than less frequent users. CONCLUSIONS: Almost all adolescence in this study used a wireless phone, girls more than boys. The most frequent use was seen among the older adolescents and those who watched TV extensively. The study further showed that perceived health and certain health symptoms seemed to be related to the use of wireless phones. However, this part of the investigation was explorative and should therefore be interpreted with caution since bias and chance findings due to multiple testing might have influenced the results. Potentially this study will stimulate more sophisticated studies that may also investigate directions of associations and whether, or to what degree, any mediation factors are involved.

Schuz J. Mobile phone use and exposures in children. Bioelectromagnetics. Suppl 7:S45-50,2005.

The main difference concerning the use of mobile phones (MPs) between today's children and adults is the longer lifetime exposure of children when they grow older, due to starting to use MPs at an early age. Additionally, recent trends lead to a higher frequency of use among children, including higher popularity of MPs and features

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specifically designed to attract children. The prevalence of MP users is already very high and reaches >90% among adolescents in some countries. In a German study, 6% of 9-10 years old children used a MP for making calls daily; 35% owned their own MP. For children, MPs are dominant sources of radio wave exposures and relevant sources of extremely low frequency magnetic fields. For very young children, however, environmental exposure to radio waves may be of concern. In conclusion, children will have a much higher cumulative exposure to radio waves than today's adults when they are at the same age. Radio wave exposure of children may be estimated more easily, because the variety of exposure sources is smaller than for adults. As long as adverse health effects cannot be ruled out with some degree of certainty, it appears to be appropriate to instruct children and their parents about a prudent use of MPs.

Heinrich S, Thomas S, Heumann C, von Kries R, Radon K. Association between exposure to radiofrequency electromagnetic fields assessed by dosimetry and acute symptoms in children and adolescents: a population based cross-sectional study. *Environ Health*. 9:75, 2010.

BACKGROUND: The increase in numbers of mobile phone users was accompanied by some concern that exposure to radiofrequency electromagnetic fields (RF EMF) might adversely affect acute health especially in children and adolescents. The authors investigated this potential association using personal dosimeters. METHODS: A 24-hour exposure profile of 1484 children and 1508 adolescents was generated in a population-based cross-sectional study in Germany between 2006 and 2008 (participation 52%). Personal interview data on socio-demographic characteristics, self-reported exposure and potential confounders were collected. Acute symptoms were assessed twice during the study day using a symptom diary. RESULTS: Only few of the large number of investigated associations were found to be statistically significant. At noon, adolescents with a measured exposure in the highest quartile during morning hours reported a statistically significant higher intensity of headache (Odd Ratio: 1.50; 95% confidence interval: 1.03, 2.19). At bedtime, adolescents with a measured exposure in the highest quartile during afternoon hours reported a statistically significant higher intensity of irritation in the evening (4th quartile 1.79; 1.23, 2.61), while children reported a statistically significant higher intensity of concentration problems (4th quartile 1.55; 1.02, 2.33). CONCLUSIONS: *We observed few statistically significant results which are not consistent over the two time points.* Furthermore, when the 10% of the participants with the highest exposure are taken into consideration the significant results of the main analysis could not be confirmed. Based on the pattern of these results, we assume that the few observed significant associations are not causal but rather occurred by chance.

Zheng F, Gao P, He M, Li M, Wang C, Zeng Q, Zhou Z, Yu Z, Zhang L. Association between mobile phone use and inattention in 7102 Chinese adolescents: a population-based cross-sectional study. *BMC Public Health*. 2014 Oct 1;14(1):1022. [Epub ahead of print]

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BACKGROUND: The dramatic growth of **mobile phone** (MP) use among young people has increased interest in its possible health hazards in this age group. The aim of this cross-sectional study was to investigate the association between MP use and inattention in adolescents. **METHODS:** A total of 7720 middle school students were involved in this cross-sectional study. Inattention was assessed as defined for the Attention Deficit component of Attention deficit/Hyperactivity disorder (ADHD) by the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev. [DSM-IV-TR]). The demographic characteristics and information on MP use were included in the questionnaire. Chi-square tests and logistic regression models were used to analyze the data. **RESULTS:** In total, 7102 (91.99%) valid questionnaires were obtained. After adjusted for confounders, inattention in adolescents was significantly associated with MP ownership, the time spent on entertainment on MP per day, the position of the MP during the day and the mode of the MP at night. The strongest association between inattention and the time spent on the MP was among students who spent more than 60 minutes per day playing on their MP. **CONCLUSIONS:** Our study shows some associations between MP use and inattention in Chinese adolescents. Decreasing MP usage to less than 60 minutes per day may help adolescents to stay focused and centered.

Chiu CT, Chang YH, Chen CC, Ko MC, Li CY. Mobile phone use and health symptoms in children. J Formos Med Assoc. 2014 Aug 9. pii: S0929-6646(14)00207-1. doi: 10.1016/j.jfma.2014.07.002. [Epub ahead of print]

BACKGROUND/PURPOSE: To investigate the mobile phone (MP) use for talking in relation to health symptoms among 2042 children aged 11-15 years in Taiwan. **METHODS:** A nationwide, cross-sectional study, using the computer assisted telephone interview (CATI) technique, was conducted in 2009 to collect information on children's utilization of MPs and the perceived health symptoms reported by their parents. **RESULTS:** The overall prevalence of MP use in the past month was estimated at 63.2% [95% confidence interval (CI) = 61.1-65.3%]. MP use was associated with a significantly increased adjusted odds ratio (AOR) for headaches and migraine (1.42, 95% CI = 1.12-1.81) and skin itches (1.84, 95% CI = 1.47-2.29). Children who regularly used MPs were also considered to have a health status worse than it was 1 year ago ($\beta = 0.27$, 95% CI = 0.17-0.37). **CONCLUSION:** Although the cross-sectional design precludes the causal inference for the observed association, our study tended to suggest a need for more cautious use of MPs in children, because children are expected to experience a longer lifetime exposure to radiofrequency electromagnetic fields (RF-EMF) from MPs.

Peyman A, Rezazadeh AA, Gabriel C. Changes in the dielectric properties of rat tissue as a function of age at microwave frequencies. Phys Med Biol 46(6):1617-1629, 2001. The dielectric properties of ten rat tissues at six different ages were measured at 37 degrees C in the frequency range of 130 MHz to 10 GHz using an open-ended coaxial probe and a computer controlled network analyser. The results show a general decrease of the dielectric properties with age. The trend is more apparent for brain, skull and skin tissues and less noticeable for abdominal tissues. The variation in the dielectric properties with age is due to the changes in the water content and the organic

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composition of tissues. The percentage decrease in the dielectric properties of certain tissues in the 30 to 70 day old rats at cellular phone frequencies have been tabulated. These data provide an important input in the provision of rigorous dosimetry in lifetime-exposure animal experiments. The results provide some insight into possible differences in the assessment of exposure for children and adults.

de Salles AA, Bulla G, Rodriguez CE. Electromagnetic absorption in the head of adults and children due to mobile phone operation close to the head. Electromagn Biol Med. 2006;25(4):349-360, 2006.

The Specific Absorption Rate (SAR) produced by mobile phones in the head of adults and children is simulated using an algorithm based on the Finite Difference Time Domain (FDTD) method. Realistic models of the child and adult head are used. The electromagnetic parameters are fitted to these models. Comparison also are made with the SAR calculated in the children model when using adult human electromagnetic parameters values. Microstrip (or patch) antennas and quarter wavelength monopole antennas are used in the simulations. The frequencies used to feed the antennas are 1850 MHz and 850 MHz. The SAR results are compared with the available international recommendations. It is shown that under similar conditions, the 1g-SAR calculated for children is higher than that for the adults. When using the 10-year old child model, SAR values higher than 60% than those for adults are obtained.

Peyman A, Holden SJ, Watts S, Perrott R, Gabriel C. Dielectric properties of porcine cerebrospinal tissues at microwave frequencies: in vivo, in vitro and systematic variation with age. Phys Med Biol. 52(8):2229-2245, 2007.

The dielectric properties of pig cerebrospinal tissues were measured in vivo and in vitro, in the frequency range of 50 MHz-20 GHz. The total combined measurement uncertainty was calculated at each frequency point and is reported over representative frequency regions. Comparisons were made for each tissue between the two sets of data and with the literature of the past decade. The in vitro study was extended to include tissue from pigs weighing approximately 10, 50 and 250 kg to re-visit the question of the variation of dielectric properties with age. White matter and spinal chord showed significant variation as function of animal age, no age-related variations were recorded for grey matter.

Oxidative Stress

Stopczyk D, Gnitecki W, Buczynski A, Markuszewski L, Buczynski J. Med Pr 53(4):311-314, 2002. [Article in Polish]

The aim of the study was to assess in vitro the effect of electromagnetic field produced by mobile phones on the activity of superoxide dismutase (SOD-1) and the level of malonyldialdehyde (MDA) in human blood platelets. The suspension of blood platelets was exposed to the electromagnetic field with the frequency of 900 MHz for 1, 3, 5, and 7 min. Our studies demonstrated that microwaves produced by mobiles significantly

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depleted SOD-1 activity after 1, 5, and 7 min of exposure and increased after 3 min in comparison with the control test. There was a significant increase in the concentration of MDA after 1, 5, and 7 min and decrease after 3 min of exposure as compared with the control test. On the grounds of our results we conclude that oxidative stress after exposure to microwaves may be the reason for many adverse changes in cells and may cause a number of systemic disturbances in the human body.

Dasdag S, Akdag MZ. The link between radiofrequencies emitted from wireless technologies and oxidative stress. J Chem Neuroanat. 2015 Sep 12. pii: S0891-0618(15)00069-1. doi: 10.1016/j.jchemneu.2015.09.001. [Epub ahead of print]

Wireless communication such as cellular telephones and other types of handheld phones working with frequencies of 900MHz, 1800MHz, 2100MHz, 2450MHz have been increasing rapidly. Therefore, public opinion concern about the potential human health hazards of short and long-term effect of exposure to radiofrequency (RF) radiation. Oxidative stress is a biochemical condition, which is defined by the imbalance between reactive oxygen species (ROS) and the anti-oxidative defense. In this review, we evaluated available in vitro and in vivo studies carried out on the relation between RF emitted from mobile phones and oxidative stress. The results of the studies we reviewed here indicated that mobile phones and similar equipment or radars can be thought as a factor, which cause oxidative stress. Even some of them claimed that oxidative stress originated from radiofrequencies can be resulted with DNA damage. For this reason one of the points to think on is relation between mobile phones and oxidative stress. However, more performance is necessary especially on human exposure studies.

Esmekaya MA, Ozer C, Seyhan N. 900 MHz pulse-modulated radiofrequency radiation induces oxidative stress on heart, lung, testis and liver tissues. Gen Physiol Biophys. 30(1):84-89, 2011.

Oxidative stress may affect many cellular and physiological processes including gene expression, cell growth, and cell death. In the recent study, we aimed to investigate whether 900 MHz pulse-modulated radiofrequency (RF) fields induce oxidative damage on lung, heart and liver tissues. We assessed oxidative damage by investigating lipid peroxidation (malondialdehyde, MDA), nitric oxide (NOx) and glutathione (GSH) levels which are the indicators of tissue toxicity. A total of 30 male Wistar albino rats were used in this study. Rats were divided randomly into three groups; control group (n = 10), sham group (device off, n = 10) and 900 MHz pulsed-modulated RF radiation group (n = 10). The RF rats were exposed to 900 MHz pulsed modulated RF radiation at a specific absorption rate (SAR) level of 1.20 W/kg 20 min/day for three weeks. MDA and NOx levels were increased significantly in liver, lung, testis and heart tissues of the exposed group compared to sham and control groups (p < 0.05). Conversely GSH levels were significantly lower in exposed rat tissues (p < 0.05). No significantly difference was observed between sham and control groups. Results of our study showed that pulse-modulated RF radiation causes oxidative injury in liver, lung, testis and heart tissues mediated by lipid peroxidation, increased level of NOx and suppression of antioxidant

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defense mechanism.

Bodera P, Stankiewicz W, Zawada K, Antkowiak B, Paluch M, Kieliszek J, Kalicki B, Bartosiński A, Wawer I. Changes in antioxidant capacity of blood due to mutual action of electromagnetic field (1800 MHz) and opioid drug (tramadol) in animal model of persistent inflammatory state. Pharmacol Rep. 65(2):421-428, 2013.

Background: The biological effects and health implications of electromagnetic field (EMF) associated with cellular mobile telephones and related wireless systems and devices have become a focus of international scientific interest and world-wide public concern. It has also been proved that EMF influences the production of reactive oxygen species (ROS) in different tissues. Methods: Experiments were performed in healthy rats and in rats with persistent inflammatory state induced by Complete Freund's Adjuvant (CFA) injection, which was given 24 h before EMF exposure and drug application. Rats were injected with CFA or the same volume of paraffin oil into the plantar surface of the left hind paw. Animals were exposed to the far-field range of an antenna at 1800 MHz with the additional modulation which was identical to that generated by mobile phone GSM 1800. Rats were given 15 min exposure, or were sham-exposed with no voltage applied to the field generator in control groups. Immediately before EMF exposure, rats were injected intraperitoneally with tramadol in the 20 mg/kg dose or vehicle in the 1 ml/kg volume. Results: Our study revealed that single EMF exposure in 1800 MHz frequency significantly reduced antioxidant capacity both in healthy animals and those with paw inflammation. A certain synergic mode of action between applied electromagnetic fields and administered tramadol in rats treated with CFA was observed. Conclusions: The aim of the study was to examine the possible, parallel/combined effects of electromagnetic radiation, artificially induced inflammation and a centrally-acting synthetic opioid analgesic drug, tramadol, (used in the treatment of severe pain) on the antioxidant capacity of blood of rats. The antioxidant capacity of blood of healthy rats was higher than that of rats which received only tramadol and were exposed to electromagnetic fields.

Moustafa YM, Moustafa RM, Belacy A, Abou-El-Ela SH, Ali FM. Effects of acute exposure to the radiofrequency fields of cellular phones on plasma lipid peroxide and antioxidase activities in human erythrocytes. J Pharm Biomed Anal 26(4):605-608, 2001.

Radiofrequency fields of cellular phones may affect biological systems by increasing free radicals, which appear mainly to enhance lipid peroxidation, and by changing the antioxidase activities of human blood thus leading to oxidative stress. To test this, we have investigated the effect of acute exposure to radiofrequency fields of commercially available cellular phones on some parameters indicative of oxidative stress in 12 healthy adult male volunteers. Each volunteer put the phone in his pocket in standby position with the keypad facing the body. The parameters measured were lipid peroxide and the activities of superoxide dismutase (SOD), total glutathione peroxidase (GSH-Px) and catalase. The results obtained showed that the plasma level of lipid peroxide was

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significantly increased after 1, 2 and 4 h of exposure to radiofrequency fields of the cellular phone in standby position. Moreover, the activities of SOD and GSH-Px in human erythrocytes showed significant reduction while the activity of catalase in human erythrocytes did not decrease significantly. These results indicate that acute exposure to radiofrequency fields of commercially available cellular phones may modulate the oxidative stress of free radicals by enhancing lipid peroxidation and reducing the activation of SOD and GSH-Px, which are free radical scavengers. Therefore, these results support the interaction of radiofrequency fields of cellular phones with biological systems.

Oral B, Guney M, Ozguner F, Karahan N, Mungan T, Comlekci S, Cesur G. Endometrial Apoptosis Induced by a 900-MHz Mobile Phone: Preventive Effects of Vitamins E and C. Adv Ther. 23(6):957-973, 2006.

Numerous reports have described the effects induced by an electromagnetic field (EMF) in various cellular systems. The purposes of this study were to examine oxidative stress that promotes production of reactive oxygen species induced by a 900-megahertz (MHz) mobile phone and the possible ameliorating effects of vitamins E and C on endometrial tissue against EMF-induced endometrial impairment and apoptosis in rats. Animals were randomly grouped as follows: (1) sham-operated control group (n=8), (2) 900 MHz EMF-exposed group (n=8; 30 min/d for 30 d), and (3) 900 MHz EMF-exposed group, treated with vitamins E and C (n=8; 50 mg/kg intramuscularly and 20 mg/kg body weight intraperitoneally before daily EMF exposure). Malondialdehyde (an index of lipid peroxidation) was used as a marker of oxidative stress-induced endometrial impairment; Bcl-2, Bax, caspase-3, and caspase-8 were assessed immunohistochemically. In this study, increased malondialdehyde levels in endometrial tissue and apoptosis illustrated the role of the oxidative mechanism induced by exposure to a 900-MHz mobile phone-like device and vitamins E and C; via free radical scavenging and antioxidant properties, oxidative tissue injury and apoptosis were ameliorated in rat endometrium. In conclusion, exposure to 900-MHz radiation emitted by mobile phones may cause endometrial apoptosis and oxidative stress, but treatment with vitamins E and C can diminish these changes and may have a beneficial effect in preventing endometrial changes in rats.

Marjanovic AM, Pavicic I, Trosic I, Cell oxidation–reduction imbalance after modulated radiofrequency radiation. Electromagnetic Biology and Medicine. Posted online on August 13, 2014.

Aim of this study was to evaluate an influence of modulated radiofrequency field (RF) of 1800 MHz, strength of 30 V/m on oxidation–reduction processes within the cell. The assigned RF field was generated within Gigahertz Transversal Electromagnetic Mode cell equipped by signal generator, modulator, and amplifier. Cell line V79, was irradiated for 10, 30, and 60 min, specific absorption rate was calculated to be 1.6 W/kg. Cell metabolic activity and viability was determined by MTT assay. In order to define total protein content, colorimetric method was used. Concentration of oxidised proteins was evaluated by enzyme-linked immunosorbent assay. Reactive oxygen species (ROS)

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marked with fluorescent probe 2',7'-dichlorofluorescein diacetate were measured by means of plate reader device. In comparison with control cell samples, metabolic activity and total protein content in exposed cells did not differ significantly. Concentrations of carbonyl derivatives, a product of protein oxidation, insignificantly but continuously increase with duration of exposure. In exposed samples, ROS level significantly ($p < 0.05$) increased after 10 min of exposure. Decrease in ROS level was observed after 30-min treatment indicating antioxidant defence mechanism activation. In conclusion, under the given laboratory conditions, modulated RF radiation might cause impairment in cell oxidation–reduction equilibrium within the growing cells.

Kahya MC, Nazıroğlu M, Ciğ B. Selenium Reduces Mobile Phone (900 MHz)-Induced Oxidative Stress, Mitochondrial Function, and Apoptosis in Breast Cancer Cells. *Biol Trace Elem Res.* 2014 Jun 27. [Epub ahead of print]

Exposure to mobile phone-induced electromagnetic radiation (EMR) may affect biological systems by increasing free oxygen radicals, apoptosis, and mitochondrial depolarization levels although selenium may modulate the values in cancer. The present study was designed to investigate the effects of 900 MHz radiation on the antioxidant redox system, apoptosis, and mitochondrial depolarization levels in MDA-MB-231 breast cancer cell line. Cultures of the cancer cells were divided into four main groups as controls, selenium, EMR, and EMR + selenium. In EMR groups, the cells were exposed to 900 MHz EMR for 1 h (SAR value of the EMR was 0.36 ± 0.02 W/kg). In selenium groups, the cells were also incubated with sodium selenite for 1 h before EMR exposure. Then, the following values were analyzed: (a) cell viability, (b) intracellular ROS production, (c) mitochondrial membrane depolarization, (d) cell apoptosis, and (e) caspase-3 and caspase-9 values. Selenium suppressed EMR-induced oxidative cell damage and cell viability (MTT) through a reduction of oxidative stress and restoring mitochondrial membrane potential. Additionally, selenium indicated anti-apoptotic effects, as demonstrated by plate reader analyses of apoptosis levels and caspase-3 and caspase-9 values. In conclusion, 900 MHz EMR appears to induce apoptosis effects through oxidative stress and mitochondrial depolarization although incubation of selenium seems to counteract the effects on apoptosis and oxidative stress.

Elhag MA, Nabil GM, Attia AM. Effects of electromagnetic field produced by mobile phones on the oxidant and antioxidant status of rats. *Pak J Biol Sci.* 10(23):4271-4274, 2007.

This study was designed to investigate the effect of EMR produced by GSM Mobile Phones (MP) on the oxidant and antioxidant status in rats. Rats were divided into three groups: (1) controls, (2) rats exposed to a fractionated dose of EMR (15 min day⁻¹) for four days (EMR-F) and (3) rats exposed to an acute dose of EMR (EMR-A). A net drop in the plasma concentration of vitamin C (-47 and -59.8%) was observed in EMR-F and EMR-A groups, respectively, when compared to controls. While, a significant decrease in the levels of lipophilic antioxidant vitamins: vitamin E (-33 and -65.8%), vitamin A (-44.4 and -46.8%) was observed in EMR-F and EMR-A groups, respectively, when compared to controls. A net drop in plasma level of reduced glutathione (GSH) (-19.8 and -35.3%) was

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observed in EMR-F and EMR-A groups, respectively. EMR exposure of rats produced a significant decrease in catalase (CAT) and superoxide dismutase (SOD) activities, with the values of these activities for EMR-A group is significantly lower than those of EMR-F. These results indicate that the effects of acute doses of EMR produced by mobile phones on the rat's antioxidant status is significantly higher than those of fractionated doses of the same type of radiation. On the basis of present results, it can be concluded that exposure to acute doses of EMR produced by mobile phones is more hazardous than that produced by fractionated doses of the same type of radiation.

Fattahi-Asl J, Baradaran-Ghahfarokhi M, Karbalaee M, Baradaran-Ghahfarokhi M, Baradaran-Ghahfarokhi HR. Effects of radiofrequency radiation on human ferritin: an in vitro enzymun assay. *J Med Signals Sens.* 2(4):235-340, 2012.

Ferritin is a macromolecule and is responsible for the long term iron storage function in human serum and plasma. Recent studies have highlighted the role of cell phone exposure on central nervous system, immune function and reproduction. The aim of this study was to investigate whether the human serum ferritin level could be interfered by the exposure to the 900 MHz GSM cell phones. Fifty human serum wells from 25 normal healthy donors were labeled with ruthenium to form a sandwich complex based on an immunoassay technique. All of them were placed into two batches, and the well heads in the first batch were exposed to 900 MHz exposure emitted from a speech mode cell phone (Nokia, Model 1202, India) for 30 min. Unexposed batch was served as the control sample under identical conditions and was compared with the exposed one in quantitative determination of ferritin using the Wilcoxon test with criterion level of $P = 0.050$. Human serum wells in the exposed batch showed a significant decrease in serum ferritin relative to the control batch ($P = 0.029$). The average \pm SD ferritin level in the exposed batch was $84.94 \pm 1.04 \mu\text{g/L}$ while it was $87.25 \pm 0.83 \mu\text{g/L}$ for the unexposed batch. Radiofrequency electromagnetic waves emitted from cell phones may lead to oxidative stress and rapid diffusion of the human ferritin level in an in vitro enzymun assay. Also, the enzyme activity can be affected. Effects of exposure from mobile phones must be considered further.

Irmak MK, Fadillioglu E, Gulec M, Erdogan H, Yagmurca M, Akyol O. Effects of electromagnetic radiation from a cellular telephone on the oxidant and antioxidant levels in rabbits. *Cell Biochem Funct.* 20(4):279-283, 2002.

The number of reports on the effects induced by electromagnetic radiation (EMR) in various cellular systems is still increasing. Until now no satisfactory mechanism has been proposed to explain the biological effects of this radiation. Oxygen free radicals may play a role in mechanisms of adverse effects of EMR. This study was undertaken to investigate the influence of electromagnetic radiation of a digital GSM mobile telephone (900 MHz) on oxidant and antioxidant levels in rabbits. Adenosine deaminase, xanthine oxidase, catalase, myeloperoxidase, superoxide dismutase (SOD) and glutathione peroxidase activities as well as nitric oxide (NO) and malondialdehyde levels were measured in sera and brains of EMR-exposed and sham-exposed rabbits. Serum SOD activity increased, and serum NO levels decreased in EMR-exposed animals compared to

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the sham group. Other parameters were not changed in either group. This finding may indicate the possible role of increased oxidative stress in the pathophysiology of adverse effect of EMR. Decreased NO levels may also suggest a probable role of NO in the adverse effect.

Guler G, Tomruk A, Ozgur E, Seyhan N. The effect of radiofrequency radiation on DNA and lipid damage in non-pregnant and pregnant rabbits and their newborns. Gen Physiol Biophys. 29(1):59-66, 2010.

The concerns of people on possible adverse health effects of radiofrequency radiation (RFR) generated from mobile phones as well as their supporting transmitters (base stations) have increased markedly. RFR effect on oversensitive people, such as pregnant women and their developing fetuses, and older people is another source of concern that should be considered. In this study, oxidative DNA damage and lipid peroxidation levels in the brain tissue of pregnant and non-pregnant New Zealand White rabbits and their newborns exposed to RFR were investigated. Thirteen-month-old rabbits were studied in four groups as non-pregnant-control, non-pregnant-RFR exposed, pregnant-control and pregnant-RFR exposed. They were exposed to RFR (1800 MHz GSM; 14 V/m as reference level) for 15 min/day during 7 days. Malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels were analyzed. MDA and 8-OHdG levels of non-pregnant and pregnant-RFR exposed animals significantly increased with respect to controls ($p < 0.001$, Mann-Whitney test). No difference was found in the newborns ($p > 0.05$, Mann-Whitney). There exist very few experimental studies on the effects of RFR during pregnancy. It would be beneficial to increase the number of these studies in order to establish international standards for the protection of pregnant women from RFR.

Burlaka A, Tsybulin O, Sidorik E, Lukin S, Polishuk V, Tsehmistrenko S, Yakymenko I. Overproduction of free radical species in embryonal cells exposed to low intensity radiofrequency radiation. Exp Oncol. 2013 Sep;35(3):219-225.

Aim: Long-term exposure of humans to low intensity radiofrequency electromagnetic radiation (RF-EMR) leads to a statistically significant increase in tumor incidence. Mechanisms of such the effects are unclear, but features of oxidative stress in living cells under RF-EMR exposure were previously reported. Our study aims to assess a production of initial free radical species, which lead to oxidative stress in the cell. Materials and Methods: Embryos of Japanese quails were exposed in ovo to extremely low intensity RF-EMR of GSM 900 MHz ($0.25 \mu\text{W}/\text{cm}^2$) during 158-360 h discontinuously (48 c - ON, 12 c - OFF) before and in the initial stages of development. The levels of superoxide (O_2^-), nitrogen oxide ($\text{NO}\cdot$), thiobarbituric acid reactive substances (TBARS), 8-oxo-2'-deoxyguanosine (8-oxo-dG) and antioxidant enzymes' activities were assessed in cells/tissues of 38-h, 5- and 10-day RF-EMR exposed and unexposed embryos. Results: The exposure resulted in a significant persistent overproduction of superoxide and nitrogen oxide in embryo cells during all period of analyses. As a result, significantly increased levels of TBARS and 8-oxo-dG followed by significantly decreased levels of superoxide dismutase and catalase activities were developed in the exposed embryo

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cells. Conclusion: Exposure of developing quail embryos to extremely low intensity RF-EMR of GSM 900 MHz during at least one hundred and fifty-eight hours leads to a significant overproduction of free radicals/reactive oxygen species and oxidative damage of DNA in embryo cells. These oxidative changes may lead to pathologies up to oncogenic transformation of cells.

Tkalec M, Malarić K, Pevalek-Kozlina B. Exposure to radiofrequency radiation induces oxidative stress in duckweed *Lemna minor* L. *Sci Total Environ.* 388(1-3):78-89, 2007.

Widespread use of radiofrequency radiation emitting devices increased the exposure to electromagnetic fields (EMFs) from 300 MHz to 300 GHz. Various biological effects of exposure to these fields have been documented so far, but very little work has been carried out on plants. The aim of the present work was to investigate the physiological responses of the plant *Lemna minor* after exposure to radiofrequency EMFs, and in particular, to clarify the possible role of oxidative stress in the observed effects. Duckweed was exposed for 2 h to EMFs of 400 and 900 MHz at field strengths of 10, 23, 41 and 120 V m⁻¹. The effect of a longer exposure time (4 h) and modulation was also investigated. After exposure, parameters of oxidative stress, such as lipid peroxidation, H₂O₂ content, activities and isoenzyme pattern of antioxidative enzymes as well as HSP70 expression were evaluated. At 400 MHz, lipid peroxidation and H₂O₂ content were significantly enhanced in duckweed exposed to EMFs of 23 and 120 V m⁻¹ while other exposure treatments did not have an effect. Compared to the controls, the activities of antioxidative enzymes showed different behaviour: catalase (CAT) activity increased after most exposure treatments while pyrogallol (PPX) and ascorbate peroxidase (APX) activities were not changed. Exceptions were reduced PPX and APX activity after longer exposure at 23 V m⁻¹ and increased PPX activity after exposures at 10 and 120 V m⁻¹. By contrast, at 900 MHz almost all exposure treatments significantly increased level of lipid peroxidation and H₂O₂ content but mostly decreased PPX activity and did not affect CAT activity. Exceptions were exposures to a modulated field and to the field of 120 V m⁻¹ which increased PPX and CAT activity. At this frequency APX activity was significantly decreased after exposure at 10 V m⁻¹ and longer exposure at 23 V m⁻¹ but it increased after a shorter exposure at 23 V m⁻¹. At both frequencies no differences in isoenzyme patterns of antioxidative enzymes or HSP70 level were found between control and exposed plants. Our results showed that non-thermal exposure to investigated radiofrequency fields induced oxidative stress in duckweed as well as unspecific stress responses, especially of antioxidative enzymes. However, the observed effects markedly depended on the field frequencies applied as well as on other exposure parameters (strength, modulation and exposure time). Enhanced lipid peroxidation and H₂O₂ content accompanied by diminished antioxidative enzymes activity caused by exposure to investigated EMFs, especially at 900 MHz, indicate that oxidative stress could partly be due to changed activities of antioxidative enzymes.

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Palumbo R, Brescia F, Capasso D, Sannino A, Sarti M, Capri M, Grassilli E, Scarfi MR.

Exposure to 900 MHz radiofrequency radiation induces caspase 3 activation in proliferating human lymphocytes. *Radiat Res.* 170(3):327-334, 2008.

In this study, the induction of apoptosis after exposure to 900 MHz radiofrequency radiation (GSM signal) was investigated by assessing caspase 3 activation in exponentially growing Jurkat cells and in quiescent and proliferating human peripheral blood lymphocytes (PBLs). The exposure was carried out at an average specific absorption rate of 1.35 W/kg in a dual wire patch cell exposure system where the temperature of cell cultures was accurately controlled. After 1 h exposure to the radiofrequency field, a slight but statistically significant increase in caspase 3 activity, measured 6 h after exposure, was observed in Jurkat cells (32.4%) and in proliferating human PBLs (22%). In contrast, no effect was detected in quiescent human PBLs. In the same experimental conditions, apoptosis was also evaluated in Jurkat cells by Western blot analysis and in both cell types by flow cytometry. To evaluate late effects due to caspase 3 activity, flow cytometry was also employed to assess apoptosis and viability 24 h after radiofrequency-radiation exposure in both cell types. Neither the former nor the latter was affected. Since in recent years it has been reported that caspases are also involved in processes other than apoptosis, additional cell cycle studies were carried out on proliferating T cells exposed to radiofrequency radiation; however, we found no differences between sham-exposed and exposed cultures. Further studies are warranted to investigate the biological significance of our findings of a dose-response increase in caspase 3 activity after exposure to radiofrequency radiation.

Obukhan KI, [The effect of ultrahigh-frequency radiation on adaptation thresholds and the damages to blood system cells]. *Lik Sprava* (7):71-73, 1998. [Article in Ukrainian]

Cytologic investigations designed to study bone marrow, peripheral blood, spleen, and thymus of albino rats irradiated by an electromagnetic field, 2375, 2450, and 3000 MEGS, revealed structural and functional changes in populations of megakaryocytes, immunocompetent cells as well as of undifferentiated cells, and of other types of cells that are dependent on the intensity of irradiation and permit establishing the probability-threshold levels of exposure taking account of reactions of perception and physiologic adaptation together with compensatory and regenerative processes and the injury sustained. It is shown that changes in bone marrow cells differentiation and reproduction rather than integral shifts in the peripheral blood that acquire the utmost significance. Subjected to a particular scrutiny in the paper are blast cells, which cells' repopulation was noted to be getting increased in low-intensity exposure as were disturbances in their mitosis pattern.

Nylund R, Leszczynski D. Mobile phone radiation causes changes in gene and protein

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expression in human endothelial cell lines and the response seems to be genome- and proteome-dependent. *Proteomics*.6(17):4769-4780, 2006.

We have examined in vitro cell response to mobile phone radiation (900 MHz GSM signal) using two variants of human endothelial cell line: EA.hy926 and EA.hy926v1. Gene expression changes were examined in three experiments using cDNA Expression Arrays and protein expression changes were examined in ten experiments using 2-DE and PDQuest software. Obtained results show that gene and protein expression were altered, in both examined cell lines, in response to one hour mobile phone radiation exposure at an average specific absorption rate of 2.8 W/kg. However, the same genes and proteins were differently affected by the exposure in each of the cell lines. This suggests that the cell response to mobile phone radiation might be genome- and proteome-dependent. Therefore, it is likely that different types of cells and from different species might respond differently to mobile phone radiation or might have different sensitivity to this weak stimulus. Our findings might also explain, at least in part, the origin of discrepancies in replication studies between different laboratories.

Zhijian C, Xiaoxue L, Wei Z, Yezhen L, Jianlin L, Deqiang L, Shijie C, Lifen J, Jiliang H. Studying the protein expression in human B lymphoblastoid cells exposed to 1.8-GHz (GSM) radiofrequency radiation (RFR) with protein microarray. *Biochem Biophys Res Commun*. 433(1):36-39, 2013.

In the present study, the protein microarray was used to investigate the protein expression in human B-cell lymphoblastoid cells intermittently exposed to 1.8-GHz GSM radiofrequency radiation (RFR) at the specific absorption rate (SAR) of 2.0W/kg for 24h. The differential expression of 27 proteins was found, which were related to DNA damage repair, apoptosis, oncogenesis, cell cycle and proliferation (ratio >1.5-fold, P<0.05). The results validated with Western blot assay indicated that the expression of RPA32 was significantly down-regulated (P<0.05) while the expression of p73 was significantly up-regulated in RFR exposure group (P<0.05). Because of the crucial roles of those proteins in DNA repair and cell apoptosis, the results of present investigation may explain the biological effects of RFR on DNA damage/repair and cell apoptosis.

Yadav AS, Sharma MK. Increased frequency of micronucleated exfoliated cells among humans exposed in vivo to mobile telephone radiations. *Mutat Res*. 650(2):175-180, 2008.

The health concerns have been raised following the enormous increase in the use of wireless mobile telephones throughout the world. This investigation had been taken, with the motive to find out whether mobile phone radiations cause any in vivo effects on the frequency of micronucleated exfoliated cells in the exposed subjects. A total of 109 subjects including 85 regular mobile phone users (exposed) and 24 non-users (controls) had participated in this study. Exfoliated cells were obtained by swabbing the buccal-mucosa from exposed as well as sex-age-matched controls. One thousand exfoliated cells were screened from each individual for nuclear anomalies including micronuclei (MN), karyolysis (KL), karyorrhexis (KH), broken egg (BE) and binucleated (BN) cells. The average daily duration of exposure to mobile phone radiations is

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61.26min with an overall average duration of exposure in term of years is 2.35 years in exposed subjects along with the 9.84 ± 0.745 micronucleated cells (MNCs) and 10.72 ± 0.889 total micronuclei (TMN) as compared to zero duration of exposure along with average 3.75 ± 0.774 MNC and 4.00 ± 0.808 TMN in controls. The means are significantly different in case of MNC and TMN at 0.01% level of significance. The mean of KL in controls is 13.17 ± 2.750 and in exposed subjects is 13.06 ± 1.793 . The value of means of KH in exposed subjects (1.84 ± 0.432) is slightly higher than in controls (1.42 ± 0.737). Mean frequency of broken egg is found to be more in exposed subjects (0.65 ± 0.276) as compared to controls (0.50 ± 0.217). Frequency of presence of more than one nucleus in a cell (binucleated) is also higher in exposed (2.72 ± 0.374) in comparison to controls (0.67 ± 0.231). Although there is a slight increase in mean frequency of KH, BE and BN in exposed subjects but the difference is not found statistically significant. Correlation between 0-1, 1-2, 2-3 and 3-4 years of exposure and the frequency of MNC and TMN has been calculated and found to be positively correlated.

Nylund R, Leszczynski D. Proteomics analysis of human endothelial cell line EA.hy926 after exposure to GSM 900 radiation. Proteomics 4:1359-1365, 2004.

The human endothelial cell line EA.hy926 was exposed to mobile phone radiation and the effect on protein expression was examined using two-dimensional electrophoresis (2-DE). Up to 38 various proteins have statistically significantly altered their expression levels following the irradiation. Four proteins were identified with matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS). Two of the affected proteins were determined to be isoforms of cytoskeletal vimentin. This finding supports our earlier presented working hypothesis which indicated that the mobile phone radiation might affect the cytoskeleton and might have an effect on the physiological functions that are regulated by the cytoskeleton.

Munoz S, Sebastian JL, Sancho M, Miranda JM. Transmembrane voltage induced on altered erythrocyte shapes exposed to RF fields. Bioelectromagnetics. 25(8):631-633, 2004.

In this article, the transmembrane voltage induced on erythrocyte, codocyte, ovalocyte and spherocyte cell models exposed to a linearly polarised electromagnetic plane wave of frequency 1800 MHz is calculated. For this purpose, a finite element (FE) numerical technique with adaptive meshing is used. The results show that the value of the induced voltage on the original erythrocyte shape is higher than the one observed on the rest of the altered cell geometries studied. The erythrocyte shape and the membrane electric permittivity are shown to play a fundamental role on the values of the induced transmembrane voltage.

Moiescu MG, Leveque P, Verjus MA, Kovacs E, Mir LM. 900 MHz modulated electromagnetic fields accelerate the clathrin-mediated endocytosis pathway. Bioelectromagnetics30(3):222-230,2009.

We report new data regarding the molecular mechanisms of GSM-induced increase of

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cell endocytosis rate. Even though endocytosis represents an important physical and biological event for cell physiology, studies on modulated electromagnetic fields (EMF) effects on this process are scarce. In a previous article, we showed that fluid phase endocytosis rate increases when cultured cells are exposed to 900 MHz EMF similar to mobile phones' modulated GSM signals (217 Hz repetition frequency, 576 micro pulse width) and to electric pulses similar to the GSM electrical component. Trying to distinguish the mechanisms sustaining this endocytosis stimulation, we exposed murine melanoma cells to Lucifer Yellow (LY) or to GSM-EMF/electric pulses in the presence of drugs inhibiting the clathrin- or the caveolin-dependent endocytosis. Experiments were performed at a specific absorption rate (SAR) of 3.2 W/kg in a wire patch cell under homogeneously distributed EMF field and controlled temperature (in the range of 28.5-29.5 degrees C). Thus, the observed increase in LY uptake was not a thermal effect. Chlorpromazine and ethanol, but not Filipin, inhibited this increase. Therefore, the clathrin-dependent endocytosis is stimulated by the GSM-EMF, suggesting that the cellular mechanism affected by the modulated EMF involves vesicles that detach from the cell membrane, mainly clathrin-coated vesicles.

Velizarov, S, Raskmark, P, Kwee, S, The effects of radiofrequency fields on cell proliferation are non-thermal. *Bioelectrochem Bioenerg* 48(1):177-180, 1999.

The number of reports on the effects induced by radiofrequency (RF) electromagnetic fields and microwave (MW) radiation in various cellular systems is still increasing. Until now no satisfactory mechanism has been proposed to explain the biological effects of these fields. One of the current theories is that heat generation by RF/MW is the cause, in spite of the fact that a great number of studies under isothermal conditions have reported significant cellular changes after exposure to RF/MW. Therefore, this study was undertaken to investigate which effect MW radiation from these fields in combination with a significant change of temperature could have on cell proliferation. The experiments were performed on the same cell line, and with the same exposure system as in a previous work [S. Kwee, P. Raskmark, Changes in cell proliferation due to environmental non-ionizing radiation: 2. Microwave radiation, *Bioelectrochem. Bioenerg.*, 44 (1998), pp. 251-255]. The field was generated by signal simulation of the Global System for Mobile communications (GSM) of 960 MHz. Cell cultures, growing in microtiter plates, were exposed in a specially constructed chamber, a Transverse Electromagnetic (TEM) cell. The Specific Absorption Rate (SAR) value for each cell well was calculated for this exposure system. However, in this study the cells were exposed to the field at a higher or lower temperature than the temperature in the field-free incubator i.e., the temperature in the TEM cell was either 39 or 35 +/- 0.1 degrees C. The corresponding sham experiments were performed under exactly the same experimental conditions. The results showed that there was a significant change in cell proliferation in the exposed cells in comparison to the non-exposed (control) cells at both temperatures. On the other hand, no significant change in proliferation rate was found in the sham-exposed cells at both temperatures. This shows that biological effects due to RF/MW cannot be attributed only to a change of temperature. Since the RF/MW induced changes were of the same order of magnitude at both temperatures and also

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comparable to our previous results under isothermal conditions at 37 degrees C, cellular stress caused by electromagnetic fields could initiate the changes in cell cycle reaction rates. It is widely accepted that certain classes of heat-shock proteins are involved in these stress reactions.

Valbonesi P, Franzellitti S, Bersani F, Contin A, Fabbri E. Effects of the exposure to intermittent 1.8 GHz radio frequency electromagnetic fields on HSP70 expression and MAPK signaling pathways in PC12 cells. Int J Radiat Biol. 2014 Feb 11. [Epub ahead of print]

Purpose: We previously reported effects on heat shock protein 70 (HSP70) mRNA expression, a cytoprotective protein induced under stressful condition, in human trophoblast cells exposed to amplitude-modulated Global System for Mobile Communication (GSM) signals. In the present work the same experimental conditions were applied to the rat PC12 cells, in order to assess the stress responses mediated by HSP70 and by the Mitogen Activated Protein Kinases (MAPK) in neuronal-like cells, an interesting model to study possible effects of mobile phone frequencies exposure. Materials and methods: HSP70 gene expression level was evaluated by reverse transcriptase polymerase chain reaction, HSP70 protein expression and MAPK phosphorylation were assessed by Western blotting. PC12 cells were exposed for 4, 16 or 24 h to 1.8 GHz continuous wave signal (CW, carrier frequency without modulation) or to two different GSM modulation schemes, GSM-217Hz and GSM-Talk (which generates temporal changes between two different GSM signals, active during talking or listening phases respectively, thus simulating a typical conversation). Specific adsorption rate (SAR) was 2 W/kg. Results: After PC12 cells exposure to the GSM-217Hz signal for 16 or 24 h, HSP70 transcription significantly increased, whereas no effect was observed in cells exposed to the CW or GSM-Talk signals. HSP70 protein expression and three different MAPK signaling pathways were not affected by the exposure to any of the three different 1.8 GHz signals. Conclusion: The positive effect on HSP70 mRNA expression, observed only in cells exposed to the GSM-217Hz signal, is a repeatable response previously reported in human trophoblast cells and now confirmed in PC12 cells. Further investigations towards a possible role of 1.8 GHz signal modulation are therefore advisable.

Xu S, Chen G, Chen C, Sun C, Zhang D, Murbach M, Kuster N, Zeng Q, Xu Z. Cell Type-Dependent Induction of DNA Damage by 1800 MHz Radiofrequency Electromagnetic Fields Does Not Result in Significant Cellular Dysfunctions. PLoS One. 2013;8(1):e54906.

BACKGROUND: Although IARC clarifies radiofrequency electromagnetic fields (RF-EMF) as possible human carcinogen, the debate on its health impact continues due to the inconsistent results. Genotoxic effect has been considered as a golden standard to determine if an environmental factor is a carcinogen, but the currently available data for RF-EMF remain controversial. As an environmental stimulus, the effect of RF-EMF on cellular DNA may be subtle. Therefore, more sensitive method and systematic research strategy are warranted to evaluate its genotoxicity. **OBJECTIVES:** To determine whether

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RF-EMF does induce DNA damage and if the effect is cell-type dependent by adopting a more sensitive method γ H2AX foci formation; and to investigate the biological consequences if RF-EMF does increase γ H2AX foci formation. **METHODS:** Six different types of cells were intermittently exposed to GSM 1800 MHz RF-EMF at a specific absorption rate of 3.0 W/kg for 1 h or 24 h, then subjected to immunostaining with anti- γ H2AX antibody. The biological consequences in γ H2AX-elevated cell type were further explored with comet and TUNEL assays, flow cytometry, and cell growth assay.

RESULTS: Exposure to RF-EMF for 24 h significantly induced γ H2AX foci formation in Chinese hamster lung cells and Human skin fibroblasts (HSFs), but not the other cells. However, RF-EMF-elevated γ H2AX foci formation in HSF cells did not result in detectable DNA fragmentation, sustainable cell cycle arrest, cell proliferation or viability change. RF-EMF exposure slightly but not significantly increased the cellular ROS level.

CONCLUSIONS: RF-EMF induces DNA damage in a cell type-dependent manner, but the elevated γ H2AX foci formation in HSF cells does not result in significant cellular dysfunctions.

Miyakoshi J, Takemasa K, Takashima Y, Ding GR, Hirose H, Koyama S. Effects of exposure to a 1950 MHz radio frequency field on expression of Hsp70 and Hsp27 in human glioma cells. *Bioelectromagnetics*. 26(4):251-257, 2005.

Human glioma MO54 cells were used to investigate whether radio frequency (RF) field exposure could activate stress response genes. Cells were exposed to continuous wave 1950 MHz or sham conditions for up to 2 h. Specific absorption rates (SARs) were 1, 2, and 10 W/kg. For the cell growth experiment, cell numbers were counted at 0-4 days after exposure. Expression of Hsp27 and Hsp70, as well as the level of phosphorylated Hsp27 (78Ser) protein, was determined by Western blotting. It was found that sham exposed and RF exposed cells demonstrated a similar growth pattern up to 4 days after RF field exposure. RF field exposure at both 2 and 10 W/kg did not affect the growth of MO54 cells. In addition, there were no significant differences in protein expression of Hsp27 and Hsp70 between sham exposed and RF exposed cells at a SAR of 1, 2, or 10 W/kg for 1 and 2 h. However, exposure to RF field at a SAR of 10 W/kg for 1 and 2 h decreased the protein level of phosphorylated Hsp27 (78Ser) significantly. Our results suggest that although exposure to a 1950 MHz RF field has no effect on cell proliferation and expression of Hsp 27 and Hsp70, it may inhibit the phosphorylation of Hsp27 at Serine 78 in MO54 cells.

Mazor R, Korenstein-Ilan A, Barbul A, Eshet Y, Shahadi A, Jerby E, Korenstein R. Increased levels of numerical chromosome aberrations after in vitro exposure of human peripheral blood lymphocytes to radiofrequency electromagnetic fields for 72 hours. *Radiat Res* 169(1):28-37, 2008.

We investigated the effects of 72 h in vitro exposure of 10 human lymphocyte samples to radiofrequency electromagnetic fields (800 MHz, continuous wave) on genomic instability. The lymphocytes were exposed in a specially designed waveguide resonator at specific absorption rates (SARs) of 2.9 and 4.1 W/kg in a temperature range of 36-37 degrees C. The induced aneuploidy of chromosomes 1, 10, 11 and 17 was determined by

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interphase FISH using semi-automated image analysis. We observed increased levels of aneuploidy depending on the chromosome studied as well as on the level of exposure. In chromosomes 1 and 10, there was increased aneuploidy at the higher SAR, while for chromosomes 11 and 17, the increases were observed only for the lower SAR. Multisomy (chromosomal gains) appeared to be the primary contributor to the increased aneuploidy. The effect of temperature on the level of aneuploidy was examined over the range of 33.5-40 degrees C for 72 h with no statistically significant difference in the level of aneuploidy compared to 37 degrees C. These findings suggest the possible existence of an athermal effect of RF radiation that causes increased levels of aneuploidy. These results contribute to the assessment of potential health risks after continuous chronic exposure to RF radiation at SARs close to the current levels set by ICNIRP guidelines.

Sefidbakht Y, Moosavi-Movahedi AA, Hosseinkhani S, Khodaghohi F, Torkzadeh-Mahani M, Foolad F, Faraji-Dana R. Effects of 940 MHz EMF on bioluminescence and oxidative response of stable luciferase producing HEK cells. Photochem Photobiol Sci. 2014 Jun 2. [Epub ahead of print]

The effects of mobile phone frequency electromagnetic field (RF-EMF, 940 MHz) on a stable cell line (HEK293T) harbouring the firefly luciferase gene were evaluated. A waveguide exposure system with 1 W input power provided the mean specific absorption rate of $\approx 0.09 \text{ W kg}^{-1}$ in 35 mm Petri dishes. The effects of exposure duration (15, 30, 45, 60 and 90 min) on luciferase activity and oxidative response elements were investigated. Endogenous luciferase activity was reduced after 30 and 45 min of continuous exposure, while after 60 min, the exposed cell lysate showed higher luciferase activity compared with the non-exposed control. Reactive oxygen species (ROS) generation was highest in the 30 min exposed cells as studied by 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) fluorescence. The observed boost in ROS was then followed by a sharp rise in catalase (CAT) and superoxide dismutase (SOD) activity and elevation of glutathione (GSH) during the 45 min exposure. Decrease in lipid peroxidation (malondialdehyde, MDA) was meaningful for the 45 and 60 min exposed cells. Therefore, it appears that an increase in the activity of luciferase after 60 min of continuous exposure could be associated with a decrease in ROS level caused by activation of the oxidative response. This ability in cells to overcome oxidative stress and compensate the luciferase activity could also be responsible for the adaptive response mechanism detected in ionizing radiation studies with RF-EMF pre-treatments.

Remondini D, Nylund R, Reivinen J, Poullietier de Gannes F, Veyret B, Lagroye I, Haro E, Trillo MA, Capri M, Franceschi C, Schlatterer K, Gminski R, Fitzner R, Tauber R, Schuderer J, Kuster N, Leszczynski D, Bersani F, Maercker C. Gene expression changes in human cells after exposure to mobile phone microwaves. Proteomics. 6(17):4745-4754, 2006.

Possible biological effects of mobile phone microwaves were investigated in vitro. In this study, which was part of the 5FP EU project REFLEX (Risk Evaluation of Potential Environmental Hazards From Low-Energy Electromagnetic Field Exposure Using

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Sensitive in vitro Methods), six human cell types, immortalized cell lines and primary cells, were exposed to 900 and 1800 MHz. RNA was isolated from exposed and sham-exposed cells and labeled for transcriptome analysis on whole-genome cDNA arrays. The results were evaluated statistically using bioinformatics techniques and examined for biological relevance with the help of different databases. NB69 neuroblastoma cells, T lymphocytes, and CHME5 microglial cells did not show significant changes in gene expression. In EA.hy926 endothelial cells, U937 lymphoblastoma cells, and HL-60 leukemia cells we found between 12 and 34 up- or down-regulated genes. Analysis of the affected gene families does not point towards a stress response. However, following microwave exposure, some but not all human cells might react with an increase in expression of genes encoding ribosomal proteins and therefore up-regulating the cellular metabolism.

Trosić I, Pavčić I. Disturbance of cell proliferation in response to mobile phone frequency radiation. *Arh Hig Rada Toksikol.* 60(1):109-115, 2009.

The aim of study was to determine the influence of mobile phone frequency radiation on the proliferation, cytoskeleton structure, and mitotic index of V79 cells after 1 h, 2 h, and 3 h of exposure. V79 cells were cultured in standard laboratory conditions and exposed to continuous-wave (CW) RF/MW radiation of 935 MHz, electric field strength of $(8.2 \pm 0.3) \text{ V m}^{-1}$, and specific absorption rate (SAR) of 0.12 W kg^{-1} . To identify proliferation kinetics, the cells were counted for each hour of exposure 24 h, 48 h, 72 h, and 96 h after respective exposures. Microtubule proteins were determined using specific immunocytochemical methods. Cell smears were analysed under a fluorescent microscope. The study included negative and positive controls. Mitotic index was determined by estimating the number of dividing cells 24 h after exposure and dividing it with the total number of cells. In comparison to the controls, cell proliferation declined in cells exposed for three hours 72 h after irradiation ($p < 0.05$). Microtubule structure was clearly altered immediately after three hours of irradiation ($p < 0.05$). The mitotic index in RF/MW-exposed cells did not differ from negative controls. However, even if exposure did not affect the number of dividing cells, it may have slowed down cell division kinetics as a consequence of microtubule impairment immediately after exposure.

Pilla AA. Electromagnetic fields instantaneously modulate nitric oxide signaling in challenged biological systems. *Biochem Biophys Res Commun.* 426(3):330-333, 2012.

This study shows that a non-thermal pulse-modulated RF signal (PRF), configured to modulate calmodulin (CaM) activation via acceleration of Ca^{2+} binding kinetics, produced an immediate nearly 3-fold increase in nitric oxide (NO) from dopaminergic MN9D cultures ($P < 0.001$). NO was measured electrochemically in real-time using a NO selective membrane electrode, which showed the PRF effect occurred within the first seconds after lipopolysaccharide (LPS) challenge. Further support that the site of action of PRF involves CaM is provided in human fibroblast cultures challenged with low serum and exposed for 15min to the identical PRF signal. In this case a CaM antagonist W-7 could be added to the culture 3h prior to PRF exposure. Those results showed the PRF

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signal produced nearly a two-fold increase in NO, which could be blocked by W-7 ($P < 0.001$). To the authors' knowledge this is the first report of a real-time effect of non-thermal electromagnetic fields (EMF) on NO release from challenged cells. The results provide mechanistic support for the many reported bioeffects of EMF in which NO plays a role. Thus, in a typical clinical application for acute post operative pain, or chronic pain from, e.g., osteoarthritis, EMF therapy could be employed to modulate the dynamics of NO via Ca/CaM-dependent constitutive nitric oxide synthase (cNOS) in the target tissue. This, in turn, would modulate the dynamics of the signaling pathways the body uses in response to the various phases of healing after physical or chemical insult or injury.

Pérez-Castejón C, Pérez-Bruzón RN, Llorente M, Pes N, Lacasa C, Figols T, Lahoz M, Maestú C, Vera-Gil A, Del Moral A, Azanza MJ. Exposure to ELF-pulse modulated X band microwaves increases in vitro human astrocytoma cell proliferation. *Histol Histopathol.* 24(12):1551-1561, 2009.

Common concern about the biological effects of electromagnetic fields (EMF) is increasing with the expansion of X-band microwaves (MW). The purpose of our work was to determine whether exposure to MW pulses in this range can induce toxic effects on human astrocytoma cells. Cultured astrocytoma cells (Clonetics line 1321N1) were submitted to 9.6 GHz carrier, 90% amplitude modulated by extremely low frequency (ELF)-EMF pulses inside a Gigahertz Transversal Electromagnetic Mode cell (GTEM-cell). Astrocytoma cultures were maintained inside a GTEM-incubator in standard culture conditions at 37 ± 0.1 degrees C, 5% CO₂, in a humidified atmosphere. Two experimental conditions were applied with field parameters respectively of: PW 100-120 ns; PRF 100-800 Hz; PRI 10-1.25 ms; power 0.34-0.60 mW; electric field strength 1.25-1.64 V/m; magnetic field peak amplitude 41.4-54.6 microOe. SAR was calculated to be 4.0×10^{-4} W/Kg. Astrocytoma samples were grown in a standard incubator. Reaching 70-80% confluence, cells were transferred to a GTEM-incubator. Experimental procedure included exposed human astrocytoma cells to MW for 15, 30, 60 min and 24 h and unexposed sham-control samples. Double blind method was applied. Our results showed that cytoskeleton proteins, cell morphology and viability were not modified. Statistically significant results showed increased cell proliferation rate under 24h MW exposure. Hsp-70 and Bcl-2 antiapoptotic proteins were observed in control and treated samples, while an increased expression of connexin 43 proteins was found in exposed samples. The implication of these results on increased proliferation is the subject of our current research.

Sebastian JL, Munoz S, Sancho M, Miranda JM, Analysis of the influence of the cell geometry, orientation and cell proximity effects on the electric field distribution from direct RF exposure. *Phys Med Biol* 46(1):213-225, 2001.

This paper shows the importance of using a cell model with the proper geometry, orientation and internal structure to study possible cellular effects from direct radiofrequency exposure. For this purpose, the electric field intensity is calculated, using the finite element numerical technique, in single- and multilayer spherical, cylindrical and ellipsoidal mammalian cell models exposed to linearly polarized electromagnetic

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plane waves of frequencies 900 and 2450 MHz. An extensive analysis is performed on the influence that the cell geometry and orientation with respect to the external field have in the value of the electric field induced in the membrane and cytoplasm. We also show the significant role that the cytoplasmic and extracellular bound water layers play in determining the electric field intensity for the cylindrical and ellipsoidal cell models. Finally, a study of the mutual interactions between cells shows that polarizing effects between cells significantly modify the values of field intensity within the cell.

Sun W, Shen X, Lu D, Lu D, Chiang H. Superposition of an incoherent magnetic field inhibited EGF receptor clustering and phosphorylation induced by a 1.8 GHz pulse-modulated radiofrequency radiation. *Int J Radiat Biol.* 2013, 89:378-383.

Purpose: The present study was conducted to investigate the effect of a temporally incoherent ('noise') magnetic field (MF) on radiofrequency radiation (RFR)-induced epidermal growth factor (EGF) receptor clustering and phosphorylation in cultured cells. Materials and methods: Human amniotic epithelial (FL) cells were exposed for 15 min to either a 1.8 GHz RFR (modulated at 217 Hz), a 2 μ T incoherent MF, or concurrently to the RFR and incoherent MF. Epidermal growth factor treatment served as the positive control. Epidermal growth factor receptor clustering on cellular membrane surface was analyzed using confocal microscopy after indirect immunofluorescence staining, and phosphorylation of EGF receptors was measured by western blot technology. Results: Exposure of FL cells to the 1.8 GHz RFR at SAR (specific absorption rate) of 0.5, 1.0, 2.0, or 4.0 W/kg for 15 min induced EGF receptor clustering and enhanced phosphorylation on tyrosine-1173 residue, whereas exposure to RFR at SAR of 0.1 W/kg for 15 min did not significantly cause these effects. Exposure to a 2 μ T incoherent MF for 15 min did not significantly affect clustering and phosphorylation of EGF receptor in FL cells. When superimposed, the incoherent MF completely inhibited EGF receptor clustering and phosphorylation induced by RFR at SAR of 0.5, 1.0, and 2.0 W/kg, but did not inhibit the effects induced at SAR of 4.0 W/kg. Conclusion: Based on the data of the experiment, it is suggested that membrane receptors could be one of the main targets by which RFR interacts with cells. An incoherent MF could block the interaction to a certain extent

Sun W, Shen X, Lu D, Fu Y, Lu D, Chiang H. A 1.8-GHz radiofrequency radiation induces EGF receptor clustering and phosphorylation in cultured human amniotic (FL) cells. *Int J Radiat Biol.* 88(3):239-244, 2012.

PURPOSE: Many studies have shown that exposure to radiofrequency radiation (RFR) could activate cellular signal transduction pathways. In the present research, we investigated the effects of exposure to a 1.8-GHz RFR at different intensities on epidermal growth factor (EGF) receptor clustering and phosphorylation in human amniotic (FL) cells. MATERIALS AND METHODS: Receptor clustering on cellular membrane surface was analyzed using immunofluorescence assessed by confocal microscopy, and phosphorylation of EGF receptors was measured by western blot technology. EGF treatment served as a positive control. RESULTS: The results showed that, compared with sham exposure, exposure to RFR at specific absorption rate (SAR) of 0.5, 1.0, 2.0, or 4.0 W/kg for 15 min significantly induced EGF receptor clustering and enhanced phosphorylation on the tyrosine-1173 residue in FL

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cells, whereas exposure to a SAR 0.1 W/kg radiation for 15 min did not cause a significant effect. CONCLUSION: Based on the results of this experiment, we conclude that membrane receptors could be one of the main targets that RFR interacts with cells, and the dose-rate threshold, in the case of EGF receptors, is between SAR of 0.1 and 0.5 W/kg. The results indicate a sigmoid dependence of RFR effects on intensity.

Margaritis LH, Manta AK, Kokkaliaris CD, Schiza D, Alimisis K, Barkas G, Georgiou E, Giannakopoulou O, Kollia I, Kontogianni G, Kourouzidou A, Myari A, Roumelioti F, Skouroliakou A, Sykioti V, Varda G, Xenos K, Ziomas K. *Drosophila* oogenesis as a bio-marker responding to EMF sources. *Electromagn Biol Med*. 2013 Aug 5. [Epub ahead of print]

The model biological organisms *Drosophila melanogaster* and *Drosophila virilis* have been utilized to assess effects on apoptotic cell death of follicles during oogenesis and reproductive capacity (fecundity) decline. A total of 280 different experiments were performed using newly emerged flies exposed for short time daily for 3-7 d to various EMF sources including: GSM 900/1800 MHz mobile phone, 1880-1900 MHz DECT wireless base, DECT wireless handset, mobile phone-DECT handset combination, 2.44 GHz wireless network (Wi-Fi), 2.44 GHz blue tooth, 92.8 MHz FM generator, 27.15 MHz baby monitor, 900 MHz CW RF generator and microwave oven's 2.44 GHz RF and magnetic field components. Mobile phone was used as a reference exposure system for evaluating factors considered very important in dosimetry extending our published work with *D. melanogaster* to the insect *D. virilis*. Distance from the emitting source, the exposure duration and the repeatability were examined. All EMF sources used created statistically significant effects regarding fecundity and cell death-apoptosis induction, even at very low intensity levels (0.3 V/m blue tooth radiation), well below ICNIRP's guidelines, suggesting that *Drosophila* oogenesis system is suitable to be used as a biomarker for exploring potential EMF bioactivity. Also, there is no linear cumulative effect when increasing the duration of exposure or using one EMF source after the other (i.e. mobile phone and DECT handset) at the specific conditions used. The role of the average versus the peak E-field values as measured by spectrum analyzers on the final effects is discussed.

Mancinelli F, Caraglia M, Abbruzzese A, d'Ambrosio G, Massa R, Bismuto E. Non-thermal effects of electromagnetic fields at mobile phone frequency on the refolding of an intracellular protein: myoglobin. *J Cell Biochem*. 93(1):188-196, 2004.

Non-thermal effects induced by exposure to microwave electromagnetic field (MW-EMF) at 1.95 MHz, a frequency used in mobile communication, have been observed on the refolding kinetics of the heme binding site in an intracellular protein: tuna myoglobin, starting from acidic conditions. We have selected myoglobin because it can be considered a good model to study protein interactions with MW-EMF for its well-known high-resolution crystallographic structure. Myoglobin solutions at pH 3.0 were subjected to 3 h exposure to microwave field (with a specific absorption rate of 51 +/- 1 mW/g); the heme site refolding has been followed by measuring the molecular absorption in the Soret spectral region and the data were fitted to a bi-exponential

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model. The kinetics of exposed samples appear to be slowed by MW-EMF action. Moreover, the tryptophanyl lifetime distribution of the exposed protein, as deduced by the analysis of the fluorescence emission decay from its single tryptophan, appears sharper if compared to non-exposed protein samples. This observation suggests that the presence of MW-EMF could affect the propensity of protein molecules to populate specific conformational substates among which myoglobin molecules fluctuate at acidic pH. Changes in the structural fluctuation caused by MW perturbation can affect differently the aggregation process that occurs competitively during the protein folding, so representing a potential risk for protein "misfolding." These data suggest that MW-EMF could have also biochemical and, consequently, biological effects on eukaryotic cells that are still under investigation.

Le Quément C, Nicolaz CN, Habauzit D, Zhadobov M, Sauleau R, Le Dréan Y. Impact of 60-GHz millimeter waves and corresponding heat effect on endoplasmic reticulum stress sensor gene expression. *Bioelectromagnetics*. 35(6):444-451, 2014.

Emerging high data rate wireless communication systems, currently under development, will operate at millimeter waves (MMW) and specifically in the 60 GHz band for broadband short-range communications. The aim of this study was to investigate potential effects of MMW radiation on the cellular endoplasmic reticulum (ER) stress. Human skin cell lines were exposed at 60.4 GHz, with incident power densities (IPD) ranging between 1 and 20 mW/cm². The upper IPD limits correspond to the ICNIRP local exposure limit for the general public. The expression of ER-stress sensors, namely BIP and ORP150, was then examined by real-time RT-PCR. Our experimental data demonstrated that MMW radiations do not change BIP or ORP150 mRNA basal levels, whatever the cell line, the exposure duration or the IPD level. Co-exposure to the well-known ER-stress inducer thapsigargin (TG) and MMW were then assessed. Our results show that MMW exposure at 20 mW/cm² inhibits TG-induced BIP and ORP150 over expression. Experimental controls showed that this inhibition is linked to the thermal effect resulting from the MMW exposure.

Kwee S, Raskmark P, Velizarov P. Changes in cellular proteins due to environmental non-ionizing radiation. i. Heat-shock proteins. *Electro- and Magnetobiology* 20: 141-152, 2001.

This paper describes the effect of weak microwave fields on the amounts of heat-shock proteins in cell cultures at various temperatures. The field was generated by signal simulation of the Global System for Mobile communications (GSM) of 960 Mhz, used in portable phones. Transformed human epithelial amnion (AMA) cells, growing on glass coverslips, were exposed in a transverse electromagnetic (TEM) cell to a microwave field, generating a specific absorption rate (SAR) of 2.1 mW.kg⁻¹ in the cells. Exposure temperatures were 35, 37, and 40 ± 0.1°C, respectively, and the exposure time was 20 min. The heat-shock proteins Hsp-70 and Hsp-27 were detected by immunofluorescence. Higher amounts of Hsp-70 were present in the cells exposed at 35 and 37°C than in the sham-exposed cells. These effects can be considered to be athermal, since the field strength was much lower than the safety standard for absence of heat

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generation by microwave fields. There was no significant response in the case of Hsp-27.

Liu YX, Tai JL, Li GQ, Zhang ZW, Xue JH, Liu HS, Zhu H, Cheng JD, Liu YL, Li AM, Zhang Y. Exposure to 1950-MHz TD-SCDMA Electromagnetic Fields Affects the Apoptosis of Astrocytes via Caspase-3-Dependent Pathway. PLoS One. 7(8):e42332, 2012.

The usage of mobile phone increases globally. However, there is still a paucity of data about the impact of electromagnetic fields (EMF) on human health. This study investigated whether EMF radiation would alter the biology of glial cells and act as a tumor-promoting agent. We exposed rat astrocytes and C6 glioma cells to 1950-MHz TD-SCDMA for 12, 24 and 48 h respectively, and found that EMF exposure had differential effects on rat astrocytes and C6 glioma cells. A 48 h of exposure damaged the mitochondria and induced significant apoptosis of astrocytes. Moreover, caspase-3, a hallmark of apoptosis, was highlighted in astrocytes after 48 h of EMF exposure, accompanied by a significantly increased expression of bax and reduced level of bcl-2. The tumorigenicity assays demonstrated that astrocytes did not form tumors in both control and exposure groups. In contrast, the unexposed and exposed C6 glioma cells show no significant differences in both biological feature and tumor formation ability. Therefore, our results implied that exposure to the EMF of 1950-MHz TD-SCDMA may not promote the tumor formation, but continuous exposure damaged the mitochondria of astrocytes and induce apoptosis through a caspase-3-dependent pathway with the involvement of bax and bcl-2.

Irmak MK, Oztas E, Yagmurca M, Fadillioglu E, Bakir B. Effects of electromagnetic radiation from a cellular telephone on epidermal Merkel cells. J Cutan Pathol. 30(2):135-138, 2003.

The number of reports on the effects induced by electromagnetic radiation (EMR) from cellular telephones in various cellular systems is still increasing. Until now, no satisfactory mechanism has been proposed to explain the biological effects of this radiation except a role suggested for mast cells. Merkel cells may also play a role in the mechanisms of biological effects of EMR. This study was undertaken to investigate the influence of EMR from a cellular telephone (900 MHz) on Merkel cells in rats. A group of rats was exposed to a cellular telephone in speech position for 30 min. Another group of rats was sham-exposed under the same environmental conditions for 30 min. Exposure led to significantly higher exocytotic activity in Merkel cells compared with the sham exposure group. This finding may indicate the possible role of Merkel cells in the pathophysiology of the effects of EMR.

Höytö A, Luukkonen J, Juutilainen J, Naarala J. Proliferation, oxidative stress and cell death in cells exposed to 872 MHz radiofrequency radiation and oxidants. Radiat. Res. 170(2):235-243, 2008.

Human SH-SY5Y neuroblastoma and mouse L929 fibroblast cells were exposed to 872 MHz radiofrequency (RF) radiation using continuous waves (CW) or a modulated signal similar to that emitted by GSM mobile phones at a specific absorption rate (SAR) of 5 W/kg in isothermal conditions. To investigate possible combined effects with other

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agents, menadione was used to induce reactive oxygen species, and tert-butylhydroperoxide (t-BOOH) was used to induce lipid peroxidation. After 1 or 24 h of exposure, reduced cellular glutathione levels, lipid peroxidation, proliferation, caspase 3 activity, DNA fragmentation and viability were measured. Two statistically significant differences related to RF radiation were observed: Lipid peroxidation induced by t-BOOH was increased in SH-SY5Y (but not in L929) cells, and menadione-induced caspase 3 activity was increased in L929 (but not in SH-SY5Y) cells. Both differences were statistically significant only for the GSM-modulated signal. The other end points were not significantly affected in any of the experimental conditions, and no effects were observed from exposure to RF radiation alone. The positive findings may be due to chance, but they may also reflect effects that occur only in cells sensitized by chemical stress. Further studies are required to investigate the reproducibility and dose response of the possible effects.

Harvey C, French PW, Effects on protein kinase C and gene expression in a human mast cell line, HMC-1, following microwave exposure. *Cell Biol Int* 23(11):739-748, 2000.

We used a resonant cavity which delivered a continuous wave exposure at 864.3 MHz at an average specific absorption rate (SAR) of 7 W/kg to determine non-thermal biological effects of microwave exposure. A human mast cell line, HMC-1, was used as the biological target. Cells were given three exposures each of 20-min duration daily for 7 days. The temperature of the cell culture medium during the exposure fell to 26.5 degrees C. Effects were seen on localization of protein kinase C, and expression of three genes of 588 screened. The affected genes included the proto-oncogene c-kit, the transcription factor Nucleoside diphosphate kinase B and the apoptosis-associated gene DAD-1. Stress response genes were variably upregulated. No significant effect on morphology or on F-actin distribution was detected. We conclude that low-power microwave exposure may act on HMC-1 cells by altering gene expression via a mechanism involving activation of protein kinase C, and at temperatures well below those known to induce a heat shock response.

Gerner C, Haudek V, Schandl U, Bayer E, Gundacker N, Hutter HP, Mosgoeller W. Increased protein synthesis by cells exposed to a 1,800-MHz radio-frequency mobile phone electromagnetic field, detected by proteome profiling. *Int Arch Occup Environ Health*.83(6):691-702, 2010.

PURPOSE: To investigate whether or not low intensity radio frequency electromagnetic field exposure (RF-EME) associated with mobile phone use can affect human cells, we used a sensitive proteome analysis method to study changes in protein synthesis in cultured human cells. METHODS: Four different cell kinds were exposed to 2 W/kg specific absorption rate in medium containing (35)S-methionine/cysteine, and autoradiography of 2D gel spots was used to measure the increased synthesis of individual proteins. RESULTS: While short-term RF-EME did not significantly alter the proteome, an 8-h exposure caused a significant increase in protein synthesis in Jurkat T-cells and human fibroblasts, and to a lesser extent in activated primary human

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mononuclear cells. Quiescent (metabolically inactive) mononuclear cells, did not detectably respond to RF-EME. Since RF exposure induced a temperature increase of less than 0.15 degrees C, we suggest that the observed cellular response is a so called "athermal" effect of RF-EME. CONCLUSION: Our finding of an association between metabolic activity and the observed cellular reaction to low intensity RF-EME may reconcile conflicting results of previous studies. We further postulate that the observed increased protein synthesis reflects an increased rate of protein turnover stemming from protein folding problems caused by the interference of radio-frequency electromagnetic fields with hydrogen bonds. Our observations do not directly imply a health risk. However, vis-a-vis a synopsis of reports on cells stress and DNA breaks, after short and longer exposure, on active and inactive cells, our findings may contribute to the re-evaluation of previous reports.

Friedman J, Kraus S, Hauptman Y, Schiff Y, Seger R. Mechanism of a short-term ERK activation by electromagnetic fields at mobile phone frequency. *Biochem J.* 405:559-568, 2007.

The exposure to non-thermal microwave electromagnetic field generated by mobile phones affects the expression of many proteins. This effect on transcription and protein stability can be mediated by the mitogen-activated protein kinase (MAPK) cascades, which serve as central signaling pathways, and govern essentially all stimulated cellular processes. Indeed, a long-term exposure of cells to mobile phone irradiation results in the activation of p38MAPKs as well as the ERK/MAPKs. Here we studied the immediate effect of irradiation on the MAPK cascades, and found that ERKs, but not stress related MAPKs are rapidly activated in response to various frequencies and intensities. Using signaling inhibitors we delineated the mechanism that is involved in this activation. We found that the first step is mediated in the plasma membrane by NADH oxidase, which rapidly generates reactive oxygen species (ROS). These ROS then directly stimulate matrix metalloproteinases and allow them to cleave and release heparin binding-EGF. This secreted factor, activates EGF receptor, which in turn further activates the ERK cascade. Thus, this study demonstrates for the first time a detailed molecular mechanism by which electromagnetic irradiation by mobile phones induces the activation of the ERK cascade and thereby induces transcription and other cellular processes.

French PW, Donnellan M, McKenzie DR, Electromagnetic radiation at 835 MHz changes the morphology and inhibits proliferation of a human astrocytoma cell line. *Bioelectrochem Bioenerg* 43:13-18, 1997.

A human astrocytoma cell line, U-87 MG, was exposed to 835 MHz electromagnetic radiation for 20 min, 3 times per day for 7 days, at a power density of either $40+15 \text{ mWcm}^{-2}$ or $8.1 + 3 \text{ mWcm}^{-2}$. At the low power density, it was observed that the rate of DNA synthesis decreased, and that the cells flattened and spread out in comparison to unexposed culture. At 40 mWcm^{-2} , there were no effects seen on cell proliferation, but alteration in cell morphology included increased cell spreading and also the appearance of actin-containing blebs at localized sites on the membrane. It is hypothesised that 835

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MHz radiation at low power density may be affecting a signal transduction pathway involved in cell proliferation.

Franzellitti S, Valbonesi P, Contin A, Biondi C, Fabbri E. HSP70 expression in human trophoblast cells exposed to different 1.8 Ghz mobile phone signals. Radiat Res. 170(4):488-497, 2008.

The heat-shock proteins (HSPs) are important cellular stress markers and have been proposed as candidates to infer biological effects of high-frequency electromagnetic fields (EMFs). In the current study, HSP70 gene and protein expression were evaluated in cells of the human trophoblast cell line HTR-8/SVneo after prolonged exposure (4 to 24 h) to 1.8 GHz continuous-wave (CW) and different GSM signals (GSM-217Hz and GSM-Talk) to assess the possible effects of time and modulation schemes on cell responses. Inducible HSP70 protein expression was not modified by high-frequency EMFs under any condition tested. The inducible HSP70A, HSP70B and the constitutive HSC70 transcripts did not change in cells exposed to high-frequency EMFs with the different modulation schemes. Instead, levels of the inducible HSP70C transcript were significantly enhanced after 24 h exposure to GSM-217Hz signals and reduced after 4 and 16 h exposure to GSM-Talk signals. As in other cell systems, in HTR-8/SVneo cells the response to high-frequency EMFs was detected at the mRNA level after exposure to amplitude-modulated GSM signals. The present results suggest that the expression analysis for multiple transcripts, though encoding the same or similar protein products, can be highly informative and may account for subtle changes not detected at the protein level.

Duan L, Shan Y, Yu X, [Observations of changes in neurobehavioral functions in workers exposed to high-frequency radiation]. Chung Hua Yu Fang I Hsueh Tsa Chih 32(2):109-111, 1998. [Article in Chinese]

OBJECTIVE: To study the effects of exposure to high-frequency radiation on neurobehavioral function of the exposed workers and its measurement in evaluating occupational hazards caused by it. **METHODS:** Four neurobehavioral functions were tested for the workers exposed to high-frequency radiation with Neurobehavioral Core Tests Battery recommended by WHO. **RESULTS:** Scores for various indicators in exposed workers were significantly lower than those in controls, and correlated to the detection of neurasthenia in the exposed workers, to certain extent. **CONCLUSION:** Changes in neurobehavioral function in workers exposed to high-frequency radiation can reflect its important adverse effects.

Dasdag S, Akdag MZ, Erdal ME, Erdal N, Ay OI, Ay ME, Yilmaz SG, Tasdelen B, Yegin K. Long term and excessive use of 900 MHz radiofrequency radiation alter microrna expression in brain. Int J Radiat Biol. 2014 Dec 20:1-22. [Epub ahead of print].

Purpose: We still do not have any information on the interaction between radiofrequency radiation (RF) and miRNAs, which play paramount role in growth, differentiation, proliferation and cell death by suppressing one or more target genes. The purpose of this study is to bridge this gap by investigating effects of long term 900

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MHz mobile phone exposure on some of the miRNAs in brain tissue.

Materials and Methods: The study was carried out on fourteen Wistar Albino adult male rats by dividing them into two groups: sham (n: 7) and exposure (n: 7). Rats in the exposure group were exposed to 900 MHz RF radiation for 3 h per day (7 d a week) for twelve months (one year). The same procedure was applied to the rats in the sham group except the generator was turned off. Immediately after the last exposure, rats were sacrificed and their brains were removed. rno-miR-9-5p, rno-miR-29a-3p, rno-miR-106b-5p, rno-miR-107 and rno-miR-125a-3p in brain were investigated in detail.

Results: Results revealed that long term exposure of 900 MHz RF radiation only decreased rno-miR107 (adjP*= 0,045) value where the whole body (rms) SAR value was 0.0369 W/kg. However, our results indicated that other micro RNAs evaluated in this study was not altered by 900 MHz RF radiation. Conclusion: 900 MHz RF radiation can alter some of the miRNAs, which, in turn, may lead to adverse effects. Therefore, further studies should be performed.

Daniells, C, Duce, I, Thomas, D, Sewell, P, Tattersall, J, de Pomerai, D, Transgenic nematodes as biomonitors of microwave-induced stress. *Mutat Res* 399:55-64, 1998.

Transgenic nematodes (*Caenorhabditis elegans* strain PC72), carrying a stress-inducible reporter gene (*Escherichia coli* beta-galactosidase) under the control of a *C. elegans* hsp16 heat-shock promoter, have been used to monitor toxicant responses both in water and soil. Because these transgenic nematodes respond both to heat and toxic chemicals by synthesising an easily detectable reporter product, they afford a useful preliminary screen for stress responses (whether thermal or non-thermal) induced by microwave radiation or other electromagnetic fields. We have used a transverse electromagnetic (TEM) cell fed from one end by a source and terminated at the other end by a matched load. Most studies were conducted using a frequency of 750 MHz, at a nominal power setting of 27 dBm. The TEM cell was held in an incubator at 25 degrees C inside a shielded room; corresponding controls were shielded and placed in the same 25 degrees C incubator; additional baseline controls were held at 15 degrees C (worm growth temperature). Stress responses were measured in terms of beta-galactosidase (reporter) induction above control levels. The time-course of response to continuous microwave radiation showed significant differences from 25 degrees C controls both at 2 and 16 h, but not at 4 or 8 h. Using a 5 x 5 multiwell plate array exposed for 2 h, the 25 microwaved samples showed highly significant responses compared with a similar control array. The wells most strongly affected were those in the rows closest to the source, whereas the most distant row did not rise above control levels, suggesting a shadow effect. These differential responses are difficult to reconcile with general heating effects, although localised power absorption affords a possible explanation. Experiments in which the frequency and/or power settings were varied suggested a greater response at 21 than at 27 dBm, both at 750 and 300 MHz, although extremely variable responses were observed at 24 dBm and 750 MHz. Thus, lower power levels tended, if anything, to induce larger responses (with the above-mentioned exception), which is opposite to the trend anticipated for any simple heating effect. These results are reproducible and data acquisition is both rapid and simple. The evidence accrued to

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date suggests that microwave radiation causes measurable stress to transgenic nematodes, presumably reflecting increased levels of protein damage within cells (the common signal thought to trigger hsp gene induction). The response levels observed are comparable to those observed with moderate concentrations (ppm) of metal ions such as Zn²⁺ and Cu²⁺. We conclude that this approach deserves further and more detailed investigation, but that it has already demonstrated clear biological effects of microwave radiation in terms of the activation of cellular stress responses (hsp gene induction).

d'Ambrosio G, Massa R, Scarfi MR, Zeni O, Cytogenetic damage in human lymphocytes following GSMK phase modulated microwave exposure. Bioelectromagnetics 23:7-13, 2002.

The present study investigated, using in vitro experiments on human lymphocytes, whether exposure to a microwave frequency used for mobile communication, either unmodulated or in presence of phase only modulation, can cause modification of cell proliferation kinetics and/or genotoxic effects, by evaluating the cytokinesis block proliferation index and the micronucleus frequency. In the GSM 1800 mobile communication systems the field is both phase (Gaussian minimum shift keying, GSMK) and amplitude (time domain multiple access, TDMA) modulated. The present study investigated only the effects of phase modulation, and no amplitude modulation was applied. Human peripheral blood cultures were exposed to 1.748 GHz, either continuous wave (CW) or phase only modulated wave (GSMK), for 15 min. The maximum specific absorption rate (~5 W/kg) was higher than that occurring in the head of mobile phone users; however, no changes were found in cell proliferation kinetics after exposure to either CW or GSMK fields. As far as genotoxicity is concerned, the micronucleus frequency result was not affected by CW exposure; however, a statistically significant micronucleus effect was found following exposure to phase modulated field. These results would suggest a genotoxic power of the phase modulation per se.

Cranfield C, Wieser HG, Al Madan J, Dobson J. Preliminary evaluation of nanoscale biogenic magnetite-based ferromagnetic transduction mechanisms for mobile phone bioeffects. IEEE Trans Nanobioscience. 2(1):40-43, 2003.

Ferromagnetic transduction models have been proposed as a potential mechanism for mobile phone bioeffects. These models are based on the coupling of RF and pulsed electromagnetic emissions to biogenic magnetite (Fe₃O₄) present in the human brain via either ferromagnetic resonance or mechanical activation of cellular ion channels. We have tested these models experimentally for the first time using a bacterial analogue (*Magnetospirillum magnetotacticum*) which produces intracellular biogenic magnetite similar to that present in the human brain. Experimental evaluation revealed that exposure to mobile phone emissions resulted in a consistent and significantly higher proportion of cell death in exposed cultures versus sham exposure (p = 0.037). Though there appears to be a repeatable trend toward higher cell mortality in magnetite-producing bacteria exposed to mobile phone emissions, it is not yet clear that this would extrapolate to a deleterious health effect in humans.

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Chiang H, Microwave and ELF electromagnetic field effects on intercellular communication, Proceedings of the 20th Annual International Conference of the IEEE Engineering in Medicine and Biology Society 20:2798-2801, 1998.

Gap junctional intercellular communication (GJIC) plays an essential role in regulation of cell growth, differentiation and wound healing. Microwave irradiation may down-regulate GJIC and the effect is strongly influenced by modulation frequency. Many studies have demonstrated that GJIC could be suppressed by ELF magnetic field (MF) and the suppression is related to the intensity of magnetic flux density and the exposure duration. Pulsed MF is more effective than sinusoidal MF in inhibiting GJIC. Inhibiting GJIC by electromagnetic field in some cases could be beneficial or detrimental. The mechanism of GJIC inhibition by ELF MF has also been studied and found that the inhibition may be mainly due to hyperphosphorylation of gap junctional connexins by PKC rather than its transcriptional or translational downregulation.

Capri M, Salvioli S, Altilia S, Sevini F, Remondini D, Mesirca P, Bersani F, Monti D, Franceschi C Age-Dependent Effects of in Vitro Radiofrequency Exposure (Mobile Phone) on CD95+ T Helper Human Lymphocytes. Ann N Y Acad Sci. 1067:493-499, 2006.

.Recent studies on "nonthermal" effects of mobile phone radiofrequency (RF) suggest that RF can interact with cellular functions and molecular pathways. To study the possible RF effects on human lymphocyte activation, we analyzed CD25, CD95, CD28 molecules in unstimulated and stimulated CD4+ e CD8+ T cells in vitro. Peripheral blood mononuclear cells (PBMCs) from young and elderly donors were exposed or sham-exposed to RF (1,800 MHz, Specific Absorption Rate 2 W/kg) with or without mitogenic stimulation. No significant changes in the percentage of these cell subsets were found between exposed and sham-exposed lymphocytes in both young and elderly donors. Nevertheless, after RF exposure we observed a slight, but significant, downregulation of CD95 expression in stimulated CD4+ T lymphocytes from elderly, but not from young donors. This age-related result is noteworthy given the importance of such a molecule in regulation of the immune response.

Chavdoula ED, Panagopoulos DJ, Margaritis LH. Comparison of biological effects between continuous and intermittent exposure to GSM-900-MHz mobile phone radiation: detection of apoptotic cell-death features. Mutat Res. 700(1-2):51-61, 2010.

In the present study we used a 6-min daily exposure of dipteran flies, *Drosophila melanogaster*, to GSM-900MHz (Global System for Mobile Telecommunications) mobile phone electromagnetic radiation (EMR), to compare the effects between the continuous and four different intermittent exposures of 6min total duration, and also to test whether intermittent exposure provides any cumulative effects on the insect's reproductive capacity as well as on the induction of apoptotic cell death. According to our previous experiments, a 6-min continuous exposure per day for five days to GSM-900MHz and DCS-1800MHz (Digital Cellular System) mobile phone radiation, brought about a large decrease in the insect's reproductive capacity, as defined by the number of F(1) pupae. This decrease was found to be non thermal and correlated with an

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increased percentage of induced fragmented DNA in the egg chambers' cells at early- and mid-oogenesis. In the present experiments we show that intermittent exposure also decreases the reproductive capacity and alters the actin cytoskeleton network of the egg chambers, another known aspect of cell death that was not investigated in previous experiments, and that the effect is also due to DNA fragmentation. Intermittent exposures with 10-min intervals between exposure sessions proved to be almost equally effective as continuous exposure of the same total duration, whereas longer intervals between the exposures seemed to allow the organism the time required to recover and partly overcome the above-mentioned effects of the GSM exposure.

Effects on Hormones

Koyu A, Cesur G, Ozguner F, Akdogan M, Mollaoglu H, Ozen S. Effects of 900MHz electromagnetic field on TSH and thyroid hormones in rats. Toxicol Lett. 157(3):257-262, 2005.

In this study, the effects of exposure to a 900megahertz (MHz) electromagnetic field (EMF) on serum thyroid stimulating hormone (TSH) and triiodothyronine-thyroxine (T(3)-T(4)) hormones levels of adult male Sprague-Dawley rats were studied. Thirty rats were used in three independent groups, 10 of which were control (without stress and EMF), 10 of which were exposed to 900MHz EMF and 10 of which were sham-exposed. The exposures were performed 30min/day, for 5days/week for 4 weeks to 900MHz EMF. Sham-exposed animals were kept under the same environmental conditions as the study groups except with no EMF exposure. The concentration of TSH and T(3)-T(4) hormones in the rat serum was measured by using an immunoradiometric assay (IRMA) method for TSH and a radio-immunoassay (RIA) method for T(3) and T(4) hormones. TSH values and T(3)-T(4) at the 900MHz EMF group were significantly lower than the sham-exposed group (p<0.01). There were no statistically significant differences in serum TSH values and T(3)-T(4) hormone concentrations between the control and the sham-exposed group (p>0.05). These results indicate that 900MHz EMF emitted by cellular telephones decrease serum TSH and T(3)-T(4) levels.

Pawlak K, Sechman A, Nieckarz Z. Plasma thyroid hormones and corticosterone levels in blood of chicken embryos and post hatch chickens exposed during incubation to 1800 MHz electromagnetic field. Int J Occup Med Environ Health. 2014 Jan 31. [Epub ahead of print]

INTRODUCTION: This study attempted to determine the effect of a 1800 MHz electromagnetic field (EMF) (only carrier frequency) on thyroxine (T4), triiodothyronine (T3) and corticosterone (CORT) concentrations in the blood plasma of chick embryos, and to investigate the effect of electromagnetic field (EMF) exposure during embryogenesis on the level of these hormones in birds that are ready for slaughter.
MATERIAL AND METHODS: Throughout the incubation period, embryos from the experimental group were exposed to a 1800 MHz EMF with power density of 0.1 W/m², 10 times during 24 h for 4 min. Blood samples were collected to determine T4, T3 and

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CORT concentrations on the 12th (E12) and 18th (E18) day of incubation, from newly hatched chicks (D1) and from birds ready for slaughter (D42). RESULTS: The experiment showed that T4 and T3 concentrations decreased markedly and CORT levels increased in the embryos and in the newly hatched chicks exposed to EMF during embryogenesis. However, no changes were found in the level of the analyzed hormones in the birds ready for slaughter. Differences in T4 and T3 plasma concentrations between the EMF-exposed group and the embryos incubated without additional EMF were the highest in the newly hatched chicks, which may be indicative of the cumulative effect of electromagnetic field on the hypothalamo-pituitary-thyroid axis (HPT). DISCUSSION: The obtained results suggest that additional 1800 MHz radio frequency electromagnetic field inhibits function of HPT axis, however, it stimulates hypothalamo-pituitary-adrenal axis by inducing adrenal steroidogenic cells to synthesize corticosterone. Further investigations are needed to elucidate the mechanisms by which radio EMFs affect HPT and HPA axis function in the chicken embryos.

Qin F, Zhang J, Cao H, Yi C, Li JX, Nie J, Chen LL, Wang J, Tong J. Effects of 1800-MHz radiofrequency fields on circadian rhythm of plasma melatonin and testosterone in male rats. *J Toxicol Environ Health A*.75(18):1120-1128, 2012.

Radiofrequency fields (RF) at 1800 MHz are known to affect melatonin (MEL) and testosterone in male rats, but it remains to be determined whether RF affected circadian rhythm of these plasma hormones. Male Sprague-Dawley rats were exposed to 1800-MHz RF at 208 $\mu\text{w}/\text{cm}^2$ power density (SAR: 0.5762 W/kg) at different zeitgeber (ZT) periods of the day, including 0 (ZT0), 4 (ZT4), 8 (ZT8), 12 (ZT12), 16 (ZT16), and 20 (ZT20) h. RF exposure was 2 h/d for 32 d. From each rat, the concentrations of plasma MEL and testosterone were determined in plasma after RF exposure and compared with controls. The results confirmed the existence of circadian rhythms in the synthesis of MEL and testosterone, but revealed an inverse relationship in peak phase of these rhythms. These rhythms were disturbed after exposure to RF, with the effect being more pronounced on MEL than testosterone. The most pronounced effect of RF exposure on MEL and testosterone appears to be in rats exposed to RF at ZT 16 and ZT0 h, respectively. Data suggest that regulation of testosterone is controlled by MEL and that MEL is more sensitive to RF exposure.

Jarupat S, Kawabata A, Tokura H, Borkiewicz A. Effects of the 1900 MHz electromagnetic field emitted from cellular phone on nocturnal melatonin secretion. *J Physiol Anthropol Appl Human Sci* 22(1):61-63, 2003.

Exposure to cellular phone EMF caused a significant reduction in salivary melatonin in female human subjects.

Eskander EF, Estefan SF, Abd-Rabou AA. How does long term exposure to base stations and mobile phones affect human hormone profiles? *Clin Biochem*. 45(1-2):157-161, 2012

OBJECTIVES: This study is concerned with assessing the role of exposure to radio frequency radiation (RFR) emitted either from mobiles or base stations and its relations

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with human's hormone profiles. **DESIGN AND METHODS:** All volunteers' samples were collected for hormonal analysis. **RESULTS:** This study showed significant decrease in volunteers' ACTH, cortisol, thyroid hormones, prolactin for young females, and testosterone levels. **CONCLUSION:** The present study revealed that high RFR effects on pituitary-adrenal axis.

Eşmekaya MA, Seyhan N, Omeroğlu S. Pulse modulated 900 MHz radiation induces hypothyroidism and apoptosis in thyroid cells: A light, electron microscopy and immunohistochemical study. *Int J Radiat Biol.* 86(12):1106-1116, 2010.

Purpose: In the present study we investigated the possible histopathological effects of pulse modulated Radiofrequency (RF) fields on the thyroid gland using light microscopy, electron microscopy and immunohistochemical methods. Materials and methods: Two months old male Wistar rats were exposed to a 900 MHz pulse-modulated RF radiation at a specific absorption rate (SAR) of 1.35 Watt/kg for 20 min/day for three weeks. The RF signals were pulse modulated by rectangular pulses with a repetition frequency of 217 Hz and a duty cycle of 1:8 (pulse width 0.576 ms). To assess thyroid endocrine disruption and estimate the degree of the pathology of the gland, we analysed structural alterations in follicular and colloidal diameters and areas, colloid content of the follicles, and height of the follicular epithelium. Apoptosis was confirmed by Transmission Electron Microscopy and assessing the activities of an initiator (caspase-9) and an effector (caspase-3) caspases that are important markers of cells undergoing apoptosis. Results: Morphological analyses revealed hypothyrophy of the gland in the 900 MHz RF exposure group. The results indicated that thyroid hormone secretion was inhibited by the RF radiation. In addition, we also observed formation of apoptotic bodies and increased caspase-3 and caspase-9 activities in thyroid cells of the rats that were exposed to modulated RF fields. Conclusion: The overall findings indicated that whole body exposure to pulse-modulated RF radiation that is similar to that emitted by global system for mobile communications (GSM) mobile phones can cause pathological changes in the thyroid gland by altering the gland structure and enhancing caspase-dependent pathways of apoptosis.

de Seze R, Fabbro-Peray P, Miro L, GSM radiocellular telephones do not disturb the secretion of antepituitary hormones in humans. *Bioelectromagnetics* 19(5):271-278, 1998.

It is known that the endocrine system of experimental animals is susceptible to perturbation by radiofrequency (RF) radiation. Because of the recent interest in health and safety issues of cellular telephones, an experiment was designed to evaluate the effect of a 900 MHz RF radiation emitted by a Global System for Mobile radiotelephone (217 Hz impulses, one-eighth duty cycle, 2 W peak power) on human endocrine functions. Twenty healthy male volunteers aged from 19 to 40 were inducted in the present experiment. Each subject was exposed to RF radiation through the use of a cellular phone 2 h/day, 5 days/wk, for 1 month. Subjects were their own control. End points were serum adrenocorticotropin, thyrotropin, growth hormone, prolactin, luteinizing hormone, and follicle stimulating hormone concentrations. These end points

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were determined in nine weekly blood samples obtained starting 3 weeks before the commencement of the exposure and ending 2 weeks after exposures. All but one blood sample was drawn 48 h after each weekly session. The seventh drawing was performed the morning after the last weekly exposure. Within each individual, the preexposure hormone concentration was used as a control. Results indicated that all hormone concentrations remained within normal physiologic ranges. A difference was not noted among the nine weekly samples in five of six hormones studied. There was a significant change only in thyrotropin concentration, showing a 21% decrease on the seventh sampling. Because this change recovered fully during the postexposure period, it is concluded that 1 month of intermittent exposures to RF radiation from a cellular telephone does not induce a long-lasting or cumulative effect on the hormone secretion rate of the anterior pituitary gland in humans.

Cervellati F, Valacchi G, Lunghi L, Fabbri E, Valbonesi P, Marci R, Biondi C, Vesce F. 17- β -estradiol counteracts the effects of high frequency electromagnetic fields on trophoblastic connexins and integrins. *Oxid Med Cell Longev.* 2013;2013:280850. doi: 10.1155/2013/280850.

We investigated the effect of high-frequency electromagnetic fields (HF-EMFs) and 17- β -estradiol on connexins (Cxs), integrins (Ints), and estrogen receptor (ER) expression, as well as on ultrastructure of trophoblast-derived HTR-8/SVneo cells. HF-EMF, 17- β -estradiol, and their combination induced an increase of Cx40 and Cx43 mRNA expression. HF-EMF decreased Int α 1 and β 1 mRNA levels but enhanced Int α 5 mRNA expression. All the Ints mRNA expressions were increased by 17- β -estradiol and exposure to both stimuli. ER- β mRNA was reduced by HF-EMF but augmented by 17- β -estradiol alone or with HF-EMF. ER- β immunofluorescence showed a cytoplasmic localization in sham and HF-EMF exposed cells which became nuclear after treatment with hormone or both stimuli. Electron microscopy evidenced a loss of cellular contact in exposed cells which appeared counteracted by 17- β -estradiol. We demonstrate that 17- β -estradiol modulates Cxs and Ints as well as ER- β expression induced by HF-EMF, suggesting an influence of both stimuli on trophoblast differentiation and migration.

Wood A, Loughran S, Stough C, Does evening exposure to mobile phone radiation affect subsequent melatonin production? *Int. J. Rad. Biol* 82:69-76, 2006.

Purpose: To test whether exposure to the emissions from a digital mobile phone handset prior to sleep alters the secretion of melatonin. Materials and methods: In a double-blind cross-over design, 55 adult volunteers were both actively exposed or sham-exposed (in random order on successive Sunday nights) to mobile phone emissions for 30 min (0.25 W average power). Urine collection occurred immediately prior to retiring to bed and on rising the next morning. Melatonin output was estimated from principal metabolite concentrations (6-sulphatoxymelatonin (aMT6s) via radioimmunoassay), urine volumes and creatinine concentrations. Results: Total melatonin metabolite output (concentration \times urine volume) was unchanged between the two exposure conditions (active 14.1 \pm 1.1 μ g; sham 14.6 \pm 1.3 μ g). The pre- and post-bedtime outputs considered separately were also not significantly different, although

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the pre-bedtime value was less for active versus sham exposure. When melatonin metabolite output was estimated from the ratio of aMT6s to creatinine concentrations, the pre-bedtime value was significantly less (p = 0.037) for active compared to sham. Examination of individual responses is suggestive of a small group of `responders'. Conclusions: Total nighttime melatonin output is unchanged by mobile phone handset emissions, but there could be an effect on melatonin onset time.

Burch JB, Reif JS, Noonan CW, Ichinose T, Bachand AM, Koleber TL, Yost MG. Melatonin metabolite excretion among cellular telephone users. Int J Rad Biol 78: 1029-1036, 2002.

Abstract: Purpose: The relationship between cellular telephone use and excretion of the melatonin metabolite 6-hydroxymelatonin sulfate (6-OHMS) was evaluated in two populations of male electric utility workers (Study 1, n=149; Study 2, n=77). Materials and methods: Participants collected urine samples and recorded cellular telephone use over 3 consecutive workdays. Personal 60-Hz magnetic field (MF) and ambient light exposures were characterized on the same days using EMDEX II meters. A repeated measures analysis was used to assess the effects of cellular telephone use, alone and combined with MF exposures, after adjustment for age, participation month and light exposure. Results: No change in 6-OHMS excretion was observed among those with daily cellular telephone use >25 min in Study 1 (5 worker-days). Study 2 workers with >25 min cellular telephone use per day (13 worker-days) had lower creatinine-adjusted mean nocturnal 6-OHMS concentrations (p=0.05) and overnight 6-OHMS excretion (p=0.03) compared with those without cellular telephone use. There was also a linear trend of decreasing mean nocturnal 6-OHMS/creatinine concentrations (p=0.02) and overnight 6-OHMS excretion (p=0.08) across categories of increasing cellular telephone use. A combined effect of cellular telephone use and occupational 60-Hz MF exposure in reducing 6-OHMS excretion was also observed in Study 2. Conclusions: Exposure-related reductions in 6-OHMS excretion were observed in Study 2, where daily cellular telephone use of >25min was more prevalent. Prolonged use of cellular telephones may lead to reduced melatonin production, and elevated 60-Hz MF exposures may potentiate the effect.

Bergamaschi A, Magrini A, Ales G, Coppetta L, Somma G. Are thyroid dysfunctions related to stress or microwave exposure (900 MHz)? Int J Immunopathol Pharmacol. 17(2 Suppl):31-36, 2004.

In the last decade, numerous scientific evidence suggested possible adverse health effects from exposure to electromagnetic fields (EMF's) and the use of mobile phones. According to some studies EMF induced changes of trans-membrane Ca⁺⁺ flux may lead to altered metabolism and/or secretion of neurohormones including TSH, ACTH, GH, prolactin and melatonin. The aim of this research was to analyse the effects of mobile phone use on thyroid function and to evaluate the possible role of occupational stress. 2598 employees (1355 men and 1243 women) with different duties (vendors, operators and network technicians) were included in the study. Exposure to EMF's, generated by mobile phones, was assessed both by submitting a questionnaire directly to the employees and acquiring data regarding conversation times. The workers were divided

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into three groups on the basis of their personal mobile phone use. Moreover, a group of 160 workers with TSH values below 0.4 UI/l was characterized. No statistically significant difference regarding TSH values below 0.4 UI/l was observed among workers with different duties but there was a greater prevalence of subjects with low TSH values among 192 employees with more than 33 hrs/month conversation time; this difference was statistically significant ($p < 0.05$). On the basis of our data, it is not possible to establish whether this result is determined by exposure to EMF's from mobile phones or by the stress of using these instruments.

Philippova TM, Novoselov VI, Alekseev SI, Influence of microwaves on different types of receptors and the role of peroxidation of lipids on receptor-protein shedding. *Bioelectromagnetics* 15(3):183-192, 1994.

The effects of a continuous wave or pulse-modulated, 900 MHz microwave field were studied by in vitro assays of rat chemoreceptors. The pulsed field was modulated as rectangular waves at rates of 1, 6, 16, 32, 75, or 100 pps. The pulse-period to pulse-duration ratio was 5 in all cases, and specific absorption rates (SARs) ranged from 0.5 to 18 W/kg. Binding of ligands to cell membranes was differentially affected by exposure to microwaves. For example, binding of H³-glutamic acid to hippocampal cells was not altered by a 15 min exposure to a continuous wave field at 1 W/kg, but binding of H³-dihydroalprenolol to liver-cell membranes of neonates underwent a fivefold decrease under the same field conditions. This effect was not dependent on modulation or on a change in the constant of stimulus-receptor binding but depended on a shedding of the membrane's receptor elements into solution. The magnitude of inhibition correlated with the oxygen concentration in the exposed suspension. Antioxidants (dithiothreitol and ionol) inhibited the shedding of receptor elements. The microwave exposure did not cause an accumulation of products from the peroxidation of lipids (POL). Ascorbate-dependent or non-enzymatic POL was not responsible for the inhibition, and POL was not found in other model systems. However, enzymatic POL mechanisms in localized areas of receptor binding remain a possibility.

Effects on The Heart

Pakhomov AG, Dubovick BV, Degtyariv IG, Pronkevich AN, Microwave influence on the isolated heart function: I. Effect of modulation. *Bioelectromagnetics* 16(4):241-249, 1995.

Dependence of the microwave effect on modulation parameters (pulse width, duty ratio, and peak intensity) was studied in an isolated frog auricle preparation. The rate and amplitude of spontaneous auricle twitches were measured during and after a 2 min exposure to 915 or 885 MHz microwaves and were compared to preexposure values. The studied ranges of modulation parameters were: pulse width, 10(-6)-10(-2) s; duty ratio, 7:100000, and peak specific absorption rate, 100-3000 W/kg. Combinations of the parameters were chosen by chance, and about 400 various exposure regimes were tested. The experiments established that no regime was effective unless the average microwave

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power was high enough to induce preparation heating (0.1-0.4 degree C). The twitch rate instantly increased, and the amplitude decreased, as the temperature rose; similar changes could be induced by equivalent conventional heating. The data provide evidence that the effect of short-term microwave exposure on the isolated heart pacemaker and contractile functions depends on pulse modulation just as much as modulation determines the average absorbed power. These functions demonstrated no specific dependence on exposure parameters such as frequency or power windows.

Andrzejak R, Poreba R, Poreba M, Derkacz A, Skalik R, Gac P, Beck B, Steinmetz-Beck A, Pilecki W. The influence of the call with a mobile phone on heart rate variability parameters in healthy volunteers. Ind Health. 46(4):409-417, 2008.

It is possible that electromagnetic field (EMF) generated by mobile phones (MP) may have an influence on the autonomic nervous system (ANS) and modulates the function of circulatory system. The aim of the study was to estimate the influence of the call with a mobile phone on heart rate variability (HRV) in young healthy people. The time and frequency domain HRV analyses were performed to assess the changes in sympathovagal balance in a group of 32 healthy students with normal electrocardiogram (ECG) and echocardiogram at rest. The frequency domain variables were computed: ultra low frequency (ULF) power, very low frequency (VLF) power, low frequency (LF) power, high frequency (HF) power and LF/HF ratio was determined. ECG Holter monitoring was recorded in standardized conditions: from 08:00 to 09:00 in the morning in a sitting position, within 20 min periods: before the telephone call (period I), during the call with use of mobile phone (period II), and after the telephone call (period III). During 20 min call with a mobile phone time domain parameters such as standard deviation of all normal sinus RR intervals (SDNN [ms]--period I: 73.94+/-25.02, period II: 91.63+/-35.99, period III: 75.06+/-27.62; I-II: p<0.05, II-III: p<0.05) and standard deviation of the averaged normal sinus RR intervals for all 5-mm segments (SDANN [ms]--period I: 47.78+/-22.69, period II: 60.72+/-27.55, period III: 47.12+/-23.21; I-II: p<0.05, II-III: p<0.05) were significantly increased. As well as very low frequency (VLF [ms²]--period I: 456.62+/-214.13, period II: 566.84+/-216.99, period III: 477.43+/-203.94; I-II: p<0.05), low frequency (LF [ms²]--period I: 607.97+/-201.33, period II: 758.28+/-307.90, period III: 627.09+/-220.33; I-II: p<0.01, II-III: p<0.05) and high frequency (HF [ms²]--period I: 538.44+/-290.63, period II: 730.31+/-445.78, period III: 590.94+/-301.64; I-II: p<0.05) components were the highest and the LF/HF ratio (period I: 1.48+/-0.38, period II: 1.16+/-0.35, period III: 1.46+/-0.40; I-II: p<0.05, II-III: p<0.05) was the lowest during a call with a mobile phone. The tone of the parasympathetic system measured indirectly by analysis of heart rate variability was increased while sympathetic tone was lowered during the call with use of a mobile phone. It was shown that the call with a mobile phone may change the autonomic balance in healthy subjects. Changes in heart rate variability during the call with a mobile phone could be affected by electromagnetic field but the influence of speaking cannot be excluded.

Ozguner F, Altinbas A, Ozaydin M, Dogan A, Vural H, Kisioglu AN, Cesur G, Yildirim NG. Mobile phone-induced myocardial oxidative stress: protection by a novel antioxidant

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agent caffeic acid phenethyl ester. Toxicol Ind Health. 21(9):223-230, 2005.

Electromagnetic radiation (EMR) or radiofrequency fields of cellular mobile phones may affect biological systems by increasing free radicals, which appear mainly to enhance lipid peroxidation, and by changing the antioxidant defense systems of human tissues, thus leading to oxidative stress. Mobile phones are used in close proximity to the heart, therefore 900 MHz EMR emitting mobile phones may be absorbed by the heart. Caffeic acid phenethyl ester (CAPE), one of the major components of honeybee propolis, was recently found to be a potent free radical scavenger and antioxidant, and is used in folk medicine. The aim of this study was to examine 900 MHz mobile phone-induced oxidative stress that promotes production of reactive oxygen species (ROS) and the role of CAPE on myocardial tissue against possible oxidative damage in rats. Thirty rats were used in the study. Animals were randomly grouped as follows: sham-operated control group (N: 10) and experimental groups: (a) group II: 900 MHz EMR exposed group (N: 10); and (b) group III: 900 MHz EMR exposed+CAPE-treated group (N: 10). A 900 MHz EMR radiation was applied to groups II and III 30 min/day, for 10 days using an experimental exposure device. Malondialdehyde (MDA, an index of lipid peroxidation), and nitric oxide (NO, a marker of oxidative stress) were used as markers of oxidative stress-induced heart impairment. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate the changes of antioxidant status. In the EMR exposed group, while tissue MDA and NO levels increased, SOD, CAT and GSH-Px activities were reduced. CAPE treatment in group III reversed these effects. In this study, the increased levels of MDA and NO and the decreased levels of myocardial SOD, CAT and GSH-Px activities demonstrate the role of oxidative mechanisms in 900 MHz mobile phone-induced heart tissue damage, and CAPE, via its free radical scavenging and antioxidant properties, ameliorates oxidative heart injury. These results show that CAPE exhibits a protective effect on mobile phone-induced and free radical mediated oxidative heart impairment in rats.

Alhousseiny A, Al-Nimer M, Majeed A. Electromagnetic energy radiated from mobile phone alters electrocardiographic records of patients with ischemic heart disease. Ann Med Health Sci Res. 2(2):146-151, 2012.

BACKGROUND: Electromagnetic energy radiated from mobile phones did not show significant effect on the blood pressure, heart rate, and electrocardiographic (ECG) parameters in animals and humans. **AIM:** This study aimed to investigate the effect of radiofrequency of mobile phone on the electrocardiographic parameters in patients with history of ischemic heart disease, taking into consideration the gender factor. **SUBJECTS AND METHODS:** A total number of 356 participants (129 males and 227 females) were admitted in this study. They were grouped into: subjects without cardiac diseases (Group I), patients with ischemic heart disease (Group II), and patients with history of cardiac diseases not related to myocardial ischemia (Group III). Electrocardiogram was obtained from each patient when the mobile phone was placed at the belt level and over precordium in turn-off mode (baseline) and turn-on mode for 40 sec ringing. The records of ECG were electronically analyzed. **RESULTS:** Prolongation of QTc interval was significantly observed in male gender of Groups I and III ($P < 0.001$).

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Male patients of Group II showed significant QTc interval prolongation ($P = 0.01$) and changes in the voltage criteria ($P = 0.001$). These changes were not observed in female patients with ischemic heart disease. The position of mobile at the belt level or over the precordium showed effects on the heart. **CONCLUSIONS:** The radiofrequency of cell phone prolongs the QT interval in human beings and it interferes with voltage criteria of ECG records in male patients with myocardial ischemia.

Parazzini M, Ravazzani P, Tognola G, Thuróczy G, Molnar FB, Sacchetti A, Ardesi G, Mainardi LT. Electromagnetic fields produced by GSM cellular phones and heart rate variability. *Bioelectromagnetics*. 28(2):122-129, 2007.

In this study, 26 healthy young volunteers were submitted to 900 MHz (2 W) GSM cellular phone exposure and to sham exposure in separate sessions. The study was designed to assess cardiac regulatory mechanism in different autonomic nervous system (ANS) states during exposure to low-intensity EMF. Rest-to-stand protocol was applied to evaluate ANS in quiet condition (rest, vagal prevalence) and after a sympathetic activation (stand). The procedure is conducted twice in a double-blind design: once with a genuine EMF exposure and once with a sham exposure (at least 24 h apart). During each session three-leads electrocardiograms were recorded and RR series extracted off-line. Time domain and frequency domain HRV parameters were calculated in every phase of the protocol and during different exposures. The analysis of the data show there was no statistically significant effect due to EMF exposure both on main (i.e., RR mean) and most of the other HRV parameters. A weak interaction between some HRV parameters (i.e., SDNN, TINN, and triangular index in time domain and LF power in frequency domain analysis) and RF exposure was observed and this effect seems to be gathered around the sympathetic response to stand.

Effects on Glucose Tolerance

Meo SA, Al Rubeaan K. Effects of exposure to electromagnetic field radiation (EMFR) generated by activated mobile phones on fasting blood glucose. *Int J Occup Med Environ Health*. 26(2):235-241, 2013.

OBJECTIVE: Extensive use of mobile phones has been accompanied by a common public debate about possible adverse effects on human health. No study has been published so far to establish any association between the fastest growing innovation of mobile phone and fasting blood glucose. The aim was to determine the effects of exposure to electromagnetic field radiation generated by mobile phones on fasting blood glucose in Wistar Albino rats. **MATERIALS AND METHODS:** 40 Male Albino rats (Wistar Strain) were divided into 5 equally numerous groups. Group A served as the control one, group B received mobile phone radiation for less than 15 min/day, group C: 15-30 min/day, group D: 31-45 min/day, and group E: 46-60 min/day for a total period of 3 months. Fasting blood glucose was determined by using Spectrophotometer and serum insulin by Enzyme-linked Immunosorbent Assay (ELISA). The Homeostatic Model (HOMA-B) was

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applied for the assessment of β -cell function and (HOMA-IR) for resistance to insulin. **RESULTS:** Wister Albino rats exposed to mobile phone radiation for longer than 15 min a day for a total period of 3 months had significantly higher fasting blood glucose ($p < 0.015$) and serum insulin ($p < 0.01$) compared to the control group. HOMA-IR for insulin resistance was significantly increased ($p < 0.003$) in the groups that were exposed for 15-30 and 46-60 min/day compared to the control rats. **CONCLUSION:** The results of the present study show an association between long-term exposure to activated mobile phones and increase in fasting blood glucose and serum insulin in Albino rats.

Bielski J, Sikorski M, [Disturbances of glucose tolerance in workers exposed to electromagnetic radiation]. Med Pr 47(3):227-231, 1996. [Article in Polish]

The study group was composed of 50 workers exposed to electromagnetic radiation (radiowaves). Out of them 31 persons (62%), employed mostly in the risk zone, showed irregular glycaemia after oral administration of 75 g of glucose. At normal blood sugar before breakfast, the glycaemia level was high following administration of glucose and it did not return to starting values after 2 hours. After 30 min from glucose administration the level accounted for 155 mg%, after 60 min-180 mg%, after 90 min-153 mg% and after 120 min-124 mg%, on average. In 10 persons (32%) with glucose tolerance disturbances, disorders in bioelectric activity of the brain (abnormal EEG record) were observed.

Effects on the Whole Body

Khalil AM, Gagaa M, Alshamali A. 8-Oxo-7, 8-dihydro-2'-deoxyguanosine as a biomarker of DNA damage by mobile phone radiation. Hum Exp Toxicol.31(7):734-740, 2012.

We examined the effect of exposure to mobile phone 1800 MHz radio frequency radiation (RFR) upon the urinary excretion of 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG), one major form of oxidative DNA damage, in adult male Sprague-Dawley rats. Twenty-four rats were used in three independent experiments (RFR exposed and control, 12 rats, each). The animals were exposed to RFR for 2 h from Global System for Mobile Communications (GSM) signal generator with whole-body-specific absorption rate of 1.0 W/kg. Urine samples were collected from the rat while housed in a metabolic cage during the exposure period over a 4-h period at 0.5, 1.0, 2.0 and 4.0 h from the beginning of exposure. In the control group, the signal generator was left in the turn-off position. The creatinine-standardized concentrations of 8-oxodG were measured. With the exception of the urine collected in the last half an hour of exposure, significant elevations were noticed in the levels of 8-oxodG in urine samples from rats exposed to RFR when compared to control animals. Significant differences were seen overall across time points of urine collection with a maximum at 1 h after exposure, suggesting repair of the DNA lesions leading to 8-oxodG formation.

Aydin B, Akar A. Effects of a 900-MHz electromagnetic field on oxidative stress

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parameters in rat lymphoid organs, polymorphonuclear leukocytes and plasma. Arch Med Res. 42(4):261-267, 2011.

BACKGROUND AND AIMS: The present study investigated the effects of a 900-MHz electromagnetic field (EMF) for 2 h/day for 45 days on lymphoid organs (spleen, thymus, bone marrow), polymorphonuclear leukocytes (PMNs) and plasma of rats, focusing on changes in the enzymatic and nonenzymatic antioxidant system. We determined whether there is any difference between immature and mature rats in terms of oxidative damage caused by EMF and tested recovery groups to determine whether EMF-induced damage is reversible in immature and mature rats. **METHODS:** Twenty four immature and 24 mature rats were divided randomly and equally into six groups as follows: two control groups, immature (2 weeks old) and mature (10 weeks old); two groups were exposed to 900 MHz (28.2 ± 2.1 V/m) EMF for 2 h/day for 45 days. Two recovery groups were kept for 15 days after EMF exposure. **RESULTS:** Substantial, deleterious biochemical changes were observed in oxidative stress metabolism after EMF exposure. Antioxidant enzyme activity, glutathione levels in lymphoid organs and the antioxidant capacity of the plasma decreased, but lipid peroxidation and nitric oxide levels in PMNs and plasma and also myeloperoxidase activity in PMNs increased. Oxidative damage was tissue specific and improvements seen after the recovery period were limited, especially in immature rats. **CONCLUSIONS:** In the present study, much higher levels of irreversible oxidative damage were observed in the major lymphoid organs of immature rats than in mature rats.

El Kholly SE, El Hussein EM. Effect of 60 minutes exposure to electromagnetic field on fecundity, learning and memory, speed of movement and whole body protein of the fruit fly *Drosophila melanogaster*. J Egypt Soc Parasitol. 42(3):639-648, 2012.

This study investigated the effect of four different electrical devices as source of electromagnetic field on fecundity, learning and memory function, speed of movement, in addition to the whole body proteins of the fruit fly *Drosophila melanogaster*. The results showed that exposure to EMF has no significant effect on adult fecundity (ANOVA and Duncan's test) but alters learning and memory function in *Drosophila* larvae, especially those exposed to mobile phone. Highly significant differences occurred in the larval speed of movement after exposure to EMF, with maximal effect occurred for larvae exposed to mobile phone (their speed of movement increased 2.5 times of wild type). Some protein bands serve as characters for exposure to certain electrical devices which suggest that exposure to EMF may affect the whole body proteins.

Chiabrera A, Bianco B, Moggia E, Kaufman JJ, Zeeman-Stark modeling of the RF EMF interaction with ligand binding. Bioelectromagnetics 21(4):312-324, 2000.

The influence of radiofrequency electromagnetic exposure on ligand binding to hydrophobic receptor proteins is a plausible early event of the interaction mechanism. A comprehensive quantum Zeeman-Stark model has been developed which takes into account the energy losses of the ligand ion due to its collisions inside the receptor crevice, the attracting nonlinear endogenous force due to the potential energy of the ion in the binding site, the out of equilibrium state of the ligand-receptor system due to the basal cell metabolism, and the thermal noise. The biophysical "output" is the change

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of the ligand binding probability that, in some instances, may be affected by a suitable low intensity exogenous electromagnetic "input" exposure, e.g., if the depth of the potential energy well of a putative receptor protein matches the energy of the radiofrequency photon. These results point toward both the possibility of the electromagnetic control of biochemical processes and the need for a new database of safety standards.

Aksen F, Dasdag S, Akdag MZ, Askin M, Dasdag MM. The effects of whole body cell phone exposure on the t1 relaxation times and trace elements in the serum of rats Electromag Biol Med. 23:7-11, 2004.

The objective of this study was to investigate the effects of radiofrequency radiation emitted from cellular phones on: (1) trace elements such as manganese, iron, copper, zinc, (2) T1 relaxation times in serum, and (3) rectal temperature of rats exposed to microwave radiation emitted from cellular phones. Sixteen Sprague–Dawley rats were separated into two groups of eight, one sham-exposed (control) and one exposed (experimental). The rats were confined in Plexiglas cages and a cellular phone was placed 0.5 cm under the cage. For the experimental group, cellular phones were activated 20 min per day, 7 days a week, for 1 month. For the control group, a cellular phone placed beneath the cage for 20 min a day was turned off. Rectal temperatures were measured weekly. For 250-mW-radiated powers, the whole body average specified absorption rate (SAR) (rms) is 0.52 W/kg and 1-g-averaged peak SAR (rms) is 3.13 W/kg. The Mann-Whitney U test was used for statistical comparisons of groups. T1 relaxation time and the values of iron and copper in the serum of the experimental group were not changed compared to the control group ($p > 0.05$). However, manganese and zinc values in the serum of the experimental group were significantly different from the control group ($p < 0.05$). The difference in rectal temperature measured before and after exposure in the experimental groups was not statistically different from control ($p > 0.05$).

Al-Khlaiwi T, Meo SA. Association of mobile phone radiation with fatigue, headache, dizziness, tension and sleep disturbance in Saudi population. Saudi Med J. 25(6):732-736, 2004.

OBJECTIVE: The widespread use of mobile phones has been increased over the past decade; they are now an essential part of business, commerce and society. The use of mobile phones can cause health problems. Therefore, the aim of the present study is to investigate the association of using mobile phones with fatigue, headache, dizziness, tension and sleep disturbance in the Saudi population and provide health and social awareness in using these devices. METHODS: This study was conducted in the Department of Physiology, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia during the year 2002 to 2003. In the present study, a total of 437 subjects (55.1% male and 39.9% female) were invited, they have and had been using mobile phones. A questionnaire was distributed regarding detailed history and association of mobile phones with health hazards. RESULTS: The results of the present study showed an association between the use of mobile phones and health hazards. The

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overall mean percentage for these clinical findings in all groups were headache (21.6%), sleep disturbance (4.%), tension (3.9%), fatigue (3%) and dizziness (2.4%). **CONCLUSION:** Based on the results of the present study, we conclude that the use of mobile phones is a risk factor for health hazards and suggest that long term or excessive use of mobile phones should be avoided by health promotion activities such as group discussions, public presentations and through electronic and print media sources.

Anghileri LJ, Mayayo E, Domingo JL, Thouvenot P. Radiofrequency-induced carcinogenesis: cellular calcium homeostasis changes as a triggering factor. *InterJ RadBiol.* 81(3):205-209, 2005.

The aim was to study the effects of radiofrequency (Rf) in a mice strain characterized by age-determined carcinogenesis of lymphatic tissues. Mice were treated with a 1 h/week Rf exposure for 4 months. A group submitted to sham exposure was used as control animals. The evolution of carcinogenesis was followed up to 18 months. The maximal life span of control mice was about 24 months. All dead animals were clinically and histologically examined to give an age-determined comparative quantification of the evolving carcinogenesis. A radiocalcium tracer method permitted the evaluation of Rf effects on transmembrane transport of extracellular calcium at 1 and 24 h after exposure. The determination of induced lipid peroxidation completed this second study. The findings show that Rf provoked an earlier general lymphocyte cell infiltration, formation of lymphoblastic ascites and extranodal tumours of different histological types, as well as an increased early mortality. The results suggest that in Rf-exposed mice, carcinogenesis may be induced earlier and with different pathological forms than in control animals. The modifications in cellular calcium homeostasis and the age-determined thymus involution appear to be important factors involved in this carcinogenesis process.

Anghileri LJ, Mayayo E, Domingo JL. Iron-radiofrequency synergism in lymphomagenesis. *Immunopharmacol Immunotoxicol.* 28(1):175-183, 2006.

The parenteral **iron** administration effects on the acceleration of lymphomagenesis by radiofrequency exposure were investigated using an animal model that develops spontaneous lymphomas with ageing. Complementary studies of the in vivo uptake of ⁵⁹Fe-labeled ferric gluconate and ferric-ATP complex showed differences of absorption and excretion between both **iron** compounds. In vitro assays of their effects on calcium cellular uptake using a cell model and tissues homogenates showed a molecular structure-dependence. The current results (mortality, clinical and histopathological examinations) demonstrated a synergism between radiofrequency and ferric gluconate, and the increased risk of radiofrequency exposure when it is simultaneous to parenteral iron administration.

Anghileri LJ, Mayayo E, Domingo JL, Thouvenot P. Evaluation of health risks caused by radio frequency accelerated carcinogenesis: the importance of processes driven by the calcium ion signal. *Eur J Cancer Prev.* 15(3):191-195, 2006.

The acceleration of carcinogenesis, which was induced either by radio frequency

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radiation from a cellular telephone or by the ferric-ATP complex, was similar in a mouse strain characterized by age-determined carcinogenesis of lymphoid tissues. Organ hypertrophy, the presence of lymphoid blood and ascites, the development of solid tumours, and mortality were very different to those found in control animals. These results emphasize the role of calcium ion signal influx in the activation of oncogenes and the failure of thymus-determined immune defences.

Balakrishnan K, Murali V, Rathika C, Manikandan T, Malini RP, Kumar RA, Krishnan M. Hsp70 is an independent stress marker among frequent users of mobile phones. J Environ Pathol Toxicol Oncol. 33(4):339-347, 2014.

The aim of this study was to measure the serum concentrations of heat shock protein (HSP) 70 and C-reactive protein (CRP) and the expression levels of the hsp70 gene among frequent users of mobile phones (FUMPs). We enrolled 120 employees of information technology (IT)/IT enabled service companies (FUMPs; IT professionals) and 102 infrequent users of mobile phones (IFUMPs; people from non-IT professions) as controls. The serum concentrations of HSP70 and CRP were measured by enzyme-linked immunosorbant assay and hsp70 gene expression by reverse transcription polymerase chain reaction. Significantly higher concentrations of serum HSP70 ($P < 0.00012$) and CRP ($P < 0.04$) were observed among FUMPs than IFUMPs. A higher level of hsp70 gene expression (fold induction) was observed among FUMPs than IFUMPs ($P < 7.06 \times 10^{-13}$). In contrast to the duration of exposure-dependent increase of serum concentration of CRP, the serum HSP70 concentration was found to be independent of the duration of exposure to mobile phones. Thus, the study convincingly demonstrated the role of serum HSP and CRP as systemic inflammatory biomarkers for mobile phone-induced radiation.

Survival Effects

Mortazavi S, Mosleh-Shirazi M, Tavassoli A, Taheri M, Mehdizadeh A, Namazi S, Jamali A, Ghalandari R, Bonyadi S, Haghani M, Shafie M. Increased Radioresistance to Lethal Doses of Gamma Rays in Mice and Rats after Exposure to Microwave Radiation Emitted by a GSM Mobile Phone Simulator. Dose Response. 11(2):281-292, 2012.

The aim of this study was to investigate the effect of pre-irradiation with microwaves on the induction of radioadaptive response. In the 1(st) phase of the study, 110 male mice were divided into 8 groups. The animals in these groups were exposed/sham-exposed to microwave, low dose rate gamma or both for 5 days. On day six, the animals were exposed to a lethal dose (LD). In the 2(nd) phase, 30 male rats were divided into 2 groups of 15 animals. The 1(st) group received microwave exposure. The 2(nd) group (controls) received the same LD but there was no treatment before the LD. On day 5, all animals were whole-body irradiated with the LD. Statistically significant differences between the survival rate of the mice only exposed to lethal dose of gamma radiation before irradiation with a lethal dose of gamma radiation with those of the animals pre-exposed to either microwave ($p=0.02$), low dose rate gamma ($p=0.001$) or both of these

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physical adapting doses ($p=0.003$) were observed. Likewise, a statistically significant difference between survival rates of the rats in control and test groups was observed. Altogether, these experiments showed that exposure to microwave radiation may induce a significant survival adaptive response.

Bartsch H, Küpper H, Scheurlen U, Deerberg F, Seebald E, Dietz K, Mecke D, Probst H, Stehle T, Bartsch C. Effect of chronic exposure to a GSM-like signal (mobile phone) on survival of female Sprague-Dawley rats: Modulatory effects by month of birth and possibly stage of the solar cycle. *Neuro Endocrinol Lett.* 31(4):457-473, 2010.

During 1997-2008 two long-term (I and II) and two life-long (III and IV) experiments were performed analyzing the effect of chronic exposure to a low-intensity GSM-like signal (900 MHz pulsed with 217 Hz, 100 microW/cm² average power flux density, 38-80 mW/kg mean specific absorption rate for whole body) on health and survival of unrestrained female Sprague-Dawley rats kept under identical conditions. Radiofrequency (RF)-exposure was started at 52-70 days of age and continued for 24 (I), 17 (II) and up to 36 and 37 months, respectively (III/IV). In the first two experiments (1997-2000) 12 exposed and 12 sham-exposed animals each were observed until they were maximally 770 or 580 days old. In experiment I no adverse health effects of chronic RF-exposure were detectable, neither by macroscopic nor detailed microscopic pathological examinations. Also in experiment II no apparent macroscopic pathological changes due to treatment were apparent. Median survival time could not be estimated since in none of the groups more than 50% of the animals had died. In the course of two complete survival experiments (2002-2005; 2005-2008) 30 RF- and 30 sham-exposed animals each were followed up until their natural end or when they became moribund and had to be euthanized. A synoptical data analysis was performed. Survival data of all four groups could be fitted well by the Weibull distribution. According to this analysis median survival was significantly shortened under RF-exposure in both experiments by 9.06% (95% CI 2.7 to 15.0%) ($p=0.0064$); i.e by 72 days in experiment III and 77 days in experiment IV as compared to the corresponding sham-treated animals (III: 799 days; IV: 852 days). Both groups of animals of experiment III showed reduced median survival times by 6.25% (95% CI -0.3 to 12.4%) ($p=0.0604$) compared to the corresponding groups of experiment IV (53 days: sham-exposed animals, 48 days: RF-exposed animals) which may be due to the fact that animals of experiment III were born in October and animals of experiment IV in May indicating that the month of birth affects life span. From the results of the last two experiments it has to be concluded that chronic exposure to a low-intensity GSM-like signal may exert negative health effects and shorten survival if treatment is applied sufficiently long and the observational period covers the full life span of the animals concerned. The current data show that survival of rats kept under controlled laboratory conditions varies within certain limits depending on the month of birth. In view of our previous observations regarding an inhibitory or no effect of RF-exposure on DMBA-induced mammary cancer during the 1997-2000 period, an additional modulatory influence on a year-to-year basis should be considered which might be related to changing solar activity during the the 11-years' sunspot cycle. These potentially complex influences of the natural environment modulating the effects of

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anthropogenic RF-signals on health and survival require a systematic continuation of such experiments throughout solar cycle 24 which started in 2009.

Medical Implants and Devices Effects

Wilke A, Grimm W, Funck R, Maisch B, Influence of D-net (European GSM -Standard) cellular phones on pacemaker function in 50 patients with permanent pacemakers. *Pacing Clin Electrophysiol* 19(10):1456-1458, 1996.

The widespread use of cellular phones in the last years has prompted some recent studies to suggest an interference of pacemaker function by cellular phone usage. To determine the risk of pacemaker patients using D-net cellular phones, we tested 50 patients with permanent pacemakers after routine pacemaker check by short phone calls using a cellular phone (Ericsson, D-net, frequency 890-915 MHz, digital information coding, equivalent to the European Groupe Systemes Mobiles standard). A six-channel surface ECG was continuously recorded from each patient to detect any interactions between pacemakers and cellular phones. Phone calls were repeated during the following pacemaker settings: (1) preexisting setting; (2) minimum ventricular rate of 90 beats/min and preexisting sensitivity; and (3) minimum ventricular rate of 90 beats/min and maximum sensitivity without T wave oversensing. Only 2 (4%) of 50 patients repeatedly showed intermittent pacemaker inhibition during calls with the cellular phone. Both pacemakers had unipolar sensing. Therefore, although interactions between cellular phone use and pacemaker function appear to be rare in our study, pacemaker dependent patients in particular should avoid the use of cellular phones.

Virtanen H, Keshvari J, Lappalainen R. The effect of authentic metallic implants on the SAR distribution of the head exposed to 900, 1800 and 2450 MHz dipole near field. *Phys Med Biol.* 52(5):1221-1236, 2007

As the use of radiofrequency (RF) electromagnetic (EM) fields has increased along with increased use of wireless communication, the possible related health risks have also been widely discussed. One safety aspect is the interaction of medical implants and RF devices like mobile phones. In the literature, effects on active implants like pacemakers have been discussed but the studies of passive metallic (i.e. conductive) implants are rare. However, some studies have shown that the EM power absorption in tissues may be enhanced due to metallic implants. In this study, the effect of authentic passive metallic implants in the head region was examined. A half-wave dipole antenna was used as an exposure source and the specific absorption rate (SAR, W kg⁻¹) in the near field was studied numerically. The idea was to model the presumably worst cases of most common implants in an accurate MRI-based phantom. As exposure frequencies GSM (900 and 1800 MHz) and UMTS (2450 MHz) regions were considered. The implants studied were skull plates, fixtures, bone plates and ear rings. The results indicate that some of the implants, under very rare exposure conditions, may cause a notable

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enhancement in peak mass averaged SAR.

Yeolekar ME, Sharma A. Use of mobile phones in ICU--why not ban? J Assoc Physicians India. 52:311-313, 2004.

Due to the rapid growth of mobile telecommunications it is predicted that by 2005 there will be 1.6 billion mobile phone users worldwide. The usage of cellphones in Intensive Care Units carries with it a high incidence of interference with a number of medical devices like implantable defibrillators, cardioverters, pacemakers, monitors and other important devices like ventilators. It is in this context that this article will throw a light on complications of cellphones use in the Intensive Care Units and various strategies that can be taken to restrict their use in the Intensive Care Units.

Vagdatli E, Konstandinidou V, Adrianakis N, Tsikopoulos I, Tsikopoulos A, Mitsopoulou K. Effects of Electromagnetic Fields on Automated Blood Cell Measurements. J Lab Autom. 2014 Jan 24. [Epub ahead of print]

The aim of this study is to investigate whether the electromagnetic fields associated with mobile phones and/or laptops interfere with blood cell counts of hematology analyzers. Random blood samples were analyzed on an Aperture Impedance hematology analyzer. The analysis was performed in four ways: (A) without the presence of any mobile phone or portable computer in use, (B) with mobile phones in use (B1: one mobile, B4: four mobiles), (C) with portable computers (laptops) in use (C1: one laptop, C3: three laptops), and (D) with four mobile phones and three laptops in use simultaneously. The results obtained demonstrated a statistically significant decrease in neutrophil, erythrocyte, and platelet count and an increase in lymphocyte count, mean corpuscular volume, and red blood cell distribution width, notably in the B4 group. Despite this statistical significance, in clinical practice, only the red blood cell reduction could be taken into account, as the mean difference between the A and B4 group was 60,000 cells/ μ L. In group D, the analyzer gave odd results after 11 measurements and finally stopped working. The combined and multiple use of mobile phones and computers affects the function of hematology analyzers, leading to false results. Consequently, the use of such electronic devices must be avoided.

Schlegel RE, Grant FH, Raman S, Reynolds D Electromagnetic compatibility study of the in-vitro interaction of wireless phones with cardiac pacemakers. Biomed Instrum Technol 32(6):645-655, 1998.

This large-scale in-vitro investigation of the interaction between hand-held wireless phones and cardiac pacemakers tested 29 pacemaker models with five different phone standards. The phones were operational and suspended on a grid above a torso simulator filled with a saline bath with the pacemaker submerged at 0.5 cm. Testing consisted of 8,296 runs, during which any interactions detected were classified by type and regularity. Only a few pacemakers were responsible for a disproportionately large number of interactions. Likewise, interactions occurred during 21% of the tests using one particular phone technology, with little or no interaction resulting from use of the other standards. Other significant factors included the relative orientation of the phone

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and the pacemaker case, as well as the presence or absence of an injected ECG signal. The ECG signal facilitated observation of certain forms of interaction to the extent that this study indicates the importance of including an injected ECG signal in all testing. The study also supports the recommendation to maintain a separation distance of at least 6 inches between pacemakers and wireless phones. Each pacemaker reverted to its normal operation when the phone creating an interaction was turned off. This study may be useful in ongoing efforts to define test protocols, evaluate pacemaker designs, and mitigate interactions, perhaps providing the basis for future certification and screening efforts.

Trigano A, Blandeau O, Dale C, Wong MF, Wiart J. Reliability of electromagnetic filters of cardiac pacemakers tested by cellular telephone ringing. Heart Rhythm. 2(8):837-841, 2005.

BACKGROUND: State-of-the art cardiac pacemakers are protected against radiofrequency signals. Although there have been earlier clinical and in vitro reports of cellular phone interference with implantable devices, only a few studies have been performed in recent years. The ringing phase of digital GSM or PCS cellular phones includes a brief period of peak radiated power. OBJECTIVES: This study tested the protection offered by electromagnetic filters of cardiac pacemakers against cellular phone ringing. METHODS: We performed 330 consecutive tests in 158 patients at the time of routine examination in our pacemaker follow-up clinic. The programmed parameters remained unchanged before testing. During electrocardiographic monitoring, 2 single-band digital cellular phones consecutively placed over the pacemaker pocket each received a call. The phone systems tested were 1) GSM at a maximal power output of 2 W, operating on a 900 MHz carrier frequency, and 2) PCS at a maximal output of 1 W, operating on a 1800 MHz carrier frequency. RESULTS: Interference was noted in only 5 tests, due to interaction by the GSM system with 4 unprotected pacemaker models. The GSM test was negative in 12 other tests of identical pulse generator models. The overall incidence of interference was 1.5% of tests. CONCLUSIONS: Interference by cellular phone ringing occurred only with unprotected pacemaker models. Standard programming of these unprotected models was associated with a low incidence of interference.

Trigano A, Blandeau O, Dale C, Wong MF, Wiart J. Risk of cellular phone interference with an implantable loop recorder. Int J Cardiol. 116(1):126-130, 2007.

This study examined the risk of cellular phone ringing interference with implantable loop recorders (ILR). The technical manual of ILR warns of potential interference by cellular phone in close proximity to the implanted device, corrupting the data stored in memory or causing inappropriate device operation. The ringing phase of a digital Global System for Mobile Communication (GSM) or Personal Communication Services (PCS) cellular phone includes a brief burst of peak emitted power. To obviate the risk of dysfunction in recipients of implanted ILRs, the testing was performed with externally applied devices. The ILR was positioned in the left parasternal region and the telemetry wand removed after regular programming. Digital cellular telephones were placed over

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the device at a 1-cm distance and calls were placed. The phone systems tested were single- or dual-band receivers. The GSM used a maximal power output of 2 W, operating on a 900 MHz carrier frequency, and the PCS a maximal output of 1 W, operating on a 1800 MHz carrier frequency. The device activator was used to store the episodes encompassing the tests. Sixty nine tests were performed in 45 patients. In 61 tests, high-frequency polymorphic artifacts were visible on manually activated recordings, beginning a few seconds before the first audible ringing tone and persisting throughout the ringing phase. Cellular phone ringing in close proximity to an externally applied ILR caused bursts of high-frequency signals during electrocardiogram monitoring, without causing permanent device dysfunction or reprogramming. Cellular telephones are a potential source of electrocardiographic artifacts on ILR recordings.

Trigano AJ, Azoulay A, Rochdi M, Campillo, A Electromagnetic interference of external pacemakers by walkie-talkies and digital cellular phones: experimental study. Pacing Clin Electrophysiol 22(4 Pt 1):588-593, 1999.

A number of experimental and clinical studies have documented the risk potential of interference with implanted pacemakers by various types of cellular phones. Radiofrequency susceptibility of external medical equipment has also been reported in experimental studies. The purpose of this experimental study was to evaluate electromagnetic interference of external pacemakers by walkie-talkies and digital cellular telephones. External bipolar pacing was monitored using a digital oscilloscope to record pacemaker pulses and electromagnetic interference separately. Tests with the walkie-talkie, Private Mobile Radio (PMR) (160 MHz, 2.5 W) were conducted during the calling phase. Tests with the cellular phones, global system for mobile communications (GSM) (900 MHz, 2 W) and Digital Cellular System (DCS) (1,800 MHz, 1 W) were conducted in the test mode. Nine widely used external pacemakers from four manufacturers were tested. Various disturbances including pacing inhibition and asynchronous pacing were observed in eight pacemakers by the PMR, in four by the GSM phone, and in two by the DCS phone. The maximum distance that interference persisted ranged from 10-200 cm. This experimental study shows a potential risk of interference of external pacemakers by walkie-talkies and cellular digital phones. Appropriate warnings should be issued against the potentially serious risks of using communication devices in the vicinity of acutely ill patients treated with temporary transvenous cardiac pacemakers.

Sakakibara Y, Mitsui T, Concerns about sources of electromagnetic interference in patients with pacemakers. Jpn Heart J 40(6):737-743, 1999.

Electromagnetic noise is rapidly increasing in our environment so electromagnetic interference (EMI) with pacemakers (PM) may become a more important problem despite technological improvements in PM. The aim of this study was to evaluate the kinds of EMI which affect the quality of life of PM patients. The participants (1,942 Japanese Association for Pacemaker Patients: Pacemaker-Tomonokai) were asked to respond to a questionnaire about their major EMI troubles, and 1,567 patients (80.7%)

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responded by mail. The main concerns were from mobile telephones (MT) (39%), magnetic resonance imaging (MRI) (17%), electronic kitchen appliances, automobile engines and high voltage power lines. If possible, PM implantation sites should be carefully selected not only according to the physician's convenience but also considering information on each patient's habits and physical limitations.

Tri JL, Hayes DL, Smith TT, Severson RP, Cellular phone interference with external cardiopulmonary monitoring devices. Mayo Clin Proc 76(1):11-15, 2001.

OBJECTIVES: To determine the potential effect (electromagnetic interference) of cellular telephones on external cardiopulmonary monitoring devices. METHODS: For this study, we tested 17 different medical devices with 5 portable telephones (4 digital, 1 analog) to assess the potential for electromagnetic interference. The telephones were tested in a normal operating mode to simulate a typical hospital environment with patients or their families using their cellular phones. The medical devices were connected to the appropriate simulators for proper operation while the tests were under way. The screens and alarms of the medical devices were monitored while the telephones were maneuvered in the y and z planes near the devices. Clinically important interference was defined as interference that may hinder interpretation of the data or cause the equipment to malfunction. RESULTS: Any type of interference occurred in 7 (41%) of the 17 devices tested during 54.7% of the 526 tests. The incidence of clinically important interference was 7.4%. CONCLUSIONS: Cellular telephones may interfere with the operation of external cardiopulmonary monitoring devices. However, most of the test results showed that the interference would rarely be clinically important.

Tat FH, Wah KC, Hung YH. A follow-up study of electromagnetic interference of cellular phones on electronic medical equipment in the emergency department. Emerg Med (Fremantle) 14(3):315-319, 2002.

OBJECTIVE: Considering the growing use of cellular phones and the fast appearance of new phone models, the electromagnetic interference of currently popular cellular phones on electronic medical equipment was tested. METHODS: Three Personal Communication System cellular phones were put at different distances from multiple electronic medical devices, the interference effect was observed and the electromagnetic field strength measured with a spectrum analyser. RESULTS: Only two small pieces of equipment, the CO2 airway adapter and the haemoglucostix meter were affected and then only when the phone was in very close proximity. CONCLUSION: Compared to the results of our study in 1997 testing Global System for Mobile Communication phones, the Personal Communication System phones generated less electromagnetic interference. However a much larger scaled study and an accurate international electromagnetic interference standard are recommended before any change in the current restrictive hospital policy on mobile phone usage could be recommended.

Naegeli B, Osswald S, Deola M, Burkart F, Intermittent pacemaker dysfunction caused by digital mobile telephones. J Am Coll Cardiol 27(6):1471-1477, 1996.

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OBJECTIVES: This study was designed to evaluate possible interactions between digital mobile telephones and implanted pacemakers. **BACKGROUND:** Electromagnetic fields may interfere with normal pacemaker function. Development of bipolar sensing leads and modern noise filtering techniques have lessened this problem. However, it remains unclear whether these features also protect from high frequency noise arising from digital cellular phones. **METHODS:** In 39 patients with an implanted pacemaker (14 dual-chamber [DDD], 8 atrial-synchronized ventricular-inhibited [VDD(R)] and 17 ventricular-inhibited [VVI(R)] pacemakers), four mobile phones with different levels of power output (2 and 8 W) were tested in the standby, dialing and operating mode. During continuous electrocardiographic monitoring, 672 tests were performed in each mode with the phones positioned over the pulse generator, the atrial and the ventricular electrode tip. The tests were carried out at different sensitivity settings and, where possible, in the unipolar and bipolar pacing modes as well. **RESULTS:** In 7 (18%) of 39 patients, a reproducible interference was induced during 26 (3.9%) of 672 tests with the operating phones in close proximity (<10 cm) to the pacemaker. In 22 dual-chamber (14 DDD, 8 VDD) pacemakers, atrial triggering occurred in 7 (2.8%) of 248 and ventricular inhibition in 5 (2.8%) of 176 tests. In 17 VVI(R) systems, pacemaker inhibition was induced in 14 (5.6%) of 248 tests. Interference was more likely to occur at higher power output of the phone and at maximal sensitivity of the pacemakers (maximal vs. nominal sensitivity, 6% vs. 1.8% positive test results, $p = 0.009$). When the bipolar and unipolar pacing modes were compared in the same patients, ventricular inhibition was induced only in the unipolar mode (12.5% positive test results, $p = 0.0003$). **CONCLUSION:** Digital mobile phones in close proximity to implanted pacemakers may cause intermittent pacemaker dysfunction with inappropriate ventricular tracking and potentially dangerous pacemaker inhibition.

Morrissey JJ, Swicord M, Balzano Q. Characterization of electromagnetic interference of medical devices in the hospital due to cell phones. Health Phys 82(1):45-51, 2002.

Concern over electromagnetic interference with medical devices due to cell phone emissions has stemmed from anecdotal reports and unpublished observations of hospital staff. In an effort to characterize electromagnetic interference concerns, representative medical devices from four large teaching hospitals were exposed to standard North American and European communication signal emissions. Of 33 medical devices tested, only 4 showed disruption of critical function due to cell phone emissions at a distance of 25 cm or greater. Although other cases of electromagnetic interference were observed, these were not critically disruptive and mainly occurred when the transmitters were at full power and placed 5 cm or closer to the medical device. Overall, no cell phone signal was exempt from producing electromagnetic interference effects. While sensitive medical devices were often affected by more than one signal type, the effects were not entirely predictable based upon the results of other signals or related medical device units or models. Because a comprehensive analysis of all medical devices in all possible electromagnetic environments was not performed, the data presented here are only intended to provide a general idea of the magnitude of electromagnetic interference effects that might be encountered in a hospital environment, as well as a

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standard protocol for clinical engineering groups to perform ad hoc electromagnetic interference surveys and methods to manage and/or eliminate electromagnetic interference with appropriate system engineering design including supplementary communication infrastructure, medical device shielding and positioning, and appropriate cell phone user guidelines.

Kompis M, Negri S, Hausler R. Electromagnetic interference of bone-anchored hearing aids by cellular phones. Acta Otolaryngol 120(7):855-859, 2000.

We report a case of electromagnetic interference between a bone-anchored hearing aid (BAHA) and a cellular phone. A 54-year-old women was successfully treated for severe mixed conductive and sensorineural hearing loss with a BAHA. Five years after implantation, the patient experienced a sudden feeling of dizziness, accompanied by a loud buzzing sound and by a sensation of head pressure while examining a digital mobile phone. During a subsequent experiment, the buzzing sound could be reproduced and was identified as electromagnetic interference between the BAHA and digital cellular phones. Seventeen adult BAHA users from our clinic participated in a subsequent survey. Of the 13 patients with some experience of digital cellular phones, 11 reported hearing annoying noises elicited by these devices. However, no other sensation, such as dizziness, was described. Owing to the increasing number of users of both hearing aids and cellular phones, the incidence of electromagnetic interference must be expected to increase as well. Although to date there is no evidence that such interference may be harmful or dangerous to users of conventional or bone-anchored hearing aids, unexpected interference can be a frightening experience.

Kompis M, Hausler R. Electromagnetic interference of bone-anchored hearing aids by cellular phones revisited. Acta Otolaryngol 122(5):510-512, 2002.

The electromagnetic interference of the recently introduced bone-anchored hearing aid (BAHA) model "BAHA Compact" by digital cellular phones is investigated and compared with that of the older "BAHA Classic 300" model. Measurements with two different digital cellular phones in a laboratory setting indicated that the noise level due to electromagnetic interference was at least 10 dB lower for the BAHA Compact device than for the BAHA Classic 300. To compare the experience of patients using the BAHA Compact with those using a BAHA Classic 300 in an earlier study, a survey was performed. Six users of a BAHA Compact who used digital cellular phones participated in the survey. Four patients did not hear any noise associated with the use of a digital cellular phone. Two patients reported hearing quiet sounds when they were on the telephone, but not when somebody else in the vicinity used a digital cellular phone. These findings confirm that the susceptibility to electromagnetic interference of the BAHA Compact device is low.

Kainz W, Neubauer G, Alesch F, Schmid G, Jahn O. Electromagnetic compatibility of electronic implants--review of the literature. Wien Klin Wochenschr 113(23-24):903-914, 2001.

The aim of the article was to provide an overview of published studies regarding the

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electromagnetic compatibility (EMC) of electronic implants. The available literature was sorted according to combinations of implant types and sources of interference. Several experiments concerning the susceptibility of pacemakers to mobile phones have been performed. The results of these experiments suggest measures that may be used to prevent the disturbance of pacemakers. For instance, instead of carrying the activated mobile phone in the breast pocket it is recommended that a distance of 30 cm be maintained between the pacemaker and the mobile phone, and that the mobile phone be used on the contralateral side of the pacemaker's location. Similar measures may be recommended for patients with implantable cardioverter defibrillators when using mobile phones. Patients with electronic implants should walk rapidly through anti theft-devices because some of these devices are liable to disturb implants. Patients with cardiac pacemakers should not be subjected to magnetic resonance imaging as far as possible. For a variety of combinations of implants and interference sources, e.g. cardiac pacemakers and base station antennas, no studies were found in the literature. It is strongly recommended that trials be carried out to evaluate the potential risk for patients in these settings.

Westermarck A, Wisten A. Miniplate osteosynthesis and cellular phone create disturbance of infraorbital nerve. J Craniofac Surg 12(5):475-478, 2001.

A 37-year-old man with a zygomatic fracture underwent surgical treatment with reduction of the fracture and osteosynthesis with a miniplate on the infraorbital rim. Postoperatively, he had numbness in the distribution area of the infraorbital nerve, but he also suffered from dysesthesia in the same area during periods when he was using his hand-held mobile phone. After surgical removal of the osteosynthesis plate, the dysesthesia associated with his mobile phone was no longer present. The plate was examined in a setup where we measured the electric current that developed on the surface of the plate under the influence of the magnetic field between the phone antenna and the metal plate. The highest currents measured on the actual plate were 141 mV in air, and 21 mV in saline. These findings indicate that there might have been a correlation between the presence of the miniplate close to the infraorbital nerve, and the dysesthesia experienced by the patient, under the influence of the energy emitted from the cellular phone.

Kainz W, Neubauer G, Alesch F, Schmid G, Jahn O. Electromagnetic compatibility of electronic implants--review of the literature. Wien Klin Wochenschr 113(23-24):903-914, 2001.

The aim of the article was to provide an overview of published studies regarding the electromagnetic compatibility (EMC) of electronic implants. The available literature was sorted according to combinations of implant types and sources of interference. Several experiments concerning the susceptibility of pacemakers to mobile phones have been performed. The results of these experiments suggest measures that may be used to prevent the disturbance of pacemakers. For instance, instead of carrying the activated mobile phone in the breast pocket it is recommended that a distance of 30 cm be maintained between the pacemaker and the mobile phone, and that the mobile phone

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be used on the contralateral side of the pacemaker's location. Similar measures may be recommended for patients with implantable cardioverter defibrillators when using mobile phones. Patients with electronic implants should walk rapidly through anti theft-devices because some of these devices are liable to disturb implants. Patients with cardiac pacemakers should not be subjected to magnetic resonance imaging as far as possible. For a variety of combinations of implants and interference sources, e.g. cardiac pacemakers and base station antennas, no studies were found in the literature. It is strongly recommended that trials be carried out to evaluate the potential risk for patients in these settings.

Jones RP, Conway DH. The effect of electromagnetic interference from mobile communication on the performance of intensive care ventilators. Eur J Anaesthesiol. 22(8):578-583, 2005.

Electromagnetic interference produced by wireless communication can affect medical devices and hospital policies exist to address this risk. During the transfer of ventilated patients, these policies may be compromised by essential communication between base and receiving hospitals. Local wireless networks (e.g. Bluetooth) may reduce the 'spaghetti syndrome' of wires and cables seen on intensive care units, but also generate electromagnetic interference. The aim of this study was to investigate these effects on displayed and actual ventilator performance. METHODS: Five ventilators were tested: Drager Oxylog 2000, BREAS LTV-1000, Respironics BiPAP VISION, Puritan Bennett 7200 and 840. Electromagnetic interference was generated by three devices: Simoco 8020 radio handset, Nokia 7210 and Nokia 6230 mobile phone, Nokia 6230 communicating via Bluetooth with a Palm Tungsten T Personal Digital Assistant. We followed the American National Standard Recommended Practice for On-Site, Ad Hoc Testing (ANSI C63) for electromagnetic interference. We used a ventilator tester, to simulate healthy adult lungs and measure ventilator performance. The communication device under test was moved in towards each ventilator from a distance of 1 m in six axes. Alarms or error codes on the ventilator were recorded, as was ventilator performance. RESULTS: All ventilators tested, except for the Respironics VISION, showed a display error when subjected to electromagnetic interference from the Nokia phones and Simoco radio. Ventilator performance was only affected by the radio which caused the Puritan Bennett 840 to stop functioning completely. The transfer ventilators' performance were not affected by radio or mobile phone, although the mobile phone did trigger a low-power alarm. Effects on intensive care ventilators included display reset, with the ventilator restoring normal display function within 2 s, and low-power/low-pressure alarms. Bluetooth transmission had no effect on the function of all the ventilators tested. CONCLUSION: In a clinical setting, high-power-output devices such as a two-way radio may cause significant interference in ventilator function. Medium-power-output devices such as mobile phones may cause minor alarm triggers. Low-power-output devices such as Bluetooth appear to cause no interference with ventilator function.

Irnich W, Batz L, Muller R, Tobisch R, electromagnetic interference of pacemakers by mobile phones. Pacing Clin Electrophysiol 19(10):1431-1446, 1996.

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The topic of interference of pacemakers by mobile phones has evoked a surprisingly strong interest, not only in pacemaker patients, but also in the public opinion. The latter is the more surprising, as in the past, the problem of interference has scarcely found the attention that it deserves in the interest of the patient. It was the intention of our investigation to test as many pacemaker models as possible to determine whether incompatibility with mobile phones of different modes may exist, using an in vitro measuring setup. We had access to 231 different models of 20 manufacturers. During the measurements, a pulse generator together with a suitable lead was situated in a 0.9 g/L saline solution, and the antenna of a mobile phone was positioned as close as possible. If the pulse generator was disturbed, the antenna was elevated until interference ceased. The gap in which interference occurred was defined as "maximum interference distance." All three nets existing in Germany, the C-net (450 MHz, analogue), the D-net (900 MHz, digital pulsed), and the E-net (1,800 MHz, digital pulsed) were tested in succession. Out of 231 pulse generator models, 103 pieces corresponding to 44.6% were influenced either by C- or D-net, if both results were totaled. However, this view is misleading as no patient will use C- and D-net phones simultaneously. Separated into C- or D-net interference, the result is 30.7% for C or 34.2% for D, respectively, of all models tested. The susceptible models represent 18.6% or 27% of today's living patients, respectively. All models were resistant to the E-net. With respect to D-net phones, all pacemakers of six manufacturers proved to be unaffected. Eleven other manufacturers possessed affected and unaffected models as well. A C-net phone only prolonged up to five pacemaker periods within 10 seconds during dialing without substantial impairment to the patient. Bipolar pacemakers are as susceptible as unipolar ones. The following advice for patients and physicians can be derived from our investigations: though 27% of all patients may have problems with D-net phones (not C- or E-net), the application should generally not be questioned. On the contrary, patients with susceptible devices should be advised that a distance of 20 cm is sufficient to guarantee integrity of the pacemaker with respect to hand held phones. Portables, on the other hand, should have a distance of about 0.5 m. Pacemaker patients really suffering from mobile phones are very rare unless the phone is just positioned in the pocket over the pulse generator. The contralateral pocket or the belt position guarantees, in 99% of all patients, undisturbed operation of the pacemaker. A risk analysis reveals that the portion of patients really suffering from mobile phones is about 1 out of 100,000. Nevertheless, it would be desirable in the future if implanting physicians would use only pacemakers with immunity against mobile phones as guaranteed by the manufacturers.

Hofgartner F, Muller T, Sigel H, [Could C- and D-network mobile phones endanger patients with pacemakers]? Dtsch Med Wochenschr 121(20):646-652, 1996. [Article in German]

OBJECTIVE: To investigate prospectively the extent of potentially harmful interference of cardiac pacemakers by mobile phones in the C (analog) and D (digital) networks in use in Germany. PATIENTS AND METHODS: 104 patients (54 men, 50 women; mean age 75.8 [40-100] years) with 58 different implanted pacemaker models (43 one-chamber and 15

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two-chamber systems) underwent uniform tests at various functional states with three different telephones (D1 portable 8 Watt, D1 Handy model 2 Watt, C Handy model 0.5 Watt). The distances between telephone aerial and pacemaker, as well as reception sensitivity and polarity of the pacemaker were varied. All tests were done during continuous ECG monitoring. RESULTS: 28 different pacemaker types (48.3%) in 43 patients (41.3%) showed interference in the form of pacemaker inhibition and switching to interference frequencies as well as triggering of pacemaker-mediated tachycardias in the DDD mode, as well as in the temperature-regulated frequency-adaptive function. D portables influenced pacemaker function more often and at greater distance than the D Handy model, which was little different from the c network hand phone. Reduction in pacemaker sensitivity as well as switching to bipolar reception only partly eliminated the interference. CONCLUSIONS: Patients with implanted pacemakers should if possible not use mobile phones in the C and D networks. Individual testing with suitable programming of pacemaker sensitivity and polarity can reduce the risk of interference.

Irnich W, Tobisch R, [Effect of mobile phone on life-saving and life-sustaining systems]. Biomed Tech (Berl) 43(6):164-173, 1998. [Article in German]

Since the beginning of the nineties there have been warnings not to use mobile phones in the vicinity of medical devices. Functional failures of dialysis machines, respirators and defibrillators prompted the banning of their use in many hospitals in Scandinavia, and then in other countries. Since we believe that a general ban in hospitals is problematic, we decided to investigate the influence of mobile telephone on life-saving and/or life-support systems, with the aim of establishing rules for its use in hospitals. We investigated available phones of varying power of the C-, D- and E-net, as also of a cordless phone meeting the DECT standard. The aim was to identify the devices susceptible to interference and determine the minimum distances at which interference occurred. A total of 224 devices classified into 23 types of devices were examined. Nine different sets of transmission conditions were applied, giving a total of 2016 tests. Our results permit the conclusion that the ban on mobile phones in hospitals is based not on actual events, but on theoretical considerations in the absence of any practical information on the actual susceptibility of devices and their reaction to the electromagnetic fields involved. The fact that hazardous situations are very rare is due firstly to the need for the simultaneous occurrence of four coincidences, and the fail-save feature of medical devices. We would therefore recommend that all life-saving and life-support systems that can also be used outside the hospital should be made mobile phone-proof. When apnoea monitors and respirators are protected from such interference, hazardous situations could be avoided by establishing the rule: "No portables, and mobile phones only at a distance of at least 1 metre from medical devices". With regard to emergency telephones, the minimum distance to medical devices should be at least 1.5 metres.

Jimenez A, Hernandez Madrid A, Pascual J, Gonzalez Rebollo JM, Fernandez E, Sanchez A, Ortega J, Lozano F, Munoz R, Moro C, [Electromagnetic interference between automatic defibrillators and digital and analog cellular telephones]. Rev Esp Cardiol

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51(5):375-382, 1998. [Article in Spanish]

BACKGROUND AND OBJECTIVES: Functional pacemaker interference by mobile telephones has been described with analogical systems and with possible greater influence, digital systems, including inhibition and inadequate pacing. The influence of both system has not been extensively studied in patients with implantable cardioverter defibrillators (ICD). **PATIENTS AND METHODS:** We studied the influence of mobile phones, both digital and analogic network, on the performance of several models of defibrillators, in a standardised test set up designed to provide high sensitivity. The purpose of our study was to establish whether there are any influences on ICD functions, both in in vivo and in in vitro models. Several mobile phones, with different transmission powers, were moved towards the defibrillator and the electrode, under continuous documentation of defibrillator sensing and interrogation afterwards. The experimental model was performed with the aid of an arrhythmia simulator (Intersim) and demo-defibrillators. The tests were repeated both in and out of a solution of saline water with an impedance within normal human limits. **RESULTS:** Partial loss of telemetry was found in 14 patients, 8 with analogical phones and 6 with digital phones. Fourteen patients showed alterations only on the surface electrocardiogram channel and five on the intracavitary channel. The same results were reproduced in the in vitro model. However, the in vitro test allowed us to simulate multiple ventricular arrhythmias, and demonstrate the normal sensing and functioning of the defibrillator during a "spontaneous" arrhythmia. After testing, we demonstrate that no real oversensing/undersensing was documented in any device. There was no evidence of ICD reprogramming or pacing inhibition. In particular, no inadequate therapies were delivered. **CONCLUSIONS:** a) in our series, we have not demonstrated clinically significant electromagnetic interferences with mobile phones of digital or analogical networks; b) the in vitro model allowed us to conclude that even if a spontaneous arrhythmia appears, the function of the defibrillator is not altered; c) the use of mobile phones seems to be safe for defibrillator patients, and d) however, some basic rules, such as to maintain the phone at least 15 cm away from the defibrillator, are advised.

Hayes DL, Wang PJ, Reynolds DW, Estes M 3rd, Griffith JL, Steffens RA, Carlo GL, Findlay GK, Johnson CM. Interference with cardiac pacemakers by cellular telephones. N Engl J Med 336(21):1473-1479, 1997.

BACKGROUND: A growing body of evidence suggests that electromagnetic interference may occur between cardiac pacemakers and wireless hand-held (cellular) telephones, posing a potential public health problem. Electromagnetic interference may occur when the pacemaker is exposed to an electromagnetic field generated by the cellular telephone. **METHODS:** In this multicenter, prospective, crossover study, we tested 980 patients with cardiac pacemakers with five types of telephones (one analogue and four digital) to assess the potential for interference. Telephones were tested in a test mode and were programmed to transmit at the maximal power, simulating the worst-case scenario; in addition, one telephone was tested during actual transmission to simulate actual use. Patients were electrocardiographically monitored while the telephones were tested at the ipsilateral ear and in a series of maneuvers directly over the pacemaker.

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Interference was classified according to the type and clinical significance of the effect. RESULTS: The incidence of any type of interference was 20 percent in the 5533 tests, and the incidence of symptoms was 7.2 percent. The incidence of clinically significant interference was 6.6 percent. There was no clinically significant interference when the telephone was placed in the normal position over the ear. Interference that was definitely clinically significant occurred in only 1.7 percent of tests, and only when the telephone was held over the pacemaker. Interference was more frequent with dual-chamber pacemakers (25.3 percent) than with single-chamber pacemakers (6.8 percent, $P < 0.001$) and more frequent with pacemakers without feed-through filters (28.9 to 55.8 percent) than with those with such filters (0.4 to 0.8 percent, $P = 0.01$). CONCLUSIONS: Cellular telephones can interfere with the function of implanted cardiac pacemakers. However, when telephones are placed over the ear, the normal position, this interference does not pose a health risk.

Geller L, Thurocz G, Merkely B. Orv Hetil 142(36):1963-1970, 2001. [Article in Hungarian]

Electromagnetic compatibility (EMC) of cellular phones and pacemakers (PM) was examined in four different cellular phone system (NMT, GSM, RLL, DCS 1800 MHz) and in fifteen different PM type in-vitro and in-vivo in humans. After more than 1100 in-vitro and 130 in-vivo tests we concluded, that the electromagnetic immunity of the PMs which are implanted in Hungary is suitable with only few exceptions. The highest rate of EMC problems was observed with NMT 450 MHz cellular phones (10.5%-63%). There was no EMC disturbance observed with GSM and DCS 1800 MHz cellular phones. There was only one case when clinically significant symptom was noticed with only one PM type and with NMT system cellular phone when the distance of cellular phone was 3-4 cms, and the power was maximal. There was not any EMC disturbance observed with none of the cellular phone systems during normal talking and when the distance of the PM and cellular phone was more than 20 cms. Our study supports guidelines which suggest that PM patients should contact their physicians when using cellular phones and cellular phones and PMs should not get closer than 20 cms.

Glenister H, How do mobile phones affect electromedical devices? Nurs Times 94(15):44-45, 1998.

Mobile telephones and other electronic communication devices can interfere with medical equipment when used in close proximity. A study of different devices by the Medical Devices Agency showed that emergency services' radio handsets were the most likely to cause interference. It recommends that cell telephones be switched off in theatres and treatment areas and at a patients' bedsides where sensitive medical devices are in use.

Fetter JG, Ivans V, Benditt DG, Collins J, Digital cellular telephone interaction with implantable cardioverter-defibrillators. J Am Coll Cardiol 31(3):623-628, 1998.

OBJECTIVES: This study sought to determine, in vivo, whether electromagnetic interference (EMI), generated by North American Digital Communications (NADC)/Time

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Division Multiple Access-50-Hz (TDMA-50) mobile cellular digital telephone model AT&T 6650, disturbs normal implantable cardioverter-defibrillator (ICD) operation and to verify these observations in vitro by testing a selection of telephones representing worldwide systems. METHODS: The effects of cellular phone interference on the operation of various models of market-released ICDs from a single manufacturer, Medtronic, Inc., were tested. The in vivo clinical test was undertaken in 41 patients using the AT&T 6650 digital telephone with the NADC/TDMA-50 technology. The in vitro component of the study was examined twofold: 1) antenna generated far field; and 2) analog/digital cellular telephone near field. RESULTS: None of the ICDs tested in 41 patients were affected by oversensing of the EMI field of the cellular telephones during the in vivo study. Therefore, the binomial upper 95% confidence limit for the failure rate of 0% is 7%. The in vitro antenna-generated field testing showed that telephone modulation frequencies used in the international Global System Mobile and TDMA-50 cellular telephone technologies did not result in ICD sensing interference at the predicted electric field intensity. The in vitro near field tests were performed using both analog and digital cellular telephones in service, or in the test mode, and indicated no interaction with normal operation. However, the static magnetic field generated by the cellular telephone placed over the ICD at a distance ≤ 0.5 cm will activate the internal reed switch, resulting in temporary suspension of ventricular tachycardia and fibrillation detection. CONCLUSIONS: We conclude that TDMA-50 cellular telephones did not interfere with these types of ICDs. However, we recommend that the patient not carry or place the digital cellular telephone within 15 cm (6 in.) of the ICD.

Altamura G, Toscano S, Gentilucci G, Ammirati F, Castro A, Pandozi C, Santini M, Influence of digital and analogue cellular telephones on implanted pacemakers. Eur Heart J 18(10):1632-4161, 1997.

The aim of this study was to find out whether digital and analogue cellular 'phones affect patients with pacemakers. The study comprised continuous ECG monitoring of 200 pacemaker patients. During the monitoring certain conditions caused by interference created by the telephone were looked for: temporary or prolonged pacemaker inhibition; a shift to asynchronous mode caused by electromagnetic interference; an increase in ventricular pacing in dual chamber pacemakers, up to the programmed upper rate. The Global System for Mobile Communications system interfered with pacing 97 times in 43 patients (21.5%). During tests on Total Access of Communication System telephones, there were 60 cases of pacing interference in 35 patients (17.5%). There were 131 interference episodes during ringing vs 26 during the on/off phase; ($P < 0.0001$); 106 at maximum sensitivity level vs 51 at the 'base' value; ($P < 0.0001$). Prolonged pacing inhibition (> 4 s) was seen at the pacemaker 'base' sensing value in six patients using the Global system but in only one patient using Total Access. CONCLUSION: Cellular 'phones may be dangerous for pacemaker patients. However, they can be used safely if patients do not carry the 'phone close to the pacemaker, which is the only place where high risk interference has been observed.

Chen WH, Lau CP, Leung SK, Ho DS, Lee IS, Interference of cellular phones with

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implanted permanent pacemakers. Clin Cardiol 19(11):881-886, 1996.

BACKGROUND AND HYPOTHESIS: Occasional reports have suggested that cellular phones may interfere with permanent pacemakers. Our investigation sought to determine systematically the effects of commercially available cellular phones on the performances of different pacing modes and sensing lead configurations of permanent implanted pacemakers. **METHODS:** We conducted the study in 29 patients implanted with single- or dual-chamber bipolar rate-adaptive permanent pacemakers (a total of nine different models and six different sensors: minute ventilation, activity sensing using either accelerometer or piezoelectric crystal, QT and oxygen saturation sensing) from four different manufacturers. Three different cellular phones with analog or digital coding with maximum power from 0.6 to 2 W were used to assess the effect of pacemaker interference. Each cellular phone was positioned at (1) above the pacemaker pocket, (2) the ear level ipsilateral to the pacemaker pocket, and (3) the contralateral ear level. Surface electrocardiograms, intracardiac electrograms, and marker channels were recorded where possible during the following maneuvers at each position: (1) calls made by a stationary phone to cellular phone, and (2) calls made from the cellular phone to a stationary phone. A total of eight different pacing modes [DDD(R), VDD(R), AAI(R) and VVI(R)] in both unipolar and bipolar sensing configurations was tested. **RESULTS:** Interference was demonstrated during cellular phone operation in 74 of 2,418 (3.1%) episodes in eight patients. Three types of interference were observed: inhibition of pacing output, rapid ventricular tracking in DDD(R) or VDD(R) mode, and asynchronous pacing. All were observed only with the cellular phone positioned above the pacemaker pocket. Interference occurred prior to and after the termination of the ringing tone of the cellular phone in 57% of cases. Cellular phones with either digital or analog technology could cause interference. Unipolar atrial lead was most susceptible to interference (relative frequency of interference: unipolar 1.8%, bipolar 0.4%, $p < 0.05$; atrial 2.9%, ventricular 1%, $p < 0.05$). There was no sensor-driven rate acceleration during all tests. In all patients, reprogramming of the sensitivity level successfully prevented cellular phone interference. **CONCLUSIONS:** Commercially available cellular phones can cause reversible interference to implanted single- or dual-chamber permanent pacemakers. The effect is maximal with high atrial unipolar sensitivity, especially in single pass VDD(R) systems. Both digital and analog cellular phones can lead to interference. Pacemaker interference can occur prior to a warning sign (ringing tone) of the phone and may have significant implications in patient safety.

Barbaro V, Bartolini P, Donato A, Militello C, Electromagnetic interference of analog cellular telephones with pacemakers. Pacing Clin Electrophysiol 19(10):1410-1418, 1996.

The aim of this study was to verify whether there is a public health risk from the interference of analog cellular telephones with pacemakers. We used a human trunk simulator to reproduce an actual implant, and two cellular telephones working with the TACS (Total Access Communication System) standard. Results showed that the electromagnetic field radiated from the analog cellular telephones interfered with a large number of the pacemakers tested (10/25). When the telephone antenna was in

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close proximity to the pacemaker head, pacemaker desensitizing and sensitizing and pulse inhibition was detected at the moment of an incoming call and throughout ringing. In the worst case of pulse inhibition, the pacemaker skipped three nonconsecutive beats and then resumed its normal pacing, while the desensitizing and sensitizing phenomena persisted as long as the interfering signal was on. Pulse inhibition was also observed when the connection did not succeed. Maximum sensing threshold variation was about 186% (increase) and 62% (decrease) for desensitizing and sensitizing phenomena, respectively. It was also demonstrated that the signal emitted by analog cellular telephones during the crossing of contiguous cells could induce pacemaker pulse inhibition, but under our experimental conditions this event did not seem to pose a risk for the pacemaker patient.

Bassen HI, Moore HJ, Ruggera PS, Cellular phone interference testing of implantable cardiac defibrillators in vitro. Pacing Clin Electrophysiol 21(9):1709-1715, 1998.

An in vitro study was undertaken to investigate the potential for cellular telephones to interfere with representative models of presently used ICDs. Digital cellular phones (DCPs) generate strong, amplitude modulated fields with pulse repetition rates near the physiological range sensed by the ICD as an arrhythmia. DCPs with Time Division Multiple Access (TDMA) pulsed amplitude modulation caused the most pronounced effect--high voltage firing or inhibition of pacing output of the ICDs. This electromagnetic interference (EMI) occurred only when the phones were within 2.3-5.8 cm of the ICD pulse generator that was submerged 0.5 cm in 0.18% saline. ICD performance always reverted to baseline when the cellular phones were removed from the immediate proximity of the ICD. Three models of ICDs were subjected to EMI susceptibility testing using two types of digital phones and one analog cellular phone, each operating at their respective maximum output power. EMI was observed in varying degrees from all DCPs. Inhibition of pacer output occurred in one ICD, and high voltage firing occurred in the two other ICDs, when a TDMA-11 Hz DCP was placed within 2.3 cm of the ICD. For the ICD that was most sensitive to delivering unintended therapy, inhibition followed by firing occurred at distances up to 5.8 cm. When a TDMA-50 Hz phone was placed at the minimum test distance of 2.3 cm, inhibition followed by firing was observed in one of the ICDs. EMI occurred most frequently when the lower portion of the monopole antenna of the cellular phone was placed over the ICD header.

Occhetta E, Plebani L, Bortnik M, Sacchetti G, Trevisi G, Implantable cardioverter defibrillators and cellular telephones: is there any interference? Pacing Clin Electrophysiol 22(7):983-989, 1999.

The aim of our study was to consider cellular telephone interference using different cellular telephones and implantable cardioverter defibrillator (ICD) models. Thirty (26 men, 4 women) patients with ICDs were considered during follow-up. The ICD models were: Telectronics (7), CPI (7), Medtronic (7), Ventritex (5), and Ela Medical (4). All patients were monitored with surface ECG; permanent telemetric endo-ECG monitoring was activated. Then, the effect of two different European telephone systems were tested: TACS system (Sony CM-R111, 2W power) and GSM system (Motorola MG1-4A11,

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2 W power). For both systems, the effect during call, reception, active conversation (dialogue), and passive conversation (listening) were observed. Cellular telephones were located first in contact with the programming head, then near the leads system, and lastly, in the hands of the patient. At the end of the evaluations, memories were interrogated again to check for false arrhythmia detections. In five of these patients during arrhythmia induction at device implant (first implant or ICD replacement), we also evaluated possible interference between cellular telephones in the reception phase and the ventricular fibrillation detection phase of the ICD. All evaluated models showed significant noise in the telemetric transmission when the cellular telephone (both TACS and GSM) was located near the ICD and the programming head; noise was particularly significant during call and reception, in most cases leading to loss of telemetry. No false arrhythmia detections have been observed during tests with cellular telephones located on the ICDs. During tests performed with cellular telephones located near the leads or in the hands of patients, no telemetric noises or false arrhythmia detections were observed. During induced ventricular fibrillation and cellular telephones in reception mode near the device, the arrhythmia recognition was always correct and not delayed. In conclusion, present ICD models seem to be well protected from electromagnetic interference caused by European cellular telephones (TACS and GSM), without under-/oversensing of ventricular arrhythmias. However, cellular telephones disturb telemetry when located near the programming head. ICD patients should not be advised against the use of cellular telephones, but it has to be avoided during ICD interrogation and programming.

Cell Phone Addiction

Bianchi A, Phillips JG. Psychological predictors of problem mobile phone use. *Cyberpsychol Behav.* 8(1):39-51, 2005.

Mobile phone use is banned or illegal under certain circumstances and in some jurisdictions. Nevertheless, some people still use their mobile phones despite recognized safety concerns, legislation, and informal bans. Drawing potential predictors from the addiction literature, this study sought to predict usage and, specifically, problematic mobile phone use from extraversion, self-esteem, neuroticism, gender, and age. To measure problem use, the Mobile Phone Problem Use Scale was devised and validated as a reliable self-report instrument, against the Addiction Potential Scale and overall mobile phone usage levels. Problem use was a function of age, extraversion, and low self-esteem, but not neuroticism. As extraverts are more likely to take risks, and young drivers feature prominently in automobile accidents, this study supports community concerns about mobile phone use, and identifies groups that should be targeted in any intervention campaigns.

Koylu H, Mollaoglu H, Ozguner F, Nazyroglu M, Delibab N. Melatonin modulates 900 Mhz microwave-induced lipid peroxidation changes in rat brain. *Toxicol Ind Health.* 22(5):211-216, 2006.

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Microwaves (MW) from cellular phones may affect biological systems by increasing free radicals, which may enhance lipid peroxidation levels of the brain, thus leading to oxidative damage. Melatonin is synthesized in and secreted by the pineal gland at night and exhibits anti-oxidant properties. Several studies suggest that supplementation with anti-oxidant can influence MW-induced brain damage. The present study was designed to determine the effects of MW on the brain lipid peroxidation system, and the possible protective effects of melatonin on brain degeneration induced by MW. Twenty-eight Sprague-Dawley male rats were randomly divided into three groups as follows: (1) sham-operated control group (N = 8); (2) study 900-MHz MW-exposed group (N = 8); and (3) 900-MHz MW-exposed+melatonin (100 microg/kg sc before daily MW exposure treated group) (N = 10). Cortex brain and hippocampus tissues were removed to study the levels of lipid peroxidation as malonyl dialdehyde. The levels of lipid peroxidation in the brain cortex and hippocampus increased in the MW group compared with the control group, although the levels in the hippocampus were decreased by MW+melatonin administration. The brain cortex lipid peroxidation levels were unaffected by melatonin treatment. We conclude that melatonin may prevent MW-induced oxidative changes in the hippocampus by strengthening the anti-oxidant defense system, by reducing oxidative stress products.

Synergistic Effects with Other Agents

Pakhomov AG, Dubovick BV, Degtyariov IG, Pronkevich AN, Microwave influence on the isolated heart function: II. Combined effect of radiation and some drugs. *Bioelectromagnetics* 16(4):250-254, 1995.

The combined effects of microwave radiation and some drugs were studied in an isolated frog auricle preparation. The experiments established that exposure to pulse-modulated 915 MHz microwaves for up to 40 min had no effect on either the rate or the amplitude of spontaneous auricle twitches, unless the average absorbed power was high enough to produce preparation heating. Treatment of the preparation with saline containing (0.6-3.0) 10^{-5} M of propranolol or (0.5-1.5) 10^{-7} M of atropine altered neither its pacemaker nor its contractile functions; these drugs also had no effect when they were combined with nonthermal microwave irradiation. Caffeine (1 mM) strongly increased the average heart power, which was calculated as the product of twitch rate and amplitude. The caffeine effect appeared to be significantly augmented (by about 15%, $P < 0.02$) under exposure to burst-type pulsed microwaves (pulse width, 1.5 msec; pause, 2.5 msec; 8 pulses/burst, 16 bursts/s; average SAR, 8-10 W/kg). By itself, this modulation was not effective; the heating of the preparation and saline during exposure was approximately 0.1 degrees C, which could not account for the detected changes. The experimental results demonstrate that caffeine treatment increases the microwave sensitivity of the frog auricle preparation and reveals primarily subthreshold, nonthermal microwave effect.

Nelson BK, Conover DL, Brightwell WS, Shaw PB, Werren D, Edwards RM, Lary JM,

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Marked increase in the teratogenicity of the combined administration of the industrial solvent 2-methoxyethanol and radiofrequency radiation in rats. *Teratology* 43(6):621-634, 1991.

Limited published animal research reports synergistic teratogenic effects following combined hyperthermia (induced by elevated ambient temperature) and administration of chemical teratogens. Radiofrequency (RF) radiation is widely used in occupational environments. Since RF radiation also elevates the body temperature of, and is teratogenic to, exposed animals, concurrent RF radiation and chemical agent administration may enhance teratogenicity. The present exploratory study, consisting of preliminary dose-finding studies and the primary study, was designed to investigate whether concurrent exposure of rats to RF radiation and the industrial solvent 2-methoxyethanol (2ME) can enhance the developmental toxicity of either agent acting alone. Preliminary dose-finding studies using small numbers of rats investigated the ability of various RF radiation conditions and doses of 2ME to produce external malformations (primarily of the paws) when administered on gestation day 13. Based on these preliminary studies, RF radiation exposure [sufficient to elevate rectal temperature to 42.0 degrees C (4 degrees C above normal for rats) for 30 min] and 2ME administration (150 mg/kg) were selected for the primary study. In the primary study, groups of 18 to 27 pregnant rats were administered RF radiation exposure and distilled water gavage, 2ME gavage and sham RF exposure, RF radiation exposure and 2ME gavage concurrently, or sham RF exposure and distilled water gavage. Pregnant rats were sacrificed on gestation day 20, and the offspring were examined for external malformations. Combined exposures enhanced the adverse effects produced by either experimental agent alone (no malformations were detected in the double sham group). Mean fetal malformations/litter increased from 14% after 2ME and sham RF (15/26 litters affected, with an average of 2 fetuses/litter malformed) and 30% after RF radiation and water gavage (10/18 litters affected, with an average of 4 fetuses/litter malformed), to 76% after the combined treatment (18/18 litters affected, with an average of 12 fetuses/litter malformed). In addition to a significant increase in the frequency of malformations, the severity of malformations also was enhanced by the combination treatment (on a relative severity ranking scale, the 2ME severity score was less than 1, the RF score was 3, and the combination score was 6). This study provided evidence of synergism between RF radiation and 2ME administration, but additional research will be required to characterize the extent of synergism between these two agents. Potential interactive effects between chemical and physical agents need to be investigated to determine the extent to which such interactions should impact occupational exposure standards.

Nelson BK, Conover DL, Shaw PB, Werren DM, Edwards RM, Hoberman AM, Interactive developmental toxicity of radiofrequency radiation and 2-methoxyethanol in rats. *Teratology* 50(4):275-293, 1994.

Concurrent exposures to chemical and physical agents occur in the workplace; exposed workers include those involved with the microelectronics industry, plastic sealers, and electrosurgical units. Previous animal research indicates that hyperthermia induced by

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an elevation in ambient temperature can potentiate the toxicity and teratogenicity of some chemical agents. We previously demonstrated that combined exposure to radiofrequency (RF; 10 MHz) radiation, which also induces hyperthermia and is teratogenic to exposed animals, and the industrial solvent, 2-methoxyethanol (2ME), produces enhanced teratogenicity in rats. The present study replicates and extends the previous research investigating the enhanced teratogenicity of combined RF radiation and 2ME exposures. The interactive dose-related teratogenicity of RF radiation (sham exposure or maintaining colonic temperatures at 42.0 degrees C for 0, 10, 20, or 30 min) and 2ME (0, 75, 100, 125, or 150 mg/kg) was investigated by administering various combinations of RF radiation and 2ME to groups of rats on gestation days 9 or 13; gestation-day 20 fetuses were examined for external, skeletal, and visceral malformations. The results are consistent with and extend our previous research findings. Synergism was observed between RF radiation and 2ME for some treatment combinations, but not for others. The study also clarified which gestational periods, RF radiation exposure durations, and 2ME doses would be most informative in future interaction studies to determine the lowest interactive effect level. Day 9 exposures generally evidenced little effect by 2ME, either by itself or in combination with RF radiation. In contrast, day 13 exposures resulted in highly significant effects from 2ME and RF radiation. The structures showing strong evidence of effects from both 2ME and RF radiation after exposure on gestation day 13 were the forepaw digits, forepaw phalanges, hindpaw digits, hindpaw phalanges, hind limbs, metacarpals, and metatarsals. Statistical analyses did not show a global synergistic effect, but did show evidence for a synergistic effect at intermediate levels of the dose ranges. Future research will address potential interactions at lower doses.

Mortazavi SMJ, Mosleh-Shirazi MA, Tavassoli AR, Taheri M, Bagheri Z, Ghalandari R, Bonyadi S, Shafie M, Haghani M. A comparative study on the increased radioresistance to lethal doses of gamma rays after exposure to microwave radiation and oral intake of flaxseed oil. Iran. J. Radiat. Res. 9(1): 9-14, 2011.

Background: Mobile phones, use electromagnetic radiation in the microwave range. On the other hand, there is only one report on radioprotective effects of flaxseed oil. The aim of this study was to investigate the effect of irradiation of rats with microwaves and/or treatment with flaxseed oil on the induction of adaptive response to a subsequent lethal dose (LD) of gamma rays. **Materials and Methods:** Eighty male rats were randomly divided into 6 groups of 13-15 animals. The animals in the 1st to 5th groups received microwave exposure, microwave+flaxseed oil (dissolved in olive oil), flaxseed (continued after LD), flaxseed, and olive oil. At day 5, all animals were whole-body irradiated with a previously reported LD 50/30 of 8 Gy gamma radiation. The 6th group (controls) received the same LD 50/30, but there was not any other treatment before or after the LD. **Results:** No death event was observed during days 1-9 after LD irradiation in either group. At day 10, death events started in the 4th group. Thirty days after irradiation of the animals, the survival fractions for the control group, as expected, was 53.3% while there was no death event in the 1st group (survival rate of 100% in

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microwave-pretreated animals). The survival fractions for the 2nd to 5th groups were 69.2%, 92.3%, 46.1%, and 61.5%, respectively. **Conclusion:** While these findings open new horizons in radiation protection, the radioresistance induced by microwave radiations emitted by a mobile phone may interfere with the outcome of any subsequent therapeutic application of photons or radioisotopes.

Gadhia PK, Shah T, Mistry A, Pithawala M, Tamakuwala D. A preliminary study to assess possible chromosomal damage among users of digital mobile phones. Electromag Biol Med 22:149-159, 2003.

In a preliminary study to examine possible lymphocyte chromosomal damage, we have tested two cytogenetic endpoints, namely, chromosomal aberrations (CA) and sister chromatid exchange frequencies (SCE), in 24 mobile phone users (12 nonsmoker–nonalcoholic subjects and 12 smoker–alcoholics), who used digital mobile phones for at least 2 years, employing Gaussian Minimum Shift Keying modulations with uplink frequencies at 935–960 MHz. and downlinks at 890–915 MHz. For comparison, the control study group included another 24 individuals, matched according to their age, sex, drinking and smoking habits, as well as similar health status, working habits, and professional careers; but did not use mobile phones. Blood samples of 12 mobile users (6 smoker–alcoholic and 6 nonsmoker–nonalcoholic) and 12 controls (identical to mobile users in every respect) were further treated with a known mutagen Mitomycin-C (MMC) to find out comutagenic/synergistic effect. A complete blood picture for each individual was assessed with an automatic particle cell counter. There was a significant increase ($P < 0.05$) in dicentric chromosomes among mobile users who were smoker–alcoholic as compared to nonsmoker–nonalcoholic; the same held true for controls of both types. After MMC treatment, there was a significant increase in dicentrics ($P < 0.05$) and ring chromosomes ($P < 0.001$) in both smoker–alcoholic and nonsmoker–nonalcoholic mobile users when compared with the controls. Although SCEs showed a significant increase among mobile users, no change in cell cycle progression was noted. The hematological picture showed only minor variations between mobile users and controls.

Del Signore A, Boscolo P, Kouri S, Di Martino G, Giuliano G, Combined effects of traffic and electromagnetic fields on the immune system of fertile atopic women. Ind Health 38(3):294-300, 2000.

Object of this preliminary study was the immune response to high or low frequency electromagnetic fields (ELMF) of non-atopic and atopic fertile women with uniform exposure to toxic compounds produced by traffic. Women were divided in group A (non-atopic, non-exposed to ELMF); B (atopic, non-exposed to ELMF); C (non-atopic, exposed to ELMF); D (atopic, exposed to ELMF). "In vitro" cell proliferation of peripheral blood mononuclear cells (PBMC) of atopic women (groups B and D) stimulated by phytohaemagglutinin (PHA) was reduced. The ELMF exposed women (groups C and D) showed lower levels of blood NK CD16(+)-CD56+ lymphocyte subpopulations and of "in vitro" production of interferon-gamma (both spontaneously and in presence of PHA) by PBMC, suggesting that ELMF reduces blood cytotoxic activity. Serum IgE of the atopic

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women exposed to ELMF (group D) was higher than that of the other groups. Linear discriminant analysis including serum zinc and copper (essential enzymes for immune functions), blood lead and urinary transtrans muconic acid, a metabolite of benzene (markers of exposure to traffic) and key parameters of immune functions (CD16(+)-CD56+ lymphocyte subset, serum IgE, interferon-gamma produced by PBMC in presence of PHA, stimulation index of blastogenesis) showed absence of significant difference between groups A and C and a marked separation of groups B and D. This datum suggests that ELMF have a greater influence on atopic women exposed to traffic than on non-atopic ones.

Boga A, Emre M, Sertdemir Y, Akillioglu K, Binokay S, Demirhan O. The effect of 900 and 1800MHz GSM-like radiofrequency irradiation and nicotine sulfate administration on the embryonic development of *Xenopus laevis*. *Ecotoxicol Environ Saf.* 2014 Dec 19;113C:378-390. doi: 10.1016/j.ecoenv.2014.12.020. [Epub ahead of print]

The aim of this study was to investigate the effects of GSM-like radiofrequency electromagnetic radiation (RF EMR) and nicotine sulfate (NS) exposure on *Xenopus* embryonic development. The developmental effects of GSM-like RF-EMR (900-1800MHz, at a SAR value of 1W/kg and NS on *Xenopus laevis* embryos were investigated). Following the application of radiofrequency radiation and/or NS administration, the embryos were closely examined in order to determine their possible teratogenic effects. *Xenopus* frogs obtained from the Department of Physiology of the Cukurova University, in accordance described by the Standard Guide of the American Society for Testing and Materials (ASTM). Following the exposure of *Xenopus* embryos to RF-EMR at 900 and 1800MHz (1.0W/kg) for 4, 6 and 8h; the whole body specific energy absorption rate (SAR) of the embryos was calculated. With the exception of irradiation at 1800MHz no dramatic developmental anomalies were observed in the *Xenopus* embryos in association with RF-EMR applications. Combined RF-EMR and NS applications resulted in dramatic abnormalities and death among the *Xenopus* embryos. The study results indicated that GSM-like RF-EMR (e.g. radiation from cell phones) was not as harmful to *Xenopus* embryos as might have been expected. However, the combined effects of GSM-like RF-EMR and NS on *Xenopus* embryos were more severe than the effect of RF-EMR or NS alone. In conclusion, the study results appear to suggest that the combined use of nicotine and cell phones might result in more pronounced detrimental effects on the health of smokers.

Byun YH, Ha M, Kwon HJ, Hong YC, Leem JH, Sakong J, Kim SY, Lee CG, Kang D, Choi HD, Kim N. Mobile phone use, blood lead levels, and attention deficit hyperactivity symptoms in children: a longitudinal study. *PLoS One.* 2013;8(3):e59742.

BACKGROUND: Concerns have developed for the possible negative health effects of radiofrequency electromagnetic field (RF-EMF) exposure to children's brains. The purpose of this longitudinal study was to investigate the association between mobile phone use and symptoms of Attention Deficit Hyperactivity Disorder (ADHD) considering the modifying effect of lead exposure. METHODS: A total of 2,422 children at 27 elementary schools in 10 Korean cities were examined and followed up 2 years later.

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Parents or guardians were administered a questionnaire including the Korean version of the ADHD rating scale and questions about mobile phone use, as well as socio-demographic factors. The ADHD symptom risk for mobile phone use was estimated at two time points using logistic regression and combined over 2 years using the generalized estimating equation model with repeatedly measured variables of mobile phone use, blood lead, and ADHD symptoms, adjusted for covariates. RESULTS: The ADHD symptom risk associated with mobile phone use for voice calls but the association was limited to children exposed to relatively high lead. CONCLUSIONS: The results suggest that simultaneous exposure to lead and RF from mobile phone use was associated with increased ADHD symptom risk, although possible reverse causality could not be ruled out.

Cao Y, Xu Q, Lu MX, Jin ZD, DU HB, Li JX, Nie JH, Tong J. [Antagonistic effect of microwave on hematopoietic damage of mice induced by gamma-ray irradiation.] *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi.* 27(9):525-529, 2009. [Article in Chinese]

OBJECTIVE: To investigate antagonistic effect of microwave on hematopoietic damage of mice induced by gamma-ray irradiation. METHODS: Male healthy Kunming mice were treated with low dose microwave radiation before exposure to (60)Co gamma-ray irradiation of 8.0 Gy. The 30-day survival rate and average survival time of the mice after the treatment were examined. Peripheral blood parameters and the organ indexes of thymus and spleen were also observed in the irradiated mice. After exposure to 5.0 Gy gamma irradiation, indexes of hematopoietic foci formation of bone marrow cells (CFU-GM) and the proliferation activity of BMNCs were examined. The serum concentration of hemopoietic factors (GM-CSF and IL-3) were detected by ELISA kits. RESULTS: Pre-exposure with 120 microW/cm(2) 900 MHz microwave increased the 30-day survival rate ($P < 0.05$) and the number of white blood cells of gamma-ray treated mice. The increases of the organ indexes of thymus and spleen, proliferation activity of BMNCs and CFU-GM hematopoietic foci numbers, as well as the higher serum concentration of GM-CSF and IL-3 were observed in the microwave pre-exposure group. CONCLUSION: Low dose microwave radiation may exert potential antagonistic effects on hematopoietic injuries induced by ionizing radiation. The underlying mechanisms might be related with stimulation of hematopoietic growth factors expression, promotion of HSCs/HPCs proliferation, suppression on the reduction of HSCs/HPCs caused by (60)Co gamma-ray, and enhanced construction of the hematopoietic system.

Cao Y, Zhang W, Lu MX, Xu Q, Meng QQ, Nie JH, Tong J. 900-MHz microwave radiation enhances gamma-ray adverse effects on SHG44 cells. *J Toxicol Environ Health A.* 72(11):727-732, 2009.

Mobile phones are widely used globally. However, the biological effects due to exposure to electromagnetic fields (EMF) produced by mobile phones are largely unknown. Environmental and occupational exposure of humans to gamma-rays is a biologically relevant phenomenon. Consequently studies were undertaken to examine the interactions between gamma-rays and EMF on human health. In this study, exposure to

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900-MHz EMF expanded gamma-ray damage to SHG44 cells. Preexposure EMF enhanced the decrease in cell proliferation induced by gamma-ray irradiation and the rate of apoptosis. The combination of EMF and gamma-ray exposure resulted in a synergistic effect by triggering stress response, which increased reactive oxygen species, but the expression of hsp70 at both mRNA and protein levels remained unaltered. Data indicate that the adverse effects of gamma-rays on cellular functions are strengthened by EMF.

Bodera P, Stankiewicz W, Antkowiak B, Paluch M, Kieliszek J, Sobiech J, Zdanowski R, Wojdas A, Siwicki AK, Skopińska-Różewska E. Suppressive effect of electromagnetic field on analgesic activity of tramadol in rats. Pol J Vet Sci. 15(1):95-100, 2012.

The electromagnetic fields (EMFs) have been shown to alter animal and human behavior, such as directional orientation, learning, pain perception (nociception or analgesia) and anxiety-related behaviors. The aim of this study was to evaluate the influence of electromagnetic fields of high-frequency microwaves on pain perception and anti-nociceptive activity of tramadol (TRAM) - analgetic effective in the treatment of moderate to severe acute and chronic pain states. Electromagnetic fields exposures of a) 1500 MHz frequency and b) modulated, 1800 MHz (which is identical to that generated by mobile phones) were applied. Paw withdrawal latency (PWL) to thermal stimulus was measured in vehicle or tramadol (TRAM) treated animals before and after 30, 60 and 90 minutes from injections. The differences in the level of pain (PWL) between control group and rats exposed to EMF alone in three measurements, were not observed. Tramadol alone significantly increased PWLs to thermal stimulus in comparison to vehicle results at 30 ($p < 0.001$) and 60 minutes ($p < 0.05$) after drug injection. EMF exposure of both frequencies transiently suppressed analgesic effect of tramadol, significantly reducing paw withdrawal latency in animals treated with this drug at 30 minutes from the drug injection.

Cao Y, Xu Q, Lu MX, Jin ZD, DU HB, Li JX, Nie JH, Tong J. [Antagonistic effect of microwave on hematopoietic damage of mice induced by gamma-ray irradiation.] Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 27(9):525-529, 2009. [Article in Chinese]

OBJECTIVE: To investigate antagonistic effect of microwave on hematopoietic damage of mice induced by gamma-ray irradiation. METHODS: Male healthy Kunming mice were treated with low dose microwave radiation before exposure to (60)Co gamma-ray irradiation of 8.0 Gy. The 30-day survival rate and average survival time of the mice after the treatment were examined. Peripheral blood parameters and the organ indexes of thymus and spleen were also observed in the irradiated mice. After exposure to 5.0 Gy gamma irradiation, indexes of hematopoietic foci formation of bone marrow cells (CFU-GM) and the proliferation activity of BMNCs were examined. The serum concentration of hemopoietic factors (GM-CSF and IL-3) were detected by ELISA kits. RESULTS: Pre-exposure with 120 microW/cm(2) 900 MHz microwave increased the 30-day survival rate ($P < 0.05$) and the number of white blood cells of gamma-ray treated mice. The increases of the organ indexes of thymus and spleen, proliferation activity of BMNCs

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and CFU-GM hematopoietic foci numbers, as well as the higher serum concentration of GM-CSF and IL-3 were observed in the microwave pre-exposure group. CONCLUSION: Low dose microwave radiation may exert potential antagonistic effects on hematopoietic injuries induced by ionizing radiation. The underlying mechanisms might be related with stimulation of hematopoietic growth factors expression, promotion of HSCs/HPCs proliferation, suppression on the reduction of HSCs/HPCs caused by (60)Co gamma-ray, and enhanced construction of the hematopoietic system.

Inflammation

Li CY, Liao MH, Lin CW, Tsai WS, Huang CC, Tang TK. Inhibitory Effects of Microwave Radiation on LPS-Induced NF κ B Expression in THP-1 Monocytes. Chin J Physiol. 55(6):421-427, 2012.

Microwave radiations can be encountered regularly in daily lives. When WHO announced that microwave radiations were a kind of environmental energy which interfere with the physiological functions of the human body, great concerns have been raised over the damages microwave frequencies can do to human physiology. The immunological performance and the activities of the cellular inflammatory factor NF κ B have been closely related in monocyte. Due to the effect of phorbol 12-myristate 13-acetate (PMA) on THP-1 monocytes, THP-1 monocytes would differentiate into macrophages and would then react with lipopolysaccharides (LPS), and the amount of NF κ B increased in the THP-1 monocytes. Expression of cytokine is affected when cells are exposed to a frequency of 2450 MHz and at 900 W. Thus, in our experiments, an observation was made when THP-1 monocytes were stimulated with PMA and LPS to differentiate into macrophage, the amount of NF κ B in cells increased exponentially, and the levels of NF κ B expression were decreased by the exposure of microwave radiation. In conclusion, microwave radiations were found to inhibit the activity functions of THP-1 monocytes stimulated with PMA and LPS.

Dabrowski MP, Stankiewicz W, Kubacki R, Sobiczewska E, Szmigielski S. Immunotropic Effects in Cultured Human Blood Mononuclear Cells Pre-exposed to Low-Level 1300 MHz Pulse-Modulated Microwave Field. Electromag. Biol. Med. 22:1-13, 2003.

The samples of mononuclear cells isolated from peripheral blood of healthy donors (N = 16) were exposed to 1300 MHz pulse-modulated microwaves at 330 pps with 5 μ s pulse width. The samples were exposed in an anechoic chamber at the average value of power density of $S = 10 \text{ W/m}^2$ (1 mW/cm^2). The average specific absorption rate (SAR) was measured in rectangular waveguide and the value of SAR = 0.18 W/kg was recorded. Subsequently, the exposed and control cells were assessed in the microculture system for several parameters characterizing their proliferative and immunoregulatory properties. Although the irradiation decreased the spontaneous incorporation of 3H-thymidine, the proliferative response of lymphocytes to phytohemagglutinin (PHA) and to Con A as well as the T-cell suppressive activity (SAT index) and the saturation of IL-2 receptors did not change. Nevertheless, the

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lymphocyte production of interleukin (IL)-10 increased ($P < .001$) and the concentration of IFN γ remained unchanged or slightly decreased in the culture supernatants. Concomitantly, the microwave irradiation modulated the monokine production by monocytes. The production of IL-1 β increased significantly ($P < .01$), the concentration of its antagonist (IL-1ra) dropped by half ($P < .01$) and the tumor necrosis factor (TNF- α) concentration remained unchanged. These changes of monokine proportion (IL-1 β vs. IL-1ra) resulted in significant increase of the value of LM index ($P < .01$), which reflects the activation of monocyte immunogenic function. The results indicate that pulse-modulated microwaves represent the potential of immunotropic influence, stimulating preferentially the immunogenic and proinflammatory activity of monocytes at relatively low levels of exposure.

Zhou ZD, Zeng QL, Zheng Y, Zhang JB, Chen HY, Lu DQ, Shao CS, Xia DJ. [Surface markers and functions of human dendritic cells exposed to mobile phone 1800 MHz electromagnetic fields.] Zhejiang Da Xue Xue Bao Yi Xue Ban. 37(1):29-33, 2008.[Article in Chinese]

OBJECTIVE: To investigate the effects of mobile phone 1800 MHz electromagnetic fields (EMF) on the surface markers and the functions of human dendritic cells (DC).
 METHODS: Human DCs were exposed to intermittent 5 min on/10 min off EMF with specific absorption rates (SAR) 4 W/kg for 0 h, 1 h, 12 h or 24 h, respectively. FACS analysis was used to detect the positive percentage of DC surface markers including HLA-DR and co-stimulatory molecules such as CD80, CD86, CD40 and CD11c. CCK-8 kit was adopted to examine the function of allo-mixed lymphocyte reaction (allo-MLR) of DC, and enzyme linked immunosorbent assay (ELISA) to identify the levels of IL-12p70 and TNF-alpha secreted by DC. RESULT: Compared with the sham radiation group, after exposure to the electromagnetic fields for 1 h, 12 h, or 24 h, HLA-DR, CD80, CD86 and CD40 were all declined except CD11c. The ability of DC allo-MLR in each exposure group was decreased significantly ($P < 0.05$), especially in the 24 h exposure group. However, the secreted levels of IL-12p70 and TNF-alpha of DC in each exposure group remained no changed. Conclusion: The study showed that EMF exposure could down-regulate the surface molecules and stimulation ability of human DC.

Effects on Behavior

Shtemberg AS, Uzbekov MG, Shikhov SN, Bazian AS, Cherniakov GM, [Species specificity, age factors, and various neurochemical correlates of the animal spontaneous behavior after exposure to electromagnetic field of the ultralow intensity]. Zh Vyssh Nerv Deiat Im I P Pavlova 50(4):703-715, 2000. [Article in Russian]
 Behavioral and neurochemical reactions of small laboratory animals (mice and rats of different age) under exposure to ultralow-intensity electromagnetic fields (EMF, frequency of 4200 and 970 MHz, modulated by a quasistochastic signal in the range of 20-20,000 Hz, power density 15 microW/cm², specific body absorption rate up to 4.5

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mJ/kg) were studied. The EMF basically inhibited the locomotor and exploratory activity in the "open-field" test. The species- and age-specific features rather than radiation conditions dominated. However, decrease in the EMF frequency considerably intensified the observed effect. Change in animal behavior was accompanied by shifts in neurochemical processes, i.e., sharp activation of serotonergic and inhibition of morepinephrnergic system.

Narayanan SN, Kumar RS, Pavai J, Kedage V, Bhat MS, Nayak S, Bhat PG. Analysis of emotionality and locomotion in radio-frequency electromagnetic radiation exposed rats. *Neurol Sci.* 34(7):1117-1124, 2013.

In the current study the modulatory role of mobile phone radio-frequency electromagnetic radiation (RF-EMR) on emotionality and locomotion was evaluated in adolescent rats. Male albino Wistar rats (6-8 weeks old) were randomly assigned into the following groups having 12 animals in each group. Group I (Control): they remained in the home cage throughout the experimental period. Group II (Sham exposed): they were exposed to mobile phone in switch-off mode for 28 days, and Group III (RF-EMR exposed): they were exposed to RF-EMR (900 MHz) from an active GSM (Global system for mobile communications) mobile phone with a peak power density of 146.60 $\mu\text{W}/\text{cm}^2$ for 28 days. On 29th day, the animals were tested for emotionality and locomotion. Elevated plus maze (EPM) test revealed that, percentage of entries into the open arm, percentage of time spent on the open arm and distance travelled on the open arm were significantly reduced in the RF-EMR exposed rats. Rearing frequency and grooming frequency were also decreased in the RF-EMR exposed rats. Defecation boli count during the EPM test was more with the RF-EMR group. No statistically significant difference was found in total distance travelled, total arm entries, percentage of closed arm entries and parallelism index in the RF-EMR exposed rats compared to controls. Results indicate that mobile phone radiation could affect the emotionality of rats without affecting the general locomotion.

Kumar RS, Sareesh NN, Nayak S, Mailankot M. Hypoactivity of Wistar rats exposed to mobile phone on elevated plus maze. *Indian J Physiol Pharmacol.* 53(3):283-286, 2009.

No abstract available. From discussion section: "In conclusion, our preliminary results indicate mobile phone exposure induced behavioral changes in rats, expressed as deficit in open arm exploration on elevated plus-maze."

Sokolovic D, Djordjevic B, Kocic G, Babovic P, Ristic G, Stanojkovic Z, Sokolovic DM, Veljkovic A, Jankovic A, Radovanovic Z. The effect of melatonin on body mass and behaviour of rats during an exposure to microwave radiation from mobile phone. *Bratisl Lek Listy.* 113(5):265-269, 2012.

BACKGROUND: Microwave radiation (MW) produced by wireless telecommunications and a number of electrical devices used in household or in healthcare institutions may cause various disorders in human organism. On the other hand, melatonin is a potent antioxidant, immunostimulator and neuromodulator. The aim of this research was to

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determine body mass and behaviour changes in rats after a chronic microwave exposure, as well as to determine the effects of melatonin on body mass and behaviour in irradiated rats. METHODS: Wistar rats were divided into the four experimental groups: I group (control) - rats treated with 0,9 % saline, II group (Mel) - rats treated with melatonin (2 mg/kg), III group (MW) - rats exposed to MW radiation (4 h/day), IV group (MW+Mel) - rats, which were both exposed to MW radiation and received melatonin premedication (2 mg/kg). RESULTS: A significant body mass reduction was noted in animals exposed to MW radiation when compared to controls after 20, 40 and 60 days ($p < 0.001$). Furthermore, body weight was significantly increased ($p < 0.05$) in irradiated rats, which received melatonin pretreatment (MW+Mel) in comparison to irradiated group (MW) after 20 days. Microwave radiation exposed animals showed an anxiety related behaviour (agitation, irritability) after 10 days of exposure. After the radiation source removal, changes in behaviour were less noticeable. Melatonin administration to irradiated rats caused a decrease in the stress induced behaviour. CONCLUSION: Microwave radiation causes body mass decrease and anxiety related behaviour in rats, however melatonin causes a reverse of those effects on both body weight and behaviour of irradiated animals (Fig. 2, Ref. 32).

Júnior LC, Guimarães ED, Musso CM, Stabler CT, Garcia RM, Mourão-Júnior CA, Andreazzi AE. Behavior and memory evaluation of Wistar rats exposed to 1.8 GHz radiofrequency electromagnetic radiation. *Neurol Res.* 2014 Jan 27:1743132813Y000000276. [Epub ahead of print]

Background: The development of communication systems has brought great social and economic benefits to society. As mobile phone use has become widespread, concerns have emerged regarding the potential adverse effects of radiofrequency electromagnetic radiation (RF-EMR) used by these devices. Objective: To verify potential effects of mobile phone radiation on the central nervous system (CNS) in an animal model. Methods: Male Wistar rats (60 days old) were exposed to RF-EMR from a Global System for Mobile (GSM) cell phone (1.8 GHz) for 3 days. At the end of the exposure, the following behavioral tests were performed: open field and object recognition. Results: Our results showed that exposed animals did not present anxiety patterns or working memory impairment, but stress behavior actions were observe. Conclusion: Given the results of the present study, we speculate that RF-EMR does not promote CNS impairment, but suggest that it may lead to stressful behavioral patterns.

Divan HA, Kheifets L, Obel C, Olsen J. Prenatal and postnatal exposure to cell phone use and behavioral problems in children. *Epidemiology.* 19(4):523-529, 2008.

BACKGROUND: The World Health Organization has emphasized the need for research into the possible effects of radiofrequency fields in children. We examined the association between prenatal and postnatal exposure to cell phones and behavioral problems in young children. METHODS: Mothers were recruited to the Danish National Birth Cohort early in pregnancy. When the children of those pregnancies reached 7 years of age in 2005 and 2006, mothers were asked to complete a questionnaire regarding the current health and behavioral status of children, as well as past exposure

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to cell phone use. Mothers evaluated the child's behavior problems using the Strength and Difficulties Questionnaire. RESULTS:: Mothers of 13,159 children completed the follow-up questionnaire reporting their use of cell phones during pregnancy as well as current cell phone use by the child. Greater odds ratios for behavioral problems were observed for children who had possible prenatal or postnatal exposure to cell phone use. After adjustment for potential confounders, the odds ratio for a higher overall behavioral problems score was 1.80 (95% confidence interval = 1.45-2.23) in children with both prenatal and postnatal exposure to cell phones. CONCLUSIONS: Exposure to cell phones prenatally-and, to a lesser degree, postnatally-was associated with behavioral difficulties such as emotional and hyperactivity problems around the age of school entry. These associations may be noncausal and may be due to unmeasured confounding. If real, they would be of public health concern given the widespread use of this technology.

Divan HA, Kheifets L, Obel C, Olsen J. Cell phone use and behavioural problems in young children. J Epidemiol Community Health.66(6):524-529, 2012.

Background: Potential health effects of cell phone use in children have not been adequately examined. As children are using cell phones at earlier ages, research among this group has been identified as the highest priority by both national and international organisations. The authors previously reported results from the Danish National Birth Cohort (DNBC), which looked at prenatal and postnatal exposure to cell phone use and behavioural problems at age 7years. Exposure to cell phones prenatally, and to a lesser degree postnatally, was associated with more behavioural difficulties. The original analysis included nearly 13 000 children who reached age 7 years by November 2006. Methods: To see if a larger, separate group of DNBC children would produce similar results after considering additional confounders, children of mothers who might better represent current users of cell phones were analysed. This 'new' dataset consisted of 28 745 children with completed Age-7 Questionnaires to December 2008. Results: The highest OR for behavioural problems were for children who had both prenatal and postnatal exposure to cell phones compared with children not exposed during either time period. The adjusted effect estimate was 1.5 (95% CI 1.4 to 1.7). Conclusions: The findings of the previous publication were replicated in this separate group of participants demonstrating that cell phone use was associated with behavioural problems at age 7years in children, and this association was not limited to early users of the technology. Although weaker in the new dataset, even with further control for an extended set of potential confounders, the associations remained.

Daniels WM, Pitout IL, Afullo TJ, Mabandla MV. The effect of electromagnetic radiation in the mobile phone range on the behaviour of the rat. Metab Brain Dis. 24(4):629-641, 2009

Electromagnetic radiation (EMR) is emitted from electromagnetic fields that surround power lines, household appliances and mobile phones. Research has shown that there are connections between EMR exposure and cancer and also that exposure to EMR may result in structural damage to neurons. In a study by Salford et al. (Environ Health

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Perspect 111:881-883, 2003) the authors demonstrated the presence of strongly stained areas in the brains of rats that were exposed to mobile phone EMR. These darker neurons were particularly prevalent in the hippocampal area of the brain. The aim of our study was to further investigate the effects of EMR. Since the hippocampus is involved in learning and memory and emotional states, we hypothesised that EMR will have a negative impact on the subject's mood and ability to learn. We subsequently performed behavioural, histological and biochemical tests on exposed and unexposed male and female rats to determine the effects of EMR on learning and memory, emotional states and corticosterone levels. We found no significant differences in the spatial memory test, and morphological assessment of the brain also yielded non-significant differences between the groups. However, in some exposed animals there were decreased locomotor activity, increased grooming and a tendency of increased basal corticosterone levels. These findings suggested that EMR exposure may lead to abnormal brain functioning.

Razavinasab M, Moazzami K, Shabani M. Maternal mobile phone exposure alters intrinsic electrophysiological properties of CA1 pyramidal neurons in rat offspring. Toxicol Ind Health. 2014 Mar 6. [Epub ahead of print]

Some studies have shown that exposure to electromagnetic field (EMF) may result in structural damage to neurons. In this study, we have elucidated the alteration in the hippocampal function of offspring Wistar rats (n = 8 rats in each group) that were chronically exposed to mobile phones during their gestational period by applying behavioral, histological, and electrophysiological tests. Rats in the EMF group were exposed to 900 MHz pulsed-EMF irradiation for 6 h/day. Whole cell recordings in hippocampal pyramidal cells in the mobile phone groups did show a decrease in neuronal excitability. Mobile phone exposure was mostly associated with a decrease in the number of action potentials fired in spontaneous activity and in response to current injection in both male and female groups. There was an increase in the amplitude of the afterhyperpolarization (AHP) in mobile phone rats compared with the control. The results of the passive avoidance and Morris water maze assessment of learning and memory performance showed that phone exposure significantly altered learning acquisition and memory retention in male and female rats compared with the control rats. Light microscopy study of brain sections of the control and mobile phone-exposed rats showed normal morphology. Our results suggest that exposure to mobile phones adversely affects the cognitive performance of both female and male offspring rats using behavioral and electrophysiological techniques.

Valentini E, Ferrara M, Presaghi F, De Gennaro L, Curcio G. Republished review: systematic review and meta-analysis of psychomotor effects of mobile phone electromagnetic fields. Postgrad Med J. 87(1031):643-651, 2011.

OBJECTIVES Over the past 10 years there has been increasing concern about the possible behavioural effects of mobile phone use. This systematic review and meta-analysis focuses on studies published since 1999 on the human cognitive and performance effects of mobile phone-related electromagnetic fields (EMF). METHODS

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PubMed, Biomed, Medline, Biological Sciences, PsychInfo, PsycARTICLES, Environmental Sciences and Pollution Management, Neurosciences Abstracts and Web of Science professional databases were searched and 24 studies selected for meta-analysis. Each study had to have at least one psychomotor measurement result as a main outcome. Data were analysed using standardised mean difference (SMD) as the effect size measure. RESULTS Only three tasks (2-back, 3-back and simple reaction time (SRT)) displayed significant heterogeneity, but after studies with extreme SMD were excluded using sensitivity analysis, the statistical significance disappeared ($\chi^2(7)=1.63$, $p=0.20$; $\chi^2(6)=1.00$, $p=0.32$; $\chi^2(10)=14.04$, $p=0.17$, respectively). Following sensitivity analysis, the effect of sponsorship and publication bias were assessed. Meta-regression indicated a significant effect ($b_1/40.12$, $p<0.05$) only for the 2-back task with mixed funding (industry and public/charity). Funnel plot inspection revealed a significant publication bias only for two cognitive tasks: SRT (Begg's rank correlation $r=0.443$; Egger's test $b=-0.652$) and the subtraction task (Egger's test $b=-0.687$). CONCLUSIONS Mobile phone-like EMF do not seem to induce cognitive and psychomotor effects. Nonetheless, the existence of sponsorship and publication biases should encourage WHO intervention to develop official research standards and guidelines. In addition, future research should address critical and neglected issues such as investigation of repeated, intensive and chronic exposures, especially in highly sensitive populations such as children.

Electromagnetic Hypersensitivity

Nordin S, Neely G, Olsson D, Sandström M. Odor and Noise Intolerance in Persons with Self-Reported Electromagnetic Hypersensitivity. Int J Environ Res Public Health. 11(9):8794-8805, 2014.

Lack of confirmation of symptoms attributed to electromagnetic fields (EMF) and triggered by EMF exposure has highlighted the role of individual factors. Prior observations indicate intolerance to other types of environmental exposures among persons with electromagnetic hypersensitivity (EHS). This study assessed differences in odor and noise intolerance between persons with EHS and healthy controls by use of subscales and global measures of the Chemical Sensitivity Scale (CSS) and the Noise Sensitivity Scale (NSS). The EHS group scored significantly higher than the controls on all CSS and NSS scales. Correlation coefficients between CSS and NSS scores ranged from 0.60 to 0.65 across measures. The findings suggest an association between EHS and odor and noise intolerance, encouraging further investigation of individual factors for understanding EMF-related symptoms.

Wilen J, Johansson A, Kalezic N, Lyskov E, Sandstrom M. Psychophysiological tests and provocation of subjects with mobile phone related symptoms. Bioelectromagnetics. 27(3):204-214, 2006.

The aim of the present study was to investigate the effect of exposure to a mobile phone-like radiofrequency (RF) electromagnetic field on persons experiencing subjective symptoms when using mobile phones (MP). Twenty subjects with MP-related symptoms

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were recruited and matched with 20 controls without MP-related symptoms. Each subject participated in two experimental sessions, one with true exposure and one with sham exposure, in random order. In the true exposure condition, the test subjects were exposed for 30 min to an RF field generating a maximum SAR(1g) in the head of 1 W/kg through an indoor base station antenna attached to a 900 MHz GSM MP. The following physiological and cognitive parameters were measured during the experiment: heart rate and heart rate variability (HRV), respiration, local blood flow, electrodermal activity, critical flicker fusion threshold (CFFT), short-term memory, and reaction time. No significant differences related to RF exposure conditions were detected. Also no differences in baseline data were found between subject groups, except for the reaction time, which was significantly longer among the cases than among the controls the first time the test was performed. This difference disappeared when the test was repeated. However, the cases differed significantly from the controls with respect to HRV as measured in the frequency domain. The cases displayed a shift in low/high frequency ratio towards a sympathetic dominance in the autonomous nervous system during the CFFT and memory tests, regardless of exposure condition. This might be interpreted as a sign of differences in the autonomous nervous system regulation between persons with MP related subjective symptoms and persons with no such symptoms.

Kato Y, Johansson O. Reported functional impairments of electrohypersensitive Japanese: A questionnaire survey. *Pathophysiology*.19(2) 95-100, 2012.

An increasing number of people worldwide complain that they have become electromagnetic hypersensitive (EHS). We conducted a questionnaire survey of EHS persons in Japan. The aim was to identify electromagnetic fields (EMF) and plausible EMF sources that caused their symptoms. Postal questionnaires were distributed via a self-help group, and 75 participants (95% women) responded. Reported major complaints were "fatigue/tiredness" (85%), "headache", "concentration, memory, and thinking" difficulty (81%, respectively). Seventy-two per cent used some form of complementary/alternative therapy. The most plausible trigger of EHS onset was a mobile phone base station or personal handy-phone system (37%). Sixty-five percent experienced health problems to be due to the radiation from other passengers' mobile phones in trains or buses, and 12% reported that they could not use public transportation at all. Fifty-three percent had a job before the onset, but most had lost their work and/or experienced a decrease in income. Moreover, 85.3% had to take measures to protect themselves from EMF, such as moving to low EMF areas, or buying low EMF electric appliances. EHS persons were suffering not only from their symptoms, but also from economical and social problems.

Johansson A, Nordin S, Heiden M, Sandström M. Symptoms, personality traits, and stress in people with mobile phone-related symptoms and electromagnetic hypersensitivity. *J Psychosom Res*. 68(1):37-45, 2010.

OBJECTIVE: Some people report symptoms that they associate with electromagnetic field (EMF) exposure. These symptoms may be related to specific EMF sources or to electrical equipment in general (perceived electromagnetic hypersensitivity, EHS).

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Research and clinical observations suggest a difference between mobile phone (MP)-related symptoms and EHS with respect to symptom prevalence, psychological factors, and health prognosis. This study assessed prevalence of EMF-related and EMF-nonrelated symptoms, anxiety, depression, somatization, exhaustion, and stress in people with MP-related symptoms or EHS versus a population-based sample and a control sample without EMF-related symptoms. METHODS: Forty-five participants with MP-related symptoms and 71 with EHS were compared with a population-based sample (n=106) and a control group (n=63) using self-report questionnaires. RESULTS: The EHS group reported more symptoms than the MP group, both EMF-related and EMF-nonrelated. The MP group reported a high prevalence of somatosensory symptoms, whereas the EHS group reported more neurasthenic symptoms. As to self-reported personality traits and stress, the case groups differed only on somatization and listlessness in a direct comparison. In comparison with the reference groups, the MP group showed increased levels of exhaustion and depression but not of anxiety, somatization, and stress; the EHS group showed increased levels for all of the conditions except for stress. CONCLUSION: The findings support the idea of a difference between people with symptoms related to specific EMF sources and people with general EHS with respect to symptoms and anxiety, depression, somatization, exhaustion, and stress. The differences are likely to be important in the management of patients.

Hagström M, Auranen J, Ekman R. Electromagnetic hypersensitive Finns: Symptoms, perceived sources and treatments, a questionnaire study. Pathophysiology. 2013 Apr 1. pii: S0928-4680(13)00002-3.

The aim was to analyze the subjective experiences of Finns who describe themselves as suffering from electromagnetic hypersensitivity (EHS), their symptoms, self-perceived sources of the health complaints and the effectiveness of medical and complementary alternative therapies. A total of 395 questionnaires were mailed to self-diagnosed EHS persons. Of the participants 345 belonged to a Finnish self-help group and 50 came from outside of the group. The return rate of the study was 52.1% (206) and 80.9% of the respondents were women. Before the onset of EHS the most common health complaints were different types of allergies (35.1%, 68). During the acute phase of EHS the most common symptoms were nervous system related: "stress" (60.3%, 117), "sleeping disorders" (59.3%, 115) and "fatigue" (57.2%, 111). The sources that were most often reported to have triggered EHS were: "personal computers" (50.8%, 94) and "mobile phones" (47.0%, 87). The same devices were also claimed to cause the most symptoms during the acute phase. After the acute phase of EHS had passed, the respondents still claimed to react to these same digital and wireless devices while their reactions to basic electrical appliances were reduced. According to 76% of 157 respondents the reduction or avoidance of electromagnetic fields (EMF) helped in their full or partial recovery. The best treatments for EHS were given as: "dietary change" (69.4%), "nutritional supplements" (67.8%) and "increased physical exercise" (61.6%). The official treatment recommendations of psychotherapy (2.6%) and medication (-4.2%) were not significantly helpful. According to the present results the official treatment protocols should take better account the EHS person's own experiences. The

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avoidance of electromagnetic radiation and fields effectively removed or lessened the symptoms in EHS persons.

De Luca C, Chung Sheun Thai J, Raskovic D, Cesareo E, Caccamo D, Trukhanov A, Korkina L. Metabolic and genetic screening of electromagnetic hypersensitive subjects as a feasible tool for diagnostics and intervention. Mediators Inflamm. 2014;2014:924184. doi: 10.1155/2014/924184. Epub 2014 Apr 9.

Growing numbers of "electromagnetic hypersensitive" (EHS) people worldwide self-report severely disabling, multiorgan, non-specific symptoms when exposed to low-dose electromagnetic radiations, often associated with symptoms of multiple chemical sensitivity (MCS) and/or other environmental "sensitivity-related illnesses" (SRI). This cluster of chronic inflammatory disorders still lacks validated pathogenetic mechanism, diagnostic biomarkers, and management guidelines. We hypothesized that SRI, not being merely psychogenic, may share organic determinants of impaired detoxification of common physic-chemical stressors. Based on our previous MCS studies, we tested a panel of 12 metabolic blood redox-related parameters and of selected drug-metabolizing-enzyme gene polymorphisms, on 153 EHS, 147 MCS, and 132 control Italians, confirming MCS altered ($P < 0.05-0.0001$) glutathione-(GSH), GSH-peroxidase/S-transferase, and catalase erythrocyte activities. We first described comparable-though milder-metabolic pro-oxidant/proinflammatory alterations in EHS with distinctively increased plasma coenzyme-Q10 oxidation ratio. Severe depletion of erythrocyte membrane polyunsaturated fatty acids with increased $\omega 6/\omega 3$ ratio was confirmed in MCS, but not in EHS. We also identified significantly ($P = 0.003$) altered distribution-versus-control of the CYP2C19*1/*2 SNP variants in EHS, and a 9.7-fold increased risk (OR: 95% C.I. = 1.3-74.5) of developing EHS for the haplotype (null)GSTT1 + (null)GSTM1 variants. Altogether, results on MCS and EHS strengthen our proposal to adopt this blood metabolic/genetic biomarkers' panel as suitable diagnostic tool for SRI.

Effects on Blood

Mousavy SJ, Riazi GH, Kamarei M, Aliakbarian H, Sattarahmady N, Sharifzadeh A, Safarian S, Ahmad F, Moosavi-Movahedi AA. Effects of mobile phone radiofrequency on the structure and function of the normal human hemoglobin. Int J Biol Macromol. 44(3):278-285, 2009

Widespread use of mobile phones has increased the human exposure to electromagnetic fields (EMFs). It is required to investigate the effect of EMFs on the biological systems. In this paper the effect of mobile phone RF (910MHz and 940 MHz) on structure and function of HbA was investigated. Oxygen affinity was measured by sodium dithionite with UV-vis spectrophotometer. Structural changes were studied by circular dichroism and fluorescence spectroscopy. The results indicated that mobile phone EMFs altered oxygen affinity and tertiary structure of HbA. Furthermore, the decrease of oxygen affinity of HbA corresponded to the EMFs intensity and time of

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exposure.

Shahbazi-Gahrouei D, Mortazavi SM, Nasri H, Baradaran A, Baradaran-Ghahfarokhi M, Baradaran-Ghahfarokhi HR. Mobile phone radiation interferes laboratory immunoassays: Example chorionic gonadotropin assays. *Pathophysiology*. 19(1):43-47, 2012.

The radiofrequency radiation is of concern in hospital laboratories as the microwaves have many health effects even on immune functions. The aim of this study was, however, to evaluate the effects of cell phone radiation on chorionic gonadotropin immunoassays of human serum. Two cell phones with 0.69 and 1.09W/kg (head SAR) emitting 900MHz radiation were used. Sixty wells with five human serum concentrations (0, 10, 100, 250, 500mIU/mL) were used in three batches. The well heads in each batch were exposed to 900MHz emitted from these phones, and the 0.69, 1.09W/kg exposed batches were compared with the unexposed controls. Radiation exposure from mobile phones altered the measured serum levels especially in the wells with 100, 250, 500mIU/mL hormone concentrations. Exposure at 1.09W/kg SAR caused a significant loss compared to 0.69W/kg SAR exposure. In conclusion, the microwave exposures may require attention in laboratories using immunoassays.

Ruan P, Yong J, Shen H, Zheng X. Monitoring dynamic reactions of red blood cells to UHF electromagnetic waves radiation using a novel micro-imaging technology. *Electromagn Biol Med*. 31(4):365-374, 2012.

Multiple state-of-the-art techniques, such as multi-dimensional micro-imaging, fast multi-channel micro-spectrophotometry, and dynamic micro-imaging analysis, were used to dynamically investigate various effects of cell under the 900 MHz electromagnetic radiation. Cell changes in shape, size, and parameters of Hb absorption spectrum under different power density electromagnetic waves radiation were presented in this article. Experimental results indicated that the isolated human red blood cells (RBCs) do not have obviously real-time responses to the ultra-low density (15 $\mu\text{W}/\text{cm}^2$), 31 $\mu\text{W}/\text{cm}^2$) electromagnetic wave radiation when the radiation time is not more than 30 min; however, the cells do have significant reactions in shape, size, and the like, to the electromagnetic waves radiation with power densities of 1 mW/cm^2 and 5 mW/cm^2 . The data also reveal the possible influences and statistical relationships among living human cell functions, radiation amount, and exposure time with high-frequency electromagnetic waves. The results of this study may be significant on protection of human being and other living organisms against possible radiation affections of the high-frequency electromagnetic waves.

Zotti-Martelli L, Peccatori M, Maggini V, Ballardini M, Barale R. Individual responsiveness to induction of micronuclei in human lymphocytes after exposure in vitro to 1800-MHz microwave radiation. *Mutat Res*. 582(1-2):42-52, 2005.

The widespread application of microwaves is of great concern in view of possible consequences for human health. Many in vitro studies have been carried out to detect possible effects on DNA and chromatin structure following exposure to microwave

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radiation. The aim of this study is to assess the capability of microwaves, at different power densities and exposure times, to induce genotoxic effects as evaluated by the in vitro **micronucleus (MN)** assay on peripheral blood lymphocytes from nine different healthy donors, and to investigate also the possible inter-individual response variability. Whole blood samples were exposed for 60, 120 and 180min to continuous microwave radiation with a frequency of 1800MHz and power densities of 5, 10 and 20mW/cm². Reproducibility was tested by repeating the experiment 3 months later. Multivariate analysis showed that lymphocyte proliferation indices were significantly different among donors ($p < 0.004$) and between experiments ($p < 0.01$), whereas the applied power density and the exposure time did not have any effect on them. Both spontaneous and induced MN frequencies varied in a highly significant way among donors ($p < 0.009$) and between experiments ($p < 0.002$), and a statistically significant increase of MN, although rather low, was observed dependent on exposure time ($p = 0.0004$) and applied power density ($p = 0.0166$). A considerable decrease in spontaneous and induced MN frequencies was measured in the second experiment. The results show that microwaves are able to induce MN in short-time exposures to medium power density fields. Our data analysis highlights a wide inter-individual variability in the response, which was confirmed to be a characteristic reproducible trait by means of the second experiment.

Zmyslony M, Politanski P, Rajkowska E, Szymczak W, Jajte J. Acute exposure to 930 MHz CW electromagnetic radiation in vitro affects reactive oxygen species level in rat lymphocytes treated by iron ions. *Bioelectromagnetics*. 25(5):324-328, 2004.

The aim of this study was to test the hypothesis that the 930 MHz continuous wave (CW) electromagnetic field, which is the carrier of signals emitted by cellular phones, affects the reactive oxygen species (ROS) level in living cells. Rat lymphocytes were used in the experiments. A portion of the lymphocytes was treated with iron ions to induce oxidative processes. Exposures to electromagnetic radiation (power density 5 W/m², theoretical calculated SAR = 1.5 W/kg) were performed within a GTEM cell. Intracellular ROS were measured by the fluorescent probe dichlorofluorescein diacetate (DCF-DA). The results show that acute (5 and 15 min) exposure does not affect the number of produced ROS. If, however, FeCl₂ with final concentration 10 microg/ml was added to the lymphocyte suspensions to stimulate ROS production, after both durations of exposure, the magnitude of fluorescence (ROS level during the experiment) was significantly greater in the exposed lymphocytes. The character of the changes in the number of free radicals observed in our experiments was qualitatively compatible with the theoretical prediction from the model of electromagnetic radiation effect on radical pairs.

Sannino A, Sarti M, Reddy SB, Prihoda TJ, Vijayalaxmi, Scarfi MR. Induction of adaptive response in human blood lymphocytes exposed to radiofrequency radiation. *Radiat Res*. 171(6):735-742, 2009.

Abstract Sannino, A., Sarti, M., Reddy, S. B., Prihoda, T. J., Vijayalaxmi and Scarfi, M. R. Induction of Adaptive Response in Human Blood Lymphocytes Exposed to

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Radiofrequency Radiation. Radiat. Res. 171, 735-742 (2009). The incidence of micronuclei was evaluated to assess the induction of an adaptive response to non-ionizing radiofrequency (RF) radiation in peripheral blood lymphocytes collected from five different human volunteers. After stimulation with phytohemagglutinin for 24 h, the cells were exposed to an adaptive dose of 900 MHz RF radiation used for mobile communications (at a peak specific absorption rate of 10 W/kg) for 20 h and then challenged with a single genotoxic dose of mitomycin C (100 ng/ml) at 48 h. Lymphocytes were collected at 72 h to examine the frequency of micronuclei in cytokinesis-blocked binucleated cells. Cells collected from four donors exhibited the induction of adaptive response (i.e., responders). Lymphocytes that were pre-exposed to 900 MHz RF radiation had a significantly decreased incidence of micronuclei induced by the challenge dose of mitomycin C compared to those that were not pre-exposed to 900 MHz RF radiation. These preliminary results suggested that the adaptive response can be induced in cells exposed to non-ionizing radiation. A similar phenomenon has been reported in cells as well as in animals exposed to ionizing radiation in several earlier studies. However, induction of adaptive response was not observed in the remaining donor (i.e., non-responder). The incidence of micronuclei induced by the challenge dose of mitomycin C was not significantly different between the cells that were pre-exposed and unexposed to 900 MHz RF radiation. Thus the overall data indicated the existence of heterogeneity in the induction of an adaptive response between individuals exposed to RF radiation and showed that the less time-consuming micronucleus assay can be used to determine whether an individual is a responder or non-responder.

Sannino A, Zeni O, Sarti M, Romeo S, Reddy SB, Belisario MA, Prihoda TJ, Vijayalaxmi, Scarfi MR. Induction of adaptive response in human blood lymphocytes exposed to 900 MHz radiofrequency fields: influence of cell cycle. Int J Radiat Biol. 87(9):993-999, 2011.

PURPOSE: To investigate the influence of cell cycle on the adaptive response (AR) induced by the exposure of human blood lymphocytes to radiofrequency fields (RF). **MATERIALS AND METHODS:** Human peripheral blood lymphocytes in G(0)-, G(1)- or S-phase of the cell cycle were exposed for 20 hours to an adaptive dose (AD) of 900 MHz RF at an average specific absorption rate of 1.25 W/kg and then treated with a challenge dose (CD) of 100 ng/ml mitomycin C (MMC). Un-exposed and sham-exposed controls as well as cells treated with MMC alone were included in the study. The incidence of micronuclei (MN) was evaluated to determine the induction of AR. **RESULTS:** The results indicated that the cells which were exposed to AD of RF in G(0)- and G(1)-phase of the cell cycle did not exhibit AR while such a response was observed when the cells were exposed to AD of RF in S-phase of the cell cycle. **CONCLUSIONS:** These results confirmed the observations reported in our previous investigation where AR was observed in human blood lymphocytes exposed to AD of RF in S-phase of the cell cycle and further suggested that the timing of AD exposure of RF is important to elicit AR.

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Sannino A, Zeni O, Romeo S, Massa R, Gialanella G, Grossi G, Manti L, Vijayalaxmi, Scarfi MR. Adaptive response in human blood lymphocytes exposed to non-ionizing radiofrequency fields: resistance to ionizing radiation-induced damage. *J Radiat Res.* 2013 Aug 26. [Epub ahead of print]

The aim of this preliminary investigation was to assess whether human peripheral blood lymphocytes which have been pre-exposed to non-ionizing radiofrequency fields exhibit an adaptive response (AR) by resisting the induction of genetic damage from subsequent exposure to ionizing radiation. Peripheral blood lymphocytes from four healthy donors were stimulated with phytohemagglutinin for 24 h and then exposed for 20 h to 1950 MHz radiofrequency fields (RF, adaptive dose, AD) at an average specific absorption rate of 0.3 W/kg. At 48 h, the cells were subjected to a challenge dose (CD) of 1.0 or 1.5 Gy X-irradiation (XR, challenge dose, CD). After a 72 h total culture period, cells were collected to examine the incidence of micronuclei (MN). There was a significant decrease in the number of MN in lymphocytes exposed to RF + XR (AD + CD) as compared with those subjected to XR alone (CD). These observations thus suggested a RF-induced AR and induction of resistance to subsequent damage from XR. There was variability between the donors in RF-induced AR. The data reported in our earlier investigations also indicated a similar induction of AR in human blood lymphocytes that had been pre-exposed to RF (AD) and subsequently treated with a chemical mutagen, mitomycin C (CD). Since XR and mitomycin-C induce different kinds of lesions in cellular DNA, further studies are required to understand the mechanism(s) involved in the RF-induced adaptive response.

Sarimov, R., Malmgren, L.O.G., Markova, E., Persson, B.R.R., Belyaev, I.Y. Nonthermal GSM microwaves affect chromatin conformation in human lymphocytes similar to heat shock. *IEEE Trans Plasma Sci* 32:1600-1608, 2004.

Here we investigated whether microwaves (MWs) of Global System for Mobile Communication (GSM) induce changes in chromatin conformation in human lymphocytes. Effects of MWs were studied at different frequencies in the range of 895-915 MHz in experiments with lymphocytes from seven healthy persons. Exposure was performed in transverse electromagnetic transmission line cell (TEM-cell) using a GSM test-mobile phone. All standard modulations included 2 W output power in the pulses, specific absorbed rate (SAR) being 5.4 mW/kg. Changes in chromatin conformation, which are indicative of stress response and genotoxic effects, were measured by the method of anomalous viscosity time dependencies (AVTD). Heat shock and treatment with the genotoxic agent camptothecin, were used as positive controls. 30-min exposure to MWs at 900 and 905 MHz resulted in statistically significant condensation of chromatin in lymphocytes from 1 of 3 tested donors. This condensation was similar to effects of heat shock within the temperature window of 40/spl deg/C-44/spl deg/C. Analysis of pooled data from all donors showed statistically significant effect of 30-min exposure to MWs. Stronger effects of MWs was found following 1-h exposure. In replicated experiments, cells from four out of five donors responded to 905 MHz. Responses to 915 MHz were observed in cells from 1 out of 5 donors, $p < 0.002$. Dependent on donor, condensation, 3 donors, or decondensation, 1 donor, of

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chromatin was found in response to 1-h exposure. Analysis of pooled data from all donors showed statistically significant effect of 1-h exposure to MWs. In cells from one donor, this effect was frequency-dependent ($p < 0.01$). Effects of MWs correlated statistically significantly with effects of heat shock and initial state of chromatin before exposure. MWs at 895 and 915 MHz affected chromatin conformation in transformed lymphocytes. The conclusion-GSM microwaves under specific conditions of exposure affected human lymphocytes similar to stress response. The data suggested that the MW effects differ at various GSM frequencies and vary between donors.

Markova E, Hillert L, Malmgren L, Persson BR, Belyaev IY. Microwaves from GSM Mobile Telephones Affect 53BP1 and gamma-H2AX Foci in Human Lymphocytes from Hypersensitive and Healthy Persons. Environ Health Perspect. 113(9):1172-1177, 2005.

The data on biologic effects of nonthermal microwaves (MWs) from mobile telephones are diverse, and these effects are presently ignored by safety standards of the International Commission for Non-Ionizing Radiation Protection (ICNIRP). In the present study, we investigated effects of MWs of Global System for Mobile Communication (GSM) at different carrier frequencies on human lymphocytes from healthy persons and from persons reporting hypersensitivity to electromagnetic fields (EMFs). We measured the changes in chromatin conformation, which are indicative of stress response and genotoxic effects, by the method of anomalous viscosity time dependence, and we analyzed tumor suppressor p53-binding protein 1 (53BP1) and phosphorylated histone H2AX (gamma-H2AX), which have been shown to colocalize in distinct foci with DNA double-strand breaks (DSBs), using immunofluorescence confocal laser microscopy. We found that MWs from GSM mobile telephones affect chromatin conformation and 53BP1/gamma-H2AX foci similar to heat shock. For the first time, we report here that effects of MWs from mobile telephones on human lymphocytes are dependent on carrier frequency. On average, the same response was observed in lymphocytes from hypersensitive and healthy subjects. Key words: 53BP1 and gamma-H2AX foci, chromatin, DNA double-strand breaks, hypersensitivity to electromagnetic fields, stress response.

Lu YS, Huang BT, Huang YX. Reactive oxygen species formation and apoptosis in human peripheral blood mononuclear cell induced by 900MHz mobile phone radiation. Oxid Med Cell Longev. 2012:740280, 2012.

We demonstrate that reactive oxygen species (ROS) plays an important role in the process of apoptosis in human peripheral blood mononuclear cell (PBMC) which is induced by the radiation of 900MHz radiofrequency electromagnetic field (RFEMF) at a specific absorption rate (SAR) of ~ 0.4 W/kg when the exposure lasts longer than two hours. The apoptosis is induced through the mitochondrial pathway and mediated by activating ROS and caspase-3, and decreasing the mitochondrial potential. The activation of ROS is triggered by the conformation disturbance of lipids, protein, and DNA induced by the exposure of GSM RFEMF. Although human PBMC was found to have a self-protection mechanism of releasing carotenoid in response to oxidative stress to lessen the further increase of ROS, the imbalance between the antioxidant defenses

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and ROS formation still results in an increase of cell death with the exposure time and can cause about 37% human PBMC death in eight hours.

El-Bediwi AB, Saad M, El-Kott AF, Eid E. Influence of Electromagnetic Radiation Produced by Mobile Phone on Some Biophysical Blood Properties in Rats. *Cell Biochem Biophys.* 2012 Oct 10. [Epub ahead of print]

Effects of electromagnetic radiation produced by mobile phone on blood viscosity, plasma viscosity, hemolysis, Osmotic fragility, and blood components of rats have been investigated. Experimental results show that there are significant change on blood components and its viscosity which affects on a blood circulation due to many body problems. Red blood cells, White blood cells, and Platelets are broken after exposure to electromagnetic radiation produced by mobile phone. Also blood viscosity and plasma viscosity values are increased but Osmotic fragility value decreased after exposure to electromagnetic radiation produced by mobile phone.

Stankiewicz W, Dąbrowski MP, Kubacki R, Sobiczewska E, Szmigielski S Immunotropic influence of 900 MHz microwave GSM signal on human blood immune cells activated in vitro. *Electromag Biol Med* 25(1): 45-51, 2006.

In an earlier study we reported that G₀ phase peripheral blood mononuclear cells (PBMC) exposed to low-level (SAR = 0.18 W/kg) pulse-modulated 1300 MHz microwaves and subsequently cultured, demonstrate changed immune activity (Dabrowski et al., 2003). We investigated whether cultured immune cells induced into the active phases of cell cycle (G₁, S) and then exposed to microwaves will also be sensitive to electromagnetic field. An anechoic chamber of our design containing a microplate with cultured cells and an antenna emitting microwaves (900 MHz simulated GSM signal, 27 V/m, SAR 0.024 W/kg) was placed inside the ASSAB incubator. The microcultures of PBMC exposed to microwaves demonstrated significantly higher response to mitogens and higher immunogenic activity of monocytes (LM index) than control cultures. LM index, described in detail elsewhere (Dabrowski et al., 2001), represents the monokine influence on lymphocyte mitogenic response. The results suggest that immune activity of responding lymphocytes and monocytes can be additionally intensified by 900 MHz microwaves.

Effects on Wellbeing

Szyjkowska A, Gadzicka E, Szymczak W, Bortkiewicz A. The risk of subjective symptoms in mobile phone users in Poland - An epidemiological study. *Int J Occup Med Environ Health.* 2014 Apr 1. [Epub ahead of print]

OBJECTIVES: To assess the type and incidence of subjective symptoms related to the use of mobile phones in Polish users. **MATERIAL AND METHODS:** The study was conducted in 2005 using a questionnaire survey. Although it has been quite a long time, up to now, no such data have been published for Poland. The questionnaire consisted of 53 questions concerning sex, age, education, general health, characteristics of a mobile

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phone (hand-held, loud-speaking unit) as well as the habits associated with its use (frequency and duration of calls, text messages, etc.) and complaints associated with using a mobile phone. **RESULTS:** As many as 1800 questionnaires were sent. The response was obtained from 587 subjects aged 32.6 ± 11.3 (48.9% women, 51.1% men); the age did not differ significantly between men and women. The subjects owned a cell phone for an average of 3 years. Majority of the respondents used the phone intensively, i.e. daily (74%) or almost daily (20%). Headaches were reported significantly more often by the people who talked frequently and long in comparison with other users (63.2% of the subjects, $p = 0.0029$), just like the symptoms of fatigue (45%, $p = 0.013$). Also, the feeling of warmth around the ear and directly to the auricle was reported significantly more frequently by the intensive mobile phone users, compared with other mobile phone users (47.3%, $p = 0.00004$ vs. 44.6%, $p = 0.00063$, respectively). Most symptoms appeared during or immediately after a call and disappeared within 2 h after the call. Continuous headache, persisting for longer than 6 h since the end of a call, was reported by 26% of the subjects. **CONCLUSIONS:** Our results show that the mobile phone users may experience subjective symptoms, the intensity of which depends on the intensity of use of mobile phones.

Szykowska A, Bortkiewicz A, Szymczak W, Makowiec-Dabrowska T. [Subjective symptoms related to mobile phone use--a pilot study] Pol Merkuriusz Lek. 19(112):529-532, 2005. [Article in Polish]

Research findings indicate that the use of mobile phones may lead to a number of symptoms such as headache, impaired concentration and memory, fatigue. In Poland this problem has not as yet been addressed by scientific studies. THE AIM: The present project was undertaken to investigate whether the symptoms of ill health reported by young people may be associated with the use of mobile phone. MATERIAL AND METHODS: A survey using a self-reported questionnaire was conducted among randomly selected university students in Lodz, Central Poland. The questionnaire was designed specifically for this study and contained items on health condition and complaints as well as on frequency of mobile phone use. The number of questionnaires necessary for the study was assessed using the simple random sample method. Out of the 160 copies distributed among the students, 140 (87.5%) were completed. Eventually, 117 questionnaires were subject to analysis; the data from respondents who reported health problems (neck trauma in a car accident, chronic sinusitis and arterial hypertension) were excluded. The following statistical methods were used to analyse questionnaire data: t-Student test for equal and unequal variances or F-Snedecor test for comparing parameters in two study groups, Fisher exact test for comparing frequency, and single and multiple logistic regression models for quantitative risk assessment of negative health outcomes in relation to exposure level and with control for confounders. The subjects were 61 (52.1%) males and 56 females (47.9%). **RESULTS:** Most of the subjects (62%) assessed their health condition as good, 31% as very good and 7% as fair. 70% complained of headache and 20% of dizziness. Impaired concentration occurred in 56% of respondents. Facial dermatitis was reported by 11%. The most prevalent symptom related to mobile phone use was the thermal sensation

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within the auricle and behind/around the ear. This was reported by 33 subjects (28.2%). Out of 82 subjects who complained of headache, only 8 (6.8%) related this symptom to mobile phone use. Only 10 subjects of 65 reporting impaired concentration thought it could be associated with their using a mobile phone. The symptoms and health complaints reported by the respondents in no case were the reason for a medical check-up or taking any medication. CONCLUSIONS: The large number of young people complaining of headache and impaired concentration calls for further research to investigate the underlying reasons. It cannot be excluded that one of them may be exposure to EMF emitted by mobile phone. The explanation should be sought through further experimental and epidemiologic studies.

Santini R, Seigne M, Bonhomme-Faivre L, Bouffet S, Defrasne E, Sage M. Symptoms experienced by users of digital cellular phones: a pilot study in a French engineering school. *Pathol Biol (Paris)* 49(3):222-226, 2001. [Article in French]

A survey study, using questionnaire, was conducted in 161 students and workers in a French engineering school on symptoms experienced during use of digital cellular phones. A significant increase in concentration difficult ($p < 0.05$) was reported by users of 1800-MHz (DCS) cellular phones compared to 900-MHz (GSM) phone users. In users of cellular phones, women significantly ($p < 0.05$) complained more often of sleep disturbance than men. This sex difference for sleep complaint is not observed between women and men non-users of cellular phone. The use of both cellular phones and VDT significantly ($p \leq 0.05$) increased concentration difficulty. Digital cellular phone users also significantly ($p < 0.05$) more often complained of discomfort, warmth, and picking on the ear during phone conversation in relation with calling duration per day and number of calls per day. The complaint warmth on the ear might be a signal to users for stopping the call.

Sandstrom M, Wilen J, Oftedal G, Hansson Mild K, Mobile phone use and subjective symptoms. Comparison of symptoms experienced by users of analogue and digital mobile phones. *Occup Med (Lond)* 51(1):25-35, 2001.

In 1995 many people reported symptoms such as headaches, feelings of discomfort, warmth behind/around or on the ear and difficulties concentrating while using mobile phones. The number of complaints was higher for people using the digital (GSM) system, i.e. with pulse modulated fields, than for those using the analogue (NMT) system. Our main hypothesis was that GSM users experience more symptoms than NMT users. An epidemiological investigation was initiated including 6379 GSM users and 5613 NMT 900 users in Sweden, and 2500 from each category in Norway. The adjusted odds ratio did not indicate any increased risk for symptoms for GSM users compared with NMT 900 users. Our hypothesis was therefore disproved. However, we observed a statistically significant lower risk for sensations of warmth on the ear for GSM users compared with NMT 900 users. The same trend was seen in Norway for sensations of warmth behind/around the ear and in Sweden for headaches and fatigue. Factors distinguishing the two systems (radio frequency emission, phone temperatures and various ergonomic factors) may be responsible for these results, as well as for a

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secondary finding: a statistically significant association between calling time/number of calls per day and the prevalence of warmth behind/around or on the ear, headaches and fatigue.

Rubin GJ, Cleare AJ, Wessely S. Psychological factors associated with self-reported sensitivity to mobile phones. J Psychosom Res. 64(1):1-9; discussion 11-12, 2008

OBJECTIVE: Some people report symptoms associated with mobile phone use. A minority also report "electrosensitivity," experiencing symptoms following exposure to other electrical devices. Research suggests that electromagnetic fields do not trigger these symptoms. In this study, we examined the differences between these two "sensitive" groups and healthy controls. METHODS: Fifty-two people who reported sensitivity to mobile phones, 19 people who reported sensitivity to mobile phones and "electrosensitivity," and 60 nonsensitive controls completed a questionnaire assessing the following: primary reason for using a mobile phone, psychological health, symptoms of depression, modern health worries (MHW), general health status, symptom severity, and the presence of other medically unexplained syndromes. RESULTS: Perceived sensitivity was associated with an increased likelihood of using a mobile phone predominantly for work (3% of controls, 13% of those sensitive to mobile phones, and 21% of those reporting "electrosensitivity") and greater MHW concerning radiation [mean (S.D.) on a scale of 1-5: 2.0 (1.0), 2.7 (0.9), and 4.0 (0.8), respectively]. Participants who reported "electrosensitivity" also experienced greater depression, greater worries about tainted food and toxic interventions, worse general health on almost every measure, and a greater number of other medically unexplained syndromes compared to participants from the other two groups. No group differences were observed with regards to psychiatric cases. CONCLUSIONS: The data illustrate that patients reporting "electrosensitivity" experience substantially worse health than either healthy individuals or people who report sensitivity to mobile phones but who do not adopt the label "electrosensitivity." Clinicians and researchers would be wise to pay greater attention to this subdivision.

Oftedal G, Wilen J, Sandstrom M, Mild KH, Symptoms experienced in connection with mobile phone use. Occup Med (Lond) 50(4):237-245, 2000.

Many people in Norway and Sweden reported headaches, fatigue, and other symptoms experienced in connection with the use of a mobile phone (MP). Therefore, we initiated a cross-sectional epidemiological study among 17,000 people, all using an MP in their job. Thirty-one percent of the respondents in Norway and 13% of those in Sweden had experienced at least one symptom in connection with MP use. Next to the sensations of warmth on the ear and behind/around the ear, burning sensations in the facial skin and headaches were most commonly reported. Most symptoms usually began during or within half an hour after the call and lasted for up to 2 h. Relatively few had consulted a physician or been on sick leave because of the symptoms, but about 45% among those with an MP attributed symptom had taken steps to reduce the symptom. These results suggest an awareness of the symptoms, but not necessarily a serious health problem.

Khan MM. Adverse effects of excessive mobile phone use. Int J Occup Med Environ

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Health. 21(4):289-293, 2008.

Introduction: Research findings indicate that the use of mobile phones may lead to a number of symptoms such as headache, impaired concentration and memory, and also fatigue. Materials and Methods: The present study was designed to investigate whether the symptoms of ill health reported by young people may be associated with the use of mobile phone (MP) and to analyze its influence on health and development of medical students. The questionnaire was designed specifically for this study and contained items regarding health condition and health complaints as well as the frequency of MP use. The response rate was 86.6% (286 of 330 forms, completed by 73.77% males and 26.22% females). Results: Most of the subjects (83.57%) had some knowledge about the adverse effects of MP use. 76.92% of the students carried one mobile, and 23.08% more than one. 55.94%, of the subjects reported the average daily MP use of less than 30 min, 27.97%, of 30-60 min, 11.53%, of 60-90 min and 4.54% of more than 90 min. 16.08% of the subjects complained of headache and 24.48% of fatigue. Impaired concentration was reported by 34.27% of respondents, memory disturbances by 40.56%, sleeplessness by 38.8%, hearing problems by 23.07%, and facial dermatitis by 16.78%. The sensation of warmth within the auricle and behind/around the ear was reported by 28.32%. Out of 286 subjects who participated in this study, 44.4% related their symptoms to mobile phone use. Conclusions: The findings of the present study indicate that mobile phones play a large part in the daily life of medical students. Therefore, its impact on psychology and health should be discussed among the students to prevent the harmful effects of mobile phone use.

Thomé S, Härenstam A, Hagberg M. Mobile phone use and stress, sleep disturbances, and symptoms of depression among young adults--a prospective cohort study. BMC Public Health. 11:66, 2011.

BACKGROUND: Because of the quick development and widespread use of mobile phones, and their vast effect on communication and interactions, it is important to study possible negative health effects of mobile phone exposure. The overall aim of this study was to investigate whether there are associations between psychosocial aspects of mobile phone use and mental health symptoms in a prospective cohort of young adults. METHODS: The study group consisted of young adults 20-24 years old (n = 4156), who responded to a questionnaire at baseline and 1-year follow-up. Mobile phone exposure variables included frequency of use, but also more qualitative variables: demands on availability, perceived stressfulness of accessibility, being awakened at night by the mobile phone, and personal overuse of the mobile phone. Mental health outcomes included current stress, sleep disorders, and symptoms of depression. Prevalence ratios (PRs) were calculated for cross-sectional and prospective associations between exposure variables and mental health outcomes for men and women separately. RESULTS: There were cross-sectional associations between high compared to low mobile phone use and stress, sleep disturbances, and symptoms of depression for the men and women. When excluding respondents reporting mental health symptoms at baseline, high mobile phone use was associated with sleep disturbances and symptoms of depression for the men and symptoms of depression for the women at 1-

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year follow-up. All qualitative variables had cross-sectional associations with mental health outcomes. In prospective analysis, overuse was associated with stress and sleep disturbances for women, and high accessibility stress was associated with stress, sleep disturbances, and symptoms of depression for both men and women. CONCLUSIONS: High frequency of mobile phone use at baseline was a risk factor for mental health outcomes at 1-year follow-up among the young adults. The risk for reporting mental health symptoms at follow-up was greatest among those who had perceived accessibility via mobile phones to be stressful. Public health prevention strategies focusing on attitudes could include information and advice, helping young adults to set limits for their own and others' accessibility.

Ikeda K, Nakamura K. Association between mobile phone use and depressed mood in Japanese adolescents: a cross-sectional study. Environ Health Prev Med. 2013 Dec 18. [Epub ahead of print]

OBJECTIVES: Mobile phones are commonly used by adolescents. The aim of this study was to clarify associations between duration of mobile phone use and psychological mood in high school students. METHODS: This cross-sectional study included 2,785 high school students in Niigata, Japan. A self-administered questionnaire was used to elicit information on sex, school year, hours of mobile phone use, psychological mood status, and possible confounders. Psychological mood outcomes were evaluated with the Mood Inventory, developed and validated in 1994, which includes five subcomponents with total scores ranging from 8 to 32 (higher score indicates stronger feeling): "Tension and excitement," "Refreshing mood," "Fatigue," "Depressed mood," and "Anxious mood." Analysis of covariance with Bonferroni's multiple comparison was used to compare mean values among quartiles of hours of mobile phone use. RESULTS: Among the respondents, mean mobile phone use per week was 24 (median 18) h. Long-duration mobile phone use was associated with female students, no participation in sports club activities, early mobile phone use, and fewer hours spent sleeping (all $P < 0.001$). Overall associations between hours of mobile phone use and total scores were significant for "Depressed mood" (P for trend = 0.005), "Tension and excitement" (P for trend < 0.001), and "Fatigue" (P for trend < 0.001). Total scores for "Depressed mood," "Tension and excitement," and "Fatigue" of the fourth quartile (≥ 33 h/week) of mobile phone use were significantly higher than for other quartiles (all $P < 0.05$). CONCLUSIONS: Increased duration of mobile phone use is associated with unfavorable psychological mood, in particular, a depressed mood. Decreasing mobile phone use may help maintain appropriate mental health in very long-duration users.

Hocking, B, Preliminary report: symptoms associated with mobile phone use. Occup Med (Lond);48(6):357-360, 1998.

Mobile phone use is ubiquitous, although the alleged health effects of low level radio-frequency radiation (RFR) used in transmission are contentious. Following isolated reports of headache-like symptoms arising in some users, a survey has been conducted to characterize the symptoms sometimes associated with mobile phone usage. A notice of interest in cases was placed in a major medical journal and this was publicized by the media. Respondents were interviewed by telephone using a structured questionnaire.

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Forty respondents from diverse occupations described unpleasant sensations such as a burning feeling or a dull ache mainly occurring in the temporal, occipital or auricular areas. The symptoms often began minutes after beginning a call, but could come on later during the day. The symptoms usually ceased within an hour after the call, but could last until evening. Symptoms did not occur when using an ordinary handset, and were different from ordinary headaches. There were several reports suggestive of intracranial effects. Three respondents reported local symptoms associated with wearing their mobile phone on their belts. There was one cluster of cases in a workplace. Seventy-five per cent of cases were associated with digital mobile phones. Most of the respondents obtained relief by altering their patterns of telephone usage or type of phone. Cranial and other diverse symptoms may arise associated with mobile phone usage. Physicians and users alike should be alert to this. Further work is needed to determine the range of effects, their mechanism and the possible implications for safety limits of RFR.

Hocking B , Microwave sickness: a reappraisal. Occup Med (Lond) 51(1):66-69, 2001.

Microwave sickness (MWS) has been a disputed condition. The syndrome involves the nervous system and includes fatigue, headaches, dysaesthesia and various autonomic effects in radiofrequency radiation workers. This paper describes the early reports of the syndrome from Eastern Europe and notes the scepticism expressed about them in the West, before considering comprehensive recent reports by Western specialists and a possible neurological basis for the condition. It is concluded that MWS is a medical entity which should be recognized as a possible risk for radiofrequency radiation workers.

Hocking B. Management of radiofrequency radiation overexposures. Aust Fam Physician 30(4):339-342, 2001.

BACKGROUND: Radiofrequency radiation (RFR) has been in use for some time but is now proliferative with the burgeoning radiocommunications industry. OBJECTIVE: To inform the profession of the possible health effects from overexposure to radiofrequency radiation (RFR) and the clinical approach to cases. An introduction to the health effects of overexposure to RFR is given. A clinical approach to integrating the patient's symptoms and the circumstances of the exposure is given. Emergency treatment and ongoing care is outlined, and sources of expert advice given. CONCLUSION: Overexposure to RFR is a complex injury. Advice is given in this article for emergency care and planning ongoing care.

Hanson Mild, K, Oftedal, G, Sandstrom, M, Wilen, J, Tynes, T, Haugsdal, B, Hauger E, Comparison of symptoms experienced by users of analogue and digital mobile phones: a Swedish-Norwegian epidemiological study. Arbetslivsrapport 1998:23.

Study of mobile phone users showed a statistically significant association between calling time/number of calls per day and the prevalence of warmth behind/around the ear, headaches, and fatigue.

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Hallberg O. Adverse health indicators correlating with sparsely populated areas in Sweden. Eur J Cancer Prev. 16(1):71-76, 2007.

Earlier studies on health characteristics in Sweden have pointed at a sudden trend change in general health indicators around 1997. The decline was worse in areas with less estimated coverage by the mobile phone system; that is, areas where the average output power from mobile phone handsets is expected to be higher. In this study, health parameters were related to the population density, which is a well defined, rather than an estimated variable. Statistics were obtained from different authorities in Sweden. Data were correlated to the population densities in the 21 different counties of Sweden as well as to estimates of average mobile phone output power. Several health quality measures showed that people in sparsely populated counties in Sweden (as well as in Denmark and Norway) have suffered more illness, and lengthier recovery than people in more densely populated areas since 1997. This is in strong contrast to the situation 20 years ago, when the countryside was the healthiest place in which to live. The indicators strongly correlated with estimated mobile phone area coverage and estimated power output. The indicator statistics suggest that the decline in health in Sweden is not a primary consequence of low population density by itself, but that other factors related to population density are causative. The two factors having the strongest correlation with decreased health quality were the estimated average power output from mobile phones (positive correlation) and the reported coverage from the global system for mobile communication base stations (negative correlation) in each county.

Hallberg O, Johansson O. Long-term sickness and mobile phone use. J Aust Coll Nutr & Env med 23:11-12, 2004.

The number of people unable to work due to long-term sickness is drastically increasing in Sweden. In this paper we take a close look at the development of mobile phone communication to see how it possibly relates to the health impairment of the Swedish population. Official data was collected regarding mobile phone use and long-term absence from work. The co-variation between those data sets was used to estimate future development of long-term absence rates under the hypothesis that there is a connection between the two sets of data. It was concluded that future long-term absence rates will continue to increase as long as the annual number of ear-heating minute per year is increasing.

Gómez-Perretta C, Navarro EA, Segura J, Portolés M. Subjective symptoms related to GSM radiation from mobile phone base stations: a cross-sectional study. BMJ Open. 3(12):e003836, 2013. doi: 10.1136/bmjopen-2013-003836.

OBJECTIVES: We performed a re-analysis of the data from Navarro et al (2003) in which health symptoms related to microwave exposure from mobile phone base stations (BSs) were explored, including data obtained in a retrospective inquiry about fear of exposure from BSs. DESIGN: Cross-sectional study. SETTING: La Ñora (Murcia), Spain. PARTICIPANTS: Participants with known illness in 2003 were subsequently disregarded: 88 participants instead of 101 (in 2003) were analysed. Since weather circumstances can influence exposure, we restricted data to measurements made under similar weather conditions. OUTCOMES

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AND METHODS: A statistical method indifferent to the assumption of normality was employed: namely, binary logistic regression for modelling a binary response (eg, suffering fatigue (1) or not (0)), and so exposure was introduced as a predictor variable. This analysis was carried out on a regular basis and bootstrapping (95% percentile method) was used to provide more accurate CIs. RESULTS: The symptoms most related to exposure were lack of appetite (OR=1.58, 95% CI 1.23 to 2.03); lack of concentration (OR=1.54, 95% CI 1.25 to 1.89); irritability (OR=1.51, 95% CI 1.23 to 1.85); and trouble sleeping (OR=1.49, 95% CI 1.20 to 1.84). Changes in -2 log likelihood showed similar results. Concerns about the BSs were strongly related with trouble sleeping (OR =3.12, 95% CI 1.10 to 8.86). The exposure variable remained statistically significant in the multivariate analysis. The bootstrapped values were similar to asymptotic CIs. CONCLUSIONS: This study confirms our preliminary results. We observed that the incidence of most of the symptoms was related to exposure levels-independently of the demographic variables and some possible risk factors. Concerns about adverse effects from exposure, despite being strongly related with sleep disturbances, do not influence the direct association between exposure and sleep.

Frick U, Rehm J, Eichhammer P. Risk perception, somatization, and self report of complaints related to electromagnetic fields--a randomized survey study. *Int J Hyg Environ Health.* 205(5):353-360, 2002.

Exposure to electromagnetic fields (EMF) as well as EMF-related complaints has increased over the past decades. However, it is unclear whether these complaints are related to the electromagnetic or other physical properties of these fields per se, to salience of EMF in media, or to both. What is the prevalence of EMF-related complaints in the general population? What are the influencing factors on this prevalence? Does reporting of EMF-related symptoms depend on cognitive factors? To answer these questions, a survey with random variation of three cognitive factors was performed. As expected, EMF-related complaints were reported more by females and people with higher somatization tendency. Age had no significant linear effect on EMF-related complaints. The cognitive condition of threat produced a significant contrast effect among people with high somatization tendency on EMF-related complaints. Cognition can influence reporting of EMF-related effects. Thus, in future research of such effects, psychologically influencing factors should be included. Also risk communication should incorporate knowledge about social cognition.

Effects on Glands

Abu Khadra KM, Khalil AM, Abu Samak M, Aljaberi A. Evaluation of selected biochemical parameters in the saliva of young males using mobile phones. *Electromagn Biol Med.* 2014 Feb 5. [Epub ahead of print]

Abstract The biochemical status in the saliva of 12 males before/after using mobile phone has been evaluated. Radio frequency signals of 1800 MHz (continuous wave transmission, 217 Hz modulate and Global System for Mobile Communications [GSM - non-DTX]) with 1.09 w/kg specific absorption rate (SAR) value were used for 15 and

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30 min. Cell phone radiation induced a significant increase of superoxide dismutase (SOD); there was a statistically significant effect of talking time on the levels of SOD, $F(2, 33) = 8.084$, $p < 0.05$, $\omega = 0.53$. The trend analysis suggests a significant quadratic trend, $F(1, 33) = 4.891$, $p < 0.05$; indicating that after 15 min of talking the levels of SOD increased, but as talking time increased the SOD activity started to drop. In contrast to this, there was no statistically significant effect of talking time on the level of salivary albumin, cytochrome c, catalase or uric acid. Results suggest that exposure to electromagnetic radiation may exert an oxidative stress on human cells as evidenced by the increase in the concentration of the superoxide radical anion released in the saliva of cell phone users.

Hashemipour MS, Yarbakht M, Gholamhosseinian A, Famori H. Effect of mobile phone use on salivary concentrations of protein, amylase, lipase, immunoglobulin A, lysozyme, lactoferrin, peroxidase and C-reactive protein of the parotid gland. J Laryngol Otol. 2014 Apr 17:1-9. [Epub ahead of print]

Background: The possibility of side effects associated with the electromagnetic waves emitted from mobile phones is a controversial issue. The present study aimed to evaluate the effect of mobile phone use on parotid gland salivary concentrations of protein, amylase, lipase, immunoglobulin A, lysozyme, lactoferrin, peroxidase and C-reactive protein. Methods: Stimulated salivary samples were collected simultaneously from both parotid glands of 86 healthy volunteers. Salivary flow rate and salivary concentrations of proteins, amylase, lipase, lysozyme, lactoferrin, peroxidase, C-reactive protein and immunoglobulin A, were measured. Data were analysed using t-tests and one-way analyses of variance. Results: Salivary flow rate and parotid gland salivary concentrations of protein were significantly higher on the right side compared to the left in those that predominantly held mobile phones on the right side. In addition, there was a decrease in concentrations of amylase, lipase, lysozyme, lactoferrin and peroxidase. Conclusion: The side of dominant mobile phone use was associated with differences in salivary flow rate and parotid gland salivary concentrations, in right-dominant users. Although mobile phone use influenced salivary composition, the relationship was not significant.

Goldwein O, Aframian DJ. The influence of handheld mobile phones on human parotid gland secretion. Oral Dis.16(2):146-150, 2010.

Abstract. BACKGROUND: Handheld mobile phones (MPHs) have become a 'cultural' accessory device, no less so than a wrist watch. Nevertheless, the use of MPHs has given rise to great concern because of possible adverse health effects from exposure to the radiofrequency radiation (RFR) emitted by the device. Previous studies suggested correlation between MPH and salivary gland tumors. OBJECTIVE: To evaluate whether MPH induces physiologic changes in the adjacent parotid gland, located on the dominant side, in terms of secretion rates and protein levels in the secreted saliva. MATERIALS AND METHOD: Stimulated parotid saliva was collected simultaneously from both glands in 50 healthy volunteers whose MPH use was on a dominant side of the head. RESULTS: A significantly higher saliva secretion rate was noticed in the dominant

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MPH side compared with that in the non-dominant side. Lower total protein concentration was obtained in the dominant compared with the non-dominant MPH side among the right dominant MPH users. CONCLUSIONS: Parotid glands adjacent to handheld MPH in use respond by elevated salivary rates and decreased protein secretion reflecting the continuous insult to the glands. This phenomenon should be revealed to the worldwide population and further exploration by means of large-scale longitudinal studies is warranted.

Pereira C, Edwards M, Parotid nodular fasciitis in a mobile phone user. J Laryngol Otol 114(11):886-887, 2000.

We describe the first case of nodular fasciitis affecting the deep lobe of the parotid gland in a 39-year-old male telephone engineer and its possible association with the high usage of mobile phones.

Hamzany Y, Feinmesser R, Shpitzer T, Mizrachi A, Hilly O, Hod R, Bahar G, Otradnov I, Gavish M, Nagler RM. Is human saliva an indicator of the adverse health effects of using mobile phones? Antioxid Redox Signal. 18(6):622-627, 2013.

Increasing use of mobile phones creates growing concern regarding harmful effects of radiofrequency non-ionizing electromagnetic radiation (NIER) on human tissues located close to the ear where phones are commonly held for long periods of time. We studied 20 subjects in the 'mobile phone group' who had a mean duration of mobile phone use of 12.5 years (range 8-15) and a mean time use of 29.6 hours per month (range 8-100). Deaf individuals served as controls. We compared salivary outcomes (secretion, oxidative damage indices, flow rate and composition) between mobile phone users and non-users. We report significant increase in all salivary oxidative stress indices studied in mobile phone users. Salivary flow, total protein, albumin and amylase activity were decreased in mobile phone users. These observations lead to the hypothesis that the use of mobile phones may cause oxidative stress and modify salivary function.

Effects on Sleep

Yogesh S, Abha S, Priyanka S. Mobile usage and sleep patterns among medical students. Indian J Physiol Pharmacol. 58(1):100-103, 2014.

Exposure of humans to radio frequency electromagnetic field (EMF) both during receiving and transmitting the signals has amplified public and scientific debate about possible adverse effects on human health. The study was designed with the objective of assessing the extent of mobile phone use amongst medical students and finding correlation if any between the hours of usage of mobile to sleep pattern and quality. hundred medical students grouped as cases (n = 57) (> 2 hours/day of mobile usage) and control (n = 43) (≤ 2 hours/day of mobile usage) were examined for their sleep quality & pattern by Pittsburg sleep Quality Index (PSQI). Differences between groups were

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examined with the Mann Whitney "U" test for proportions (Quantitative values) and with Student's 't' test for continuous variables. The association of variables was analyzed by Spearman Rank's correlation. Probability was set at < 0.05 as significant. Sleep disturbance, latency and day dysfunction was more in cases especially females. A significant association of hours of usage and sleep indices were observed in both genders (males $r = 0.25$; $p = 0.04$, females $r = 0.31$; $p = 0.009$). Evening usage of mobile phone in cases showed a statistically significant negative association (-0.606 ; $p = 0.042$) with Sleep quality (higher PSQI means sleep deprivation). Students using mobile for > 2 hours/day may cause sleep deprivation and day sleepiness affecting cognitive and learning abilities of medical students.

Mohammed HS, Fahmy HM, Radwah NM, Elsayed AA. Non-thermal continuous and modulated electromagnetic radiation fields effects on sleep EEG of rats. J Adv Res 4(2) 181-187, 2013.

In the present study, the alteration in the sleep EEG in rats due to chronic exposure to low-level non-thermal electromagnetic radiation was investigated. Two types of radiation fields were used; 900 MHz unmodulated wave and 900 MHz modulated at 8 and 16 Hz waves. Animals has exposed to radiation fields for 1 month (1 h/day). EEG power spectral analyses of exposed and control animals during slow wave sleep (SWS) and rapid eye movement sleep (REM sleep) revealed that the REM sleep is more susceptible to modulated radiofrequency radiation fields (RFR) than the SWS. The latency of REM sleep increased due to radiation exposure indicating a change in the ultradian rhythm of normal sleep cycles. The cumulative and irreversible effect of radiation exposure was proposed and the interaction of the extremely low frequency radiation with the similar EEG frequencies was suggested.

Mann, K, Roschke, J, Effects of pulsed high-frequency electromagnetic fields on human sleep. Neuropsychobiology 33(1):41-47, 1996.

In the present study we investigated the influence of pulsed high-frequency electromagnetic fields of digital mobile radio telephones on sleep in healthy humans. Besides a hypnotic effect with shortening of sleep onset latency, a REM suppressive effect with reduction of duration and percentage of REM sleep was found. Moreover, spectral analysis revealed qualitative alterations of the EEG signal during REM sleep with an increased spectral power density. Knowing the relevance of REM sleep for adequate information processing in the brain, especially concerning mnestic functions and learning processes, the results emphasize the necessity to carry out further investigations on the interaction of this type of electromagnetic fields and the human organism.

Lustenberger C, Murbach M, Dürr R, Schmid MR, Kuster N, Achermann P, Huber R. Stimulation of the brain with radiofrequency electromagnetic field pulses affects sleep-dependent performance improvement. Brain Stimul. 6(5):805-811, 2013.

BACKGROUND: Sleep-dependent performance improvements seem to be closely related to sleep spindles (12-15 Hz) and sleep slow-wave activity (SWA, 0.75-4.5 Hz). Pulse-modulated

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radiofrequency electromagnetic fields (RF EMF, carrier frequency 900 MHz) are capable to modulate these electroencephalographic (EEG) characteristics of sleep. **OBJECTIVE:** The aim of our study was to explore possible mechanisms how RF EMF affect cortical activity during sleep and to test whether such effects on cortical activity during sleep interact with sleep-dependent performance changes. **METHODS:** Sixteen male subjects underwent 2 experimental nights, one of them with all-night 0.25-0.8 Hz pulsed RF EMF exposure. All-night EEG was recorded. To investigate RF EMF induced changes in overnight performance improvement, subjects were trained for both nights on a motor task in the evening and the morning. **RESULTS:** We obtained good sleep quality in all subjects under both conditions (mean sleep efficiency > 90%). After pulsed RF EMF we found increased SWA during exposure to pulse-modulated RF EMF compared to sham exposure ($P < 0.05$) toward the end of the sleep period. Spindle activity was not affected. Moreover, subjects showed an increased RF EMF burst-related response in the SWA range, indicated by an increase in event-related EEG spectral power and phase changes in the SWA range. Notably, during exposure, sleep-dependent performance improvement in the motor sequence task was reduced compared to the sham condition (-20.1%, $P = 0.03$). **CONCLUSION:** The changes in the time course of SWA during the exposure night may reflect an interaction of RF EMF with the renormalization of cortical excitability during sleep, with a negative impact on sleep-dependent performance improvement.

Lowden A, Akerstedt T, Ingre M, Wiholm C, Hillert L, Kuster N, Nilsson JP, Arnetz B. Sleep after mobile phone exposure in subjects with mobile phone-related symptoms. *Bioelectromagnetics*. 32(1):4-14, 2011.

Several studies show increases in activity for certain frequency bands (10-14 Hz) and visually scored parameters during sleep after exposure to radiofrequency electromagnetic fields. A shortened REM latency has also been reported. We investigated the effects of a double-blind radiofrequency exposure (884 MHz, GSM signaling standard including non-DTX and DTX mode, time-averaged 10 g psSAR of 1.4 W/kg) on self-evaluated sleepiness and objective EEG measures during sleep. Forty-eight subjects (mean age 28 years) underwent 3 h of controlled exposure (7:30-10:30 PM; active or sham) prior to sleep, followed by a full-night polysomnographic recording in a sleep laboratory. The results demonstrated that following exposure, time in Stages 3 and 4 sleep (SWS, slow-wave sleep) decreased by 9.5 min (12%) out of a total of 78.6 min, and time in Stage 2 sleep increased by 8.3 min (4%) out of a total of 196.3 min compared to sham. The latency to Stage 3 sleep was also prolonged by 4.8 min after exposure. Power density analysis indicated an enhanced activation in the frequency ranges 0.5-1.5 and 5.75-10.5 Hz during the first 30 min of Stage 2 sleep, with 7.5-11.75 Hz being elevated within the first hour of Stage 2 sleep, and bands 4.75-8.25 Hz elevated during the second hour of Stage 2 sleep. No pronounced power changes were observed in SWS or for the third hour of scored Stage 2 sleep. No differences were found between controls and subjects with prior complaints of mobile phone-related symptoms. The results confirm previous findings that RF exposure increased the EEG alpha range in the sleep EEG, and indicated moderate impairment of SWS. Furthermore, reported differences in sensitivity to mobile phone use were not reflected in sleep

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parameters.

Wiholm C, Lowden A, Kuster N, Hillert L, Arnetz BB, Akerstedt T, Moffat SD. Mobile phone exposure and spatial memory. *Bioelectromagnetics*. 30(1):59-65, 2009.

Radiofrequency (RF) emission during mobile phone use has been suggested to impair cognitive functions, that is, working memory. This study investigated the effects of a 2 1/2 h RF exposure (884 MHz) on spatial memory and learning, using a double-blind repeated measures design. The exposure was designed to mimic that experienced during a real-life mobile phone conversation. The design maximized the exposure to the left hemisphere. The average exposure was peak spatial specific absorption rate (psSAR10g) of 1.4 W/kg. The primary outcome measure was a "virtual" spatial navigation task modeled after the commonly used and validated Morris Water Maze. The distance traveled on each trial and the amount of improvement across trials (i.e., learning) were used as dependent variables. The participants were daily mobile phone users, with and without symptoms attributed to regular mobile phone use. Results revealed a main effect of RF exposure and a significant RF exposure by group effect on distance traveled during the trials. The symptomatic group improved their performance during RF exposure while there was no such effect in the non-symptomatic group. Until this new finding is further investigated, we can only speculate about the cause.

Loughran SP, McKenzie RJ, Jackson ML, Howard ME, Croft RJ. Individual differences in the effects of mobile phone exposure on human sleep: rethinking the problem. *Bioelectromagnetics*. 33(1):86-93, 2012.

Mobile phone exposure-related effects on the human electroencephalogram (EEG) have been shown during both waking and sleep states, albeit with slight differences in the frequency affected. This discrepancy, combined with studies that failed to find effects, has led many to conclude that no consistent effects exist. We hypothesized that these differences might partly be due to individual variability in response, and that mobile phone emissions may in fact have large but differential effects on human brain activity. Twenty volunteers from our previous study underwent an adaptation night followed by two experimental nights in which they were randomly exposed to two conditions (Active and Sham), followed by a full-night sleep episode. The EEG spectral power was increased in the sleep spindle frequency range in the first 30 min of non-rapid eye movement (non-REM) sleep following Active exposure. This increase was more prominent in the participants that showed an increase in the original study. These results confirm previous findings of mobile phone-like emissions affecting the EEG during non-REM sleep. Importantly, this low-level effect was also shown to be sensitive to individual variability. Furthermore, this indicates that previous negative results are not strong evidence for a lack of an effect and, given the far-reaching implications of mobile phone research, we may need to rethink the interpretation of results and the manner in which research is conducted in this field.

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Loughran SP, Wood AW, Barton JM, Croft RJ, Thompson B, Stough C. The effect of electromagnetic fields emitted by mobile phones on human sleep. Neuroreport. 16(17):1973-1976, 2005.

Previous research has suggested that exposure to radiofrequency electromagnetic fields increases electroencephalogram spectral power in non-rapid eye movement sleep. Other sleep parameters have also been affected following exposure. We examined whether aspects of sleep architecture show sensitivity to electromagnetic fields emitted by digital mobile phone handsets. Fifty participants were exposed to electromagnetic fields for 30 min prior to sleep. Results showed a decrease in rapid eye movement sleep latency and increased electroencephalogram spectral power in the 11.5-12.25 Hz frequency range during the initial part of sleep following exposure. These results are evidence that mobile phone exposure prior to sleep may promote rapid eye movement sleep and modify the sleep electroencephalogram in the first non-rapid eye movement sleep period.

Liu H, Chen G, Pan Y, Chen Z, Jin W, Sun C, Chen C, Dong X, Chen K, Xu Z, Zhang S, Yu Y. (2014) Occupational Electromagnetic Field Exposures Associated with Sleep Quality: A Cross-Sectional Study. PLoS ONE 9(10): e110825. doi:10.1371/journal.pone.0110825.

BACKGROUND: Exposure to electromagnetic field (EMF) emitted by mobile phone and other machineries concerns half the world's population and raises the problem of their impact on human health. The present study aims to explore the effects of electromagnetic field exposures on sleep quality and sleep duration among workers from electric power plant. METHODS: A cross-sectional study was conducted in an electric power plant of Zhejiang Province, China. A total of 854 participants were included in the final analysis. The detailed information of participants was obtained by trained investigators using a structured questionnaire, which including socio-demographic characteristics, lifestyle variables, sleep variables and electromagnetic exposures. Physical examination and venous blood collection were also carried out for every study subject. RESULTS: After grouping daily occupational electromagnetic exposure into three categories, subjects with long daily exposure time had a significantly higher risk of poor sleep quality in comparison to those with short daily exposure time. The adjusted odds ratios were 1.68 (95%CI: 1.18, 2.39) and 1.57 (95%CI: 1.10, 2.24) across tertiles. Additionally, among the subjects with long-term occupational exposure, the longer daily occupational time apparently increased the risk of poor sleep quality (OR (95%CI): 2.12 (1.23~3.66) in the second tertile; 1.83 (1.07~3.15) in the third tertile). There was no significant association of long-term occupational exposure duration, monthly electric fee or years of mobile-phone use with sleep quality or sleep duration. CONCLUSIONS: The findings showed that daily occupational EMF exposure was positively associated with poor sleep quality. It implies EMF exposure may damage human sleep quality rather than sleep duration.

Lebedeva NN, Sulimov AV, Sulimova OP, Korotkovskaya TI, Gailus T, Investigation of brain potentials in sleeping humans exposed to the electromagnetic field of mobile

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phones. Crit Rev Biomed Eng 29(1):125-133, 2001.

An investigation was made of 8-hour EEG tracings of sleeping humans exposed to the electromagnetic field of a GSM-standard mobile phone. To analyze the EEG-patterns, manual scoring, nonlinear dynamics, and spectral analysis were employed. It was found that, when human beings were exposed to the electromagnetic field of a cellular phone, their cerebral cortex biopotentials revealed an increase in the alpha-range power density as compared to the placebo experiment. It was also found that the dimension of EEG correlation dynamics and the relation of sleep stages changed under the influence of the electromagnetic field of a mobile phone.

Huber R, Graf T, Cote KA, Wittmann L, Gallmann E, Matter D, Schuderer J, Kuster N, Borbely AA, Achermann P, Exposure to pulsed high-frequency electromagnetic field during waking affects human sleep EEG. Neuroreport 11(15):3321-3325, 2000.

The aim of the study was to investigate whether the electromagnetic field (EMF) emitted by digital radiotelephone handsets affects brain physiology. Healthy, young male subjects were exposed for 30 min to EMF (900 MHz; spatial peak specific absorption rate 1 W/kg) during the waking period preceding sleep. Compared with the control condition with sham exposure, spectral power of the EEG in non-rapid eye movement sleep was increased. The maximum rise occurred in the 9.75-11.25 Hz and 12.5-13.25 Hz band during the initial part of sleep. These changes correspond to those obtained in a previous study where EMF was intermittently applied during sleep. Unilateral exposure induced no hemispheric asymmetry of EEG power. The present results demonstrate that exposure during waking modifies the EEG during subsequent sleep. Thus the changes of brain function induced by pulsed high-frequency EMF outlast the exposure period.

Regel SJ, Tinguely G, Schuderer J, Adam M, Kuster N, Landolt HP, Achermann P. Pulsed radio-frequency electromagnetic fields: dose-dependent effects on sleep, the sleep EEG and cognitive performance. J Sleep Res. 16(3):253-258, 2007.

To establish a dose-response relationship between the strength of electromagnetic fields (EMF) and previously reported effects on the brain, we investigated the influence of EMF exposure by varying the signal intensity in three experimental sessions. The head of 15 healthy male subjects was unilaterally exposed for 30 min prior to sleep to a pulse-modulated EMF (GSM handset like signal) with a 10 g-averaged peak spatial specific absorption rate of (1) 0.2 W kg⁻¹, (2) 5 W kg⁻¹, or (3) sham exposed in a double-blind, crossover design. During exposure, subjects performed two series of three computerized cognitive tasks, each presented in a fixed order [simple reaction time task, two-choice reaction time task (CRT), 1-, 2-, 3-back task]. Immediately after exposure, night-time sleep was polysomnographically recorded for 8 h. Sleep architecture was not affected by EMF exposure. Analysis of the sleep electroencephalogram (EEG) revealed a dose-dependent increase of power in the spindle frequency range in non-REM sleep. Reaction speed decelerated with increasing field intensity in the 1-back task, while accuracy in the CRT and N-back task were not affected in a dose-dependent manner. In summary, this study reveals first indications of a dose-response relationship between

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EMF field intensity and its effects on brain physiology as demonstrated by changes in the sleep EEG and in cognitive performance.

Pelletier A, Delanaud S, de Seze R, Bach V, Libert JP, Loos N. Does Exposure to a Radiofrequency Electromagnetic Field Modify Thermal Preference in Juvenile Rats? PLoS One. 2014 Jun 6;9(6):e99007. doi: 10.1371/journal.pone.0099007. eCollection 2014.

Some studies have shown that people living near a mobile phone base station may report sleep disturbances and discomfort. Using a rat model, we have previously shown that chronic exposure to a low-intensity radiofrequency electromagnetic field (RF-EMF) was associated with paradoxical sleep (PS) fragmentation and greater vasomotor tone in the tail. Here, we sought to establish whether sleep disturbances might result from the disturbance of thermoregulatory processes by a RF-EMF. We recorded thermal preference and sleep stage distribution in 18 young male Wistar rats. Nine animals were exposed to a low-intensity RF-EMF (900 MHz, 1 V.m⁻¹) for five weeks and nine served as non-exposed controls. Thermal preference was assessed in an experimental chamber comprising three interconnected compartments, in which the air temperatures (Ta) were set to 24°C, 28°C and 31°C. Sleep and tail skin temperature were also recorded. Our results indicated that relative to control group, exposure to RF-EMF at 31°C was associated with a significantly lower tail skin temperature (-1.6°C) which confirmed previous data. During the light period, the exposed group preferred to sleep at Ta = 31°C and the controls preferred Ta = 28°C. The mean sleep duration in exposed group was significantly greater (by 15.5%) than in control group (due in turn to a significantly greater amount of slow wave sleep (SWS, +14.6%). Similarly, frequency of SWS was greater in exposed group (by 4.9 episodes.h⁻¹). The PS did not differ significantly between the two groups. During the dark period, there were no significant intergroup differences. We conclude that RF-EMF exposure induced a shift in thermal preference towards higher temperatures. The shift in preferred temperature might result from a cold thermal sensation. The change in sleep stage distribution may involve signals from thermoreceptors in the skin. Modulation of SWS may be a protective adaptation in response to RF-EMF exposure.

HuberR, TreyerV, BorbélyAA, SchudererJ, GottseligJM, LandoltH-P, WerthE, BertholdT, KusterN, BuckA, AchermannP, Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. J Sleep Res 11: 289-295, 2002.

Usage of mobile phones is rapidly increasing, but there is limited data on the possible effects of electromagnetic field (EMF) exposure on brain physiology. We investigated the effect of EMF vs. sham control exposure on waking regional cerebral blood flow (rCBF) and on waking and sleep electroencephalogram (EEG) in humans. In Experiment 1, positron emission tomography (PET) scans were taken after unilateral head exposure to 30-min pulse-modulated 900 MHz electromagnetic field (pm-EMF). In Experiment 2, night-time sleep was polysomnographically recorded after EMF exposure. Pulse-modulated EMF exposure increased relative rCBF in the dorsolateral prefrontal cortex

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ipsilateral to exposure. Also, pm-EMF exposure enhanced EEG power in the alpha frequency range prior to sleep onset and in the spindle frequency range during stage 2 sleep. Exposure to EMF without pulse modulation did not enhance power in the waking or sleep EEG. We previously observed EMF effects on the sleep EEG (A. A. Borbély, R. Huber, T. Graf, B. Fuchs, E. Gallmann and P. Achermann. *Neurosci. Lett.*, 1999, 275: 207-210; R. Huber, T. Graf, K. A. Cote, L. Wittmann, E. Gallmann, D. Matter, J. Schuderer, N. Kuster, A. A. Borbély, and P. Achermann. *Neuroreport*, 2000, 11: 3321-3325), but the basis for these effects was unknown. The present results show for the first time that (1) pm-EMF alters waking rCBF and (2) pulse modulation of EMF is necessary to induce waking and sleep EEG changes. Pulse-modulated EMF exposure may provide a new, non-invasive method for modifying brain function for experimental, diagnostic and therapeutic purposes.

Huber R, Schuderer J, Graf T, Jutz K, Borbely AA, Kuster N, Achermann P. Radio frequency electromagnetic field exposure in humans: Estimation of SAR distribution in the brain, effects on sleep and heart rate. *Bioelectromagnetics* 24(4):262-276, 2003.

In two previous studies we demonstrated that radiofrequency electromagnetic fields (RF EMF) similar to those emitted by digital radiotelephone handsets affect brain physiology of healthy young subjects exposed to RF EMF (900 MHz; spatial peak specific absorption rate [SAR] 1 W/kg) either during sleep or during the waking period preceding sleep. In the first experiment, subjects were exposed intermittently during an 8 h nighttime sleep episode and in the second experiment, unilaterally for 30 min prior to a 3 h daytime sleep episode. Here we report an extended analysis of the two studies as well as the detailed dosimetry of the brain areas, including the assessment of the exposure variability and uncertainties. The latter enabled a more in depth analysis and discussion of the findings. Compared to the control condition with sham exposure, spectral power of the non-rapid eye movement sleep electroencephalogram (EEG) was initially increased in the 9-14 Hz range in both experiments. No topographical differences with respect to the effect of RF EMF exposure were observed in the two experiments. Even unilateral exposure during waking induced a similar effect in both hemispheres. Exposure during sleep reduced waking after sleep onset and affected heart rate variability. Exposure prior to sleep reduced heart rate during waking and stage 1 sleep. The lack of asymmetries in the effects on sleep EEG, independent of bi- or unilateral exposure of the cortex, may indicate involvement of subcortical bilateral projections to the cortex in the generation of brain function changes, especially since the exposure of the thalamus was similar in both experiments (approx. 0.1 W/kg).

Huber R, Treyer V, Schuderer J, Berthold T, Buck A, Kuster N, Landolt HP, Achermann P. Exposure to pulse-modulated radio frequency electromagnetic fields affects regional cerebral blood flow. *Eur J Neurosci.* 21(4):1000-1006, 2005.

We investigated the effects of radio frequency electromagnetic fields (RF EMF) similar to those emitted by mobile phones on waking regional cerebral blood flow (rCBF) in 12 healthy young men. Two types of RF EMF exposure were applied: a 'base-station-like' and a 'handset-like' signal. Positron emission tomography scans were taken after 30 min

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unilateral head exposure to pulse-modulated 900 MHz RF EMF (10 g tissue-averaged spatial peak-specific absorption rate of 1 W/kg for both conditions) and sham control. We observed an increase in relative rCBF in the dorsolateral prefrontal cortex on the side of exposure. The effect depended on the spectral power in the amplitude modulation of the RF carrier such that only 'handset-like' RF EMF exposure with its stronger low-frequency components but not the 'base-station-like' RF EMF exposure affected rCBF. This finding supports our previous observation that pulse modulation of RF EMF is necessary to induce changes in the waking and sleep EEG, and substantiates the notion that pulse modulation is crucial for RF EMF-induced alterations in brain physiology.

Hung CS, Anderson C, Horne JA, McEvoy P. Mobile phone 'talk-mode' signal delays EEG-determined sleep onset. *Neurosci Lett.* 421: 82-86, 2007.

Mobile phones signals are pulse-modulated microwaves, and EEG studies suggest that the extremely low-frequency (ELF) pulse modulation has sleep effects. However, 'talk', 'listen' and 'standby' modes differ in the ELF (2, 8, and 217Hz) spectral components and specific absorption rates, but no sleep study has differentiated these modes. We used a GSM900 mobile phone controlled by a base-station simulator and a test SIM card to simulate these three specific modes, transmitted at 12.5% (23dBm) of maximum power. At weekly intervals, 10 healthy young adults, sleep restricted to 6h, were randomly and single-blind exposed to one of: talk, listen, standby and sham (nil signal) modes, for 30min, at 13:30h, whilst lying in a sound-proof, lit bedroom, with a thermally insulated silent phone beside the right ear. Bipolar EEGs were recorded continuously, and subjective ratings of sleepiness obtained every 3min (before, during and after exposure). After exposure the phone and base-station were switched off, the bedroom darkened, and a 90min sleep opportunity followed. We report on sleep onset using: (i) visually scored latency to onset of stage 2 sleep, (ii) EEG power spectral analysis. There was no condition effect for subjective sleepiness. Post-exposure, sleep latency after talk mode was markedly and significantly delayed beyond listen and sham modes. This condition effect over time was also quite evident in 1-4Hz EEG frontal power, which is a frequency range particularly sensitive to sleep onset. It is possible that 2, 8, 217Hz modulation may differentially affect sleep onset.

Rusterholz T, Bersagliere A, Kuster N, Achermann P. Sleep EEG alterations: effects of different pulse-modulated radio frequency electromagnetic fields. *J Sleep Res.* 21(1):50-58, 2012.

Previous studies have observed increases in electroencephalographic power during sleep in the spindle frequency range (approximately 11-15 Hz) after exposure to mobile phone-like radio frequency electromagnetic fields (RF EMF). Results also suggest that pulse modulation of the signal is crucial to induce these effects. Nevertheless, it remains unclear which specific elements of the field are responsible for the observed changes. We investigated whether pulse-modulation frequency components in the range of sleep spindles may be involved in mediating these effects. Thirty young healthy men were exposed, at weekly intervals, to three different conditions for 30 min

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directly prior to an 8-h sleep period. Exposure consisted of a 900-MHz RF EMF, pulse modulated at 14 Hz or 217 Hz, and a sham control condition. Both active conditions had a peak spatial specific absorption rate of 2 W kg^{-1} . During exposure subjects performed three different cognitive tasks (measuring attention, reaction speed and working memory), which were presented in a fixed order. Electroencephalographic power in the spindle frequency range was increased during non-rapid eye movement sleep (2nd episode) following the 14-Hz pulse-modulated condition. A similar but non-significant increase was also observed following the 217-Hz pulse-modulated condition. Importantly, this exposure-induced effect showed considerable individual variability. Regarding cognitive performance, no clear exposure-related effects were seen. Consistent with previous findings, our results provide further evidence that pulse-modulated RF EMF alter brain physiology, although the time-course of the effect remains variable across studies. Additionally, we demonstrated that modulation frequency components within a physiological range may be sufficient to induce these effects.

Schmid MR, Loughran SP, Regel SJ, Murbach M, Bratic Grunauer A, Schmid MR, Murbach M, Lustenberger C, Maire M, Kuster N, Achermann P, Loughran SP. Sleep EEG alterations: effects of pulsed magnetic fields versus pulse-modulated radio frequency electromagnetic fields. *J Sleep Res.*21(6):620-629, 2012.

Studies have repeatedly shown that electroencephalographic power during sleep is enhanced in the spindle frequency range following radio frequency electromagnetic field exposures pulse-modulated with fundamental frequency components of 2, 8, 14 or 217 Hz and combinations of these. However, signals used in previous studies also had significant harmonic components above 20 Hz. The current study aimed: (i) to determine if modulation components above 20 Hz, in combination with radio frequency, are necessary to alter the electroencephalogram; and (ii) to test the demodulation hypothesis, if the same effects occur after magnetic field exposure with the same pulse sequence used in the pulse-modulated radio frequency exposure. In a randomized double-blind crossover design, 25 young healthy men were exposed at weekly intervals to three different conditions for 30 min before sleep. Cognitive tasks were also performed during exposure. The conditions were a 2-Hz pulse-modulated radio frequency field, a 2-Hz pulsed magnetic field, and sham. Radio frequency exposure increased electroencephalogram power in the spindle frequency range. Furthermore, delta and theta activity (non-rapid eye movement sleep), and alpha and delta activity (rapid eye movement sleep) were affected following both exposure conditions. No effect on sleep architecture and no clear impact of exposure on cognition was observed. These results demonstrate that both pulse-modulated radio frequency and pulsed magnetic fields affect brain physiology, and the presence of significant frequency components above 20 Hz are not fundamental for these effects to occur. Because responses were not identical for all exposures, the study does not support the hypothesis that effects of radio frequency exposure are based on demodulation of the signal only.

Studies that show **Cell Phone Health Effects****Effects On Skin**

Pacini S, Ruggiero M, Sardi I, Aterini S, Gulisano F, Gulisano M. Exposure to global system for mobile communication (GSM) cellular phone radiofrequency alters gene expression, proliferation, and morphology of human skin fibroblasts. *Oncol Res* 13(1):19-24, 2002.

Human skin fibroblasts were exposed to global system for mobile communication (GSM) cellular phone radiofrequency for 1 h. GSM exposure induced alterations in cell morphology and increased the expression of mitogenic signal transduction genes (e.g., MAP kinase kinase 3, G2/mitotic-specific cyclin G1), cell growth inhibitors (e.g., transforming growth factor-beta), and genes controlling apoptosis (e.g., bax). A significant increase in DNA synthesis and intracellular mitogenic second messenger formation matched the high expression of MAP kinase family genes. These findings show that these electromagnetic fields have significant biological effects on human skin fibroblasts.

Strobos MA, Coenraads PJ, De Jongste MJ, Ubels FL. Dermatitis caused by radio-frequency electromagnetic radiation. *Contact Dermatitis* 44(5):309, 2001.

A case report of a woman who developed dermatitis to a transmitter placed on the abdomen that sent radio waves to an implanted neurostimulatory receiver for angina. Patch tests with the plastic, rubber and glue of the transmitter were negative, as well as those with various components of the device from the manufacturer. She had skin symptoms only after starting stimulation, with spontaneous improvement in between times.

Ozguner F, Aydin G, Mollaoglu H, Gokalp O, Koyu A, Cesur G. Prevention of mobile phone induced skin tissue changes by melatonin in rat: an experimental study. *Toxicol Ind Health*. 20(6-10):133-139, 2004.

Most of the mobile phones in Turkey emit 900 MHz radiation which is mainly absorbed by the skin and, to a lesser extent, muscle. The aim of this study was to investigate the effects the 900 MHz electromagnetic irradiation emitted by these devices on the induction of histopathologic changes in skin and the effect of melatonin (Mel) on any of these changes. Thirty male Wistar-Albino rats were used in the study. The experimental groups were composed of: a nontreated control group, an irradiated group (IR) without Mel and an irradiated with Mel treatment group (IR + Mel). 900 MHz radiation was applied to IR group for 10 days (30 min/day). The IR + Mel group received 10 mg/kg per day melatonin in tap water for 10 days before irradiation. At the end of the tenth day, the skin graft was excized from the thoraco-abdominal area. Histopathologic changes in skin were analyzed. In the IR group, increased thickness of stratum corneum, atrophy of epidermis, papillomatosis, basal cell proliferation, increased granular cell layer (hypergranulosis) in epidermis and capillary proliferation, impairment in collagen tissue distribution and separation of collagen bundles in dermis were all observed compared to the control group. Most of these changes, except hypergranulosis, were prevented

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with melatonin treatment. In conclusion, exposure to 900 MHz radiation emitted by mobile phones caused mild skin changes. Furthermore, melatonin treatment can reduce these changes and may have a beneficial effect to prevent 900 MHz mobile phone-induced rat skin changes.

Nam KC, Kim SW, Kim SC, Kim DW. Effects of RF exposure of teenagers and adults by CDMA cellular phones. *Bioelectromagnetics*. 27(7):509-514, 2006.

Many cellular phone provocation studies have been conducted since the question of increased health risk from extended usage of cellular phones became a social issue. Internationally, most studies have been conducted regarding the effects of GSM cellular phones on blood pressure and heart rate of adult volunteers. On the other hand, very few provocation studies have been conducted regarding the physiological effects of CDMA phones on teenagers. In this study, two volunteer groups consisting of 21 teenagers and 21 adults were exposed to 300 mW of radio frequency (RF) electromagnetic field emitted by a CDMA cellular phone for half an hour. Physiological parameters such as systolic and diastolic blood pressures, heart rate, respiration rate, and skin resistance were simultaneously measured. All the parameters for both groups were unaffected during the exposure except for decreased skin resistance of the teenager group (P < .0001). For the regrouped 23 male and 19 female subjects, all the parameters for both groups were unaffected during the exposure except for decreased skin resistance of the male subjects (P = .0026). Those resistances at 10 min after the terminated exposure returned to the resistances at rest regardless of the different groups of age and sex.

Monfrecola G, Moffa G, Procaccini EM. Non-ionizing electromagnetic radiations, emitted by a cellular phone, modify cutaneous blood flow. *Dermatology*. 207(1):10-14, 2003.

BACKGROUND: Our surroundings are full of non-ionizing electromagnetic radiation (EMR) of different frequency and power. The non-ionizing EMRs emitted by television, computer and cellular phone (CF) sets have been increasing over the past few years. OBJECTIVE: The aim of our study was to assess the effects of non-ionizing EMRs (frequency 3×10^8 to 3×10^{11} Hz), emitted by CFs, on cutaneous blood flow in healthy volunteers. METHODS: Thirty healthy volunteers (14 male and 16 female; age: 18-53 years) entered the study. Measurements of cutaneous blood flow were taken under standard conditions (temperature and humidity), using a laser Doppler He-Ne flowmeter that was applied to the ear skin by an optical fibre probe. Microflow values were recorded without CF contact with the skin (T0), with the CF turned off but in contact with the ear skin (T1), with CF contact and turned on (T2), with CF contact, turned on and receiving (T3). The microflow values were also recorded backwards: with CF contact and set turned on (T4), with CF contact and turned off (T5), without CF contact (T6). RESULTS: The mean value of basal microflow (T0), expressed as perfusion units (PU), was 51.26 ± 11.93 PU. During the T1 phase, the microflow increase was 61.38%; in T2 it was 131.74%, in T3 157.67%, in T4 139.21% and in T5 122.90%; in T6, the microflow value was 57.58 ± 10 PU (similar to the basal microflow). Statistically

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significant cutaneous microflow values ($p < 0.050$) were observed comparing the T1 to T5 values with basal microflow (T0). Furthermore, in comparison with T1 values (CF turned off in contact with the ear skin), the T2, T3 and T4 data were statistically significant (T2 vs. T1: $t = 7.763$ with $p < 0.050$; T3 vs. T1: $t = 9.834$ with $p < 0.050$; T4 vs. T1: $t = 8.885$ with $p < 0.050$).

Simon D, Daubos A, Pain C, Fitoussi R, Vié K, Taieb A, de Benetti L, Cario-André M. Exposure to acute electromagnetic radiation of mobile phone exposure range alters transiently skin homeostasis of a model of pigmented reconstructed epidermis. *Int J Cosmet Sci.* 35(1):27-34, 2013.

Exposure to electromagnetic radiations (EMR) produced by mobile phone concerns half the world's population and raises the problem of their impact on human health. In this study, we looked at the effects of mobile phone exposure (GSM basic, 900MHz, SAR 2 mW g⁻¹), 6 h) on a model of pigmented skin. We have analysed the expression and localization of various markers of keratinocyte and melanocyte differentiation 2, 6, 18 and 24 h after EMR exposure of reconstructed epidermis containing either only keratinocytes or a combination of keratinocytes and melanocytes grown on dead de-epidermized dermis, using histology, immunohistochemistry and Western blot. No changes were found in epidermal architecture, localization of epidermal markers, presence of apoptotic cells and the induction of p53 in both types of epidermis (with or without melanocytes) after exposure to EMR. In pigmented reconstructs, no change in the location and dendricity of melanocytes and in melanin transfer to neighbouring keratinocytes was detected after EMR exposure. Loricrin, cytokeratin 14 were significantly decreased at 6 h. The level of all markers increased at 24 h as compared to 6 h post-EMR exposure, associated with a significant decrease of the 20S proteasome activity. Our data indicate that exposure to 900MHz frequency induces a transient alteration of epidermal homeostasis, which may alter the protective capacity of the skin against external factors. Presence or absence of melanocytes did not modify the behaviour of reconstructs after EMR exposure.

Seishima M, Oyama Z, Oda M. Cellular phone dermatitis with chromate allergy. *Dermatology.* 207(1):48-50, 2003.

BACKGROUND: A patient with allergic contact dermatitis caused by hexavalent chromium plating on a cellular phone has already been reported. **OBJECTIVES:** This study described the clinical characteristics and results of patch tests in 8 patients with contact dermatitis possibly caused by handling a cellular phone. **PATIENTS:** The 8 patients were 4 males and 4 females aged from 14 to 54 years. They each noticed skin eruptions after 9-25 days of using a cellular phone. All patients had erythema, and 7 had papules on the hemilateral auricle or in the preauricular region. Three of 8 patients had a history of metal allergy. Chromate, aluminium and acrylnitrile-butadiene-styrene copolymer were used as plating on the cellular phones used by these patients. **METHODS:** Closed patch tests and photopatch tests were performed using metal standard antigens. **RESULTS:** The patch test was positive for 0.5, 0.1 and 0.05%

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potassium dichromate in all 8 patients. The photopatch test showed the same results. One patient was positive for 2% cobalt chloride and one for 5% nickel sulfate.

CONCLUSION: It is important to consider the possibility of contact dermatitis due to a cellular phone, possibly caused by chromate, when the patients have erythema and papules on the hemilateral auricle or in the preauricular region.

Loos N, György T, Ghosn R, Brenet-Dufour V, Liabeuf S, Selmaoui B, Jean-Pierre L, Bach V, Diouf M, de Seze R. Is the effect of mobile phone radiofrequency waves on human skin perfusion non-thermal? Microcirculation. 2013 Apr 17. doi: 10.1111/micc.12062. [Epub ahead of print]

OBJECTIVE: to establish whether skin micro blood flow can be modified by exposure to the radiofrequency waves emitted by a mobile phone when the latter is held against the jaw and ear. METHODS: Variations in skin micro blood flow and skin temperature in adult volunteers were simultaneously recorded with a thermostatic laser Doppler system during a 20-minute "radiofrequency" exposure session and a 20-minute "sham" session. The skin microvessels' vasodilatory reserve was assessed with a heat challenge at the end of the protocol. RESULTS: During the radiofrequency exposure session, skin micro blood flow increased (vs. baseline) more than during the sham exposure session. The sessions did not differ significant in terms of the skin temperature time-course response. The skin microvessels' vasodilatory ability was found to be greater during radiofrequency exposure than during sham exposure. CONCLUSIONS: Our results reveal the existence of a specific vasodilatory effect of mobile phone radiofrequency emission from mobile phones.

Karinen A, Heinavaara S, Nylund R, Leszczynski D. Mobile phone radiation might alter protein expression in human skin. BMC Genomics. 9(1):77, 2008.

ABSTRACT: BACKGROUND: Earlier we have shown that the mobile phone radiation (radiofrequency modulated electromagnetic fields; RF-EMF) alters protein expression in human endothelial cell line. This does not mean that similar response will take place in human body exposed to this radiation. Therefore, in this pilot human volunteer study, using proteomics approach, we have examined whether a local exposure of human skin to RF-EMF will cause changes in protein expression in living people. RESULTS: Small area of forearm's skin in 10 female volunteers was exposed to RF-EMF (specific absorption rate SAR=1.3W/kg) and punch biopsies were collected from exposed and non exposed areas of skin. Proteins extracted from biopsies were separated using 2-DE and protein expression changes were analyzed using PDQuest software. Analysis has identified 8 proteins that were statistically significantly affected (Anova and Wilcoxon tests). Two of the proteins were present in all 10 volunteers. This suggests that protein expression in human skin might be affected by the exposure to RF-EMF. The number of affected proteins was similar to the number of affected proteins observed in our earlier in vitro studies. CONCLUSIONS: This is the first study showing that molecular level changes might take place in human volunteers in response to exposure to RF-EMF. Our study confirms that proteomics screening approach can identify protein targets of RF-EMF in human volunteers.

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Sanchez S, Milochau A, Ruffie G, Poulletier de Gannes F, Lagroye I, Haro E, Surleve-Bazeille JE, Billaudel B, Lassegues M, Veyret B. Human skin cell stress response to GSM-900 mobile phone signals. *FEBS J.* 273(24):5491-5507, 2006.

In recent years, possible health hazards due to radiofrequency radiation (RFR) emitted by mobile phones have been investigated. Because several publications have suggested that RFR is stressful, we explored the potential biological effects of Global System for Mobile phone communication at 900 MHz (GSM-900) exposure on cultures of isolated human skin cells and human reconstructed epidermis (hRE) using human keratinocytes. As cell stress markers, we studied Hsc70, Hsp27 and Hsp70 heat shock protein (HSP) expression and epidermis thickness, as well as cell proliferation and apoptosis. Cells were exposed to GSM-900 under optimal culture conditions, for 48 h, using a specific absorption rate (SAR) of 2 W.kg(-1). This SAR level represents the recommended limit for local exposure to a mobile phone. The various biological parameters were analysed immediately after exposure. Apoptosis was not induced in isolated cells and there was no alteration in hRE thickness or proliferation. No change in HSP expression was observed in isolated keratinocytes. By contrast, a slight but significant increase in Hsp70 expression was observed in hREs after 3 and 5 weeks of culture. Moreover, fibroblasts showed a significant decrease in Hsc70, depending on the culture conditions. These results suggest that adaptive cell behaviour in response to RFR exposure, depending on the cell type and culture conditions, is unlikely to have deleterious effects at the skin level.

Allergies Effects

Kimata H. Enhancement of allergic skin wheal responses by microwave radiation from mobile phones in patients with atopic eczema/dermatitis syndrome. *Int Arch Allergy Immunol* 129(4):348-350, 2002.

Microwave radiation from mobile phones enhanced skin wheal responses induced by house dust mite and Japanese cedar pollen while it had no effect on wheal responses induced by histamine in patients with atopic eczema/dermatitis syndrome (AEDS). Microwave radiation also increased plasma levels of substance P (SP) and vasoactive intestinal peptide (VIP) in patients with AEDS. These results indicate that microwave radiation from mobile phones may enhance allergen-induced wheal responses in association with the release of SP and VIP. This finding may be useful in elucidating the pathophysiology and treatment of AEDS.

Kimata H. Enhancement of allergic skin wheal responses in patients with atopic eczema/dermatitis syndrome by playing video games or by a frequently ringing mobile phone. *Eur J Clin Invest.* 33(6):513-517, 2003.

BACKGROUND: Playing video games causes physical and psychological stress, including increased heart rate and blood pressure and aggression-related feelings. Use of mobile phones is very popular in Japan, and frequent ringing is a common and intrusive part of

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Japanese life. Atopic eczema/dermatitis syndrome is often exacerbated by stress. Stress increases serum IgE levels, skews cytokine pattern towards Th2 type, enhances allergen-induced skin wheal responses, and triggers mast cell degranulation via substance P, vasoactive intestinal peptide and nerve growth factor. MATERIALS AND METHODS: (1) In the video game study, normal subjects (n = 25), patients with allergic rhinitis (n = 25) or atopic eczema/dermatitis syndrome (n = 25) played a video game (STREET FIGHTER II) for 2 h. Before and after the study, allergen-induced wheal responses, plasma levels of substance P, vasoactive intestinal peptide and nerve growth factor, and in vitro production of total IgE, anti-house dust mite IgE and cytokines were measured. (2) In the mobile phone study, normal subjects (n = 27), patients with allergic rhinitis (n = 27) or atopic eczema/dermatitis syndrome (n = 27) were exposed to 30 incidences of ringing mobile phones during 30 min. Before and after the study, allergen-induced wheal responses, plasma levels of substance P, vasoactive intestinal peptide and nerve growth factor were measured. RESULTS: Playing video games had no effect on the normal subjects or the patients with allergic rhinitis. In contrast, playing video games significantly enhanced allergen-induced skin wheal responses and increased plasma levels of substance P, vasoactive intestinal peptide and nerve growth factors in the patients with atopic eczema/dermatitis syndrome. Moreover, playing video games enhanced in vitro production of total IgE and anti-house dust mite IgE with concomitant increased production of IL-4, IL-10 and IL-13 and decreased production of IFN-gamma and IL-12 in the patients with atopic eczema/dermatitis syndrome. However, exposure to frequently ringing mobile phones significantly enhanced allergen-induced skin wheal responses, plasma levels of substance P, vasoactive intestinal peptide and nerve growth factors in the patients with atopic eczema/dermatitis syndrome, but not in the normal subjects or the patients with allergic rhinitis. CONCLUSION: Playing video games enhanced allergic responses with a concomitant increased release of substance P, vasoactive intestinal peptide and nerve growth factor, and skewing of the cytokine pattern toward Th2 type in the patients with atopic eczema/dermatitis syndrome. In addition, exposure to frequently ringing mobile phones also enhanced allergic responses with a concomitant increased release of substance P, vasoactive intestinal peptide and nerve growth factor Collectively, high technology causes stress, which in turn may aggravate symptoms of atopic eczema/dermatitis syndrome.

Kimata H. Laughter counteracts enhancement of plasma neurotrophin levels and allergic skin wheal responses by mobile phone-mediated stress. Behav Med. 29(4):149-152, 2004.

Laughter caused by viewing a comic video (Rowan Atkinson's The Best Bits of Mr. Bean) reduced the plasma nerve growth factor, neurotrophin-3 levels, and allergic skin wheal responses in patients with atopic dermatitis, whereas viewing a nonhumorous video (weather information) failed to do so. In contrast, stress induced by writing mail on a mobile phone enhanced the plasma nerve growth factor, neurotrophin-3 levels, and allergic skin wheal responses. However, previewing the comic video counteracted mobile phone-mediated enhancement of plasma neurotrophins or allergic skin wheal responses, whereas previewing the weather information failed to do so. Taken together,

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these results suggest that, in patients with atopic dermatitis, writing mail on a mobile phone causes stress and enhances allergic responses with a concomitant increase in plasma neurotrophins that are counteracted by laughter. These results may be useful in the study of pathophysiology and treatment of atopic dermatitis.

Kimata H. Microwave radiation from cellular phones increases allergen-specific IgE production. *Allergy* 60(6):838-839, 2005. (no abstract available).

Effects on Critical Organs

Ozgur E, Sahin D, Tomruk A, Guler G, Sepici-Dinçel A, Altan N, Seyhan N. The Effects of N-acetyl-L-cysteine and Epigallocatechin-3-gallate on Liver Tissue Protein Oxidation and Antioxidant Enzyme Levels After the Exposure to Radio Frequency Radiation. *Int J Radiat Biol.* 2014 Sep 24:1-19. [Epub ahead of print]

PURPOSE: The widespread and sustained use of mobile and cordless phones causes unprecedented increase of radiofrequency radiation (RFR). The aim of this experimental study was to investigate the effect of 900 MHz Global System for Mobile Communications (GSM) modulated RFR (average whole body Specific Absorption Rate (SAR) of 0,4 W/kg, 10 or 20 min daily for consecutive 7 days) to the liver tissue of guinea pigs and the protective effects of antioxidant treatments. **MATERIALS and METHODS:** Adult male guinea pigs were randomly divided into nine groups as; Group I (Sham/saline), Group II (Sham/EGCG), Group III (Sham/NAC), Group IV (10-min RF-exposure/saline), Group V (20-min RF-exposure/saline), Group VI (10-min RF-exposure/EGCG), Group VII (20-min RF-exposure/EGCG), Group VIII (10-min RF-exposure/NAC), Group IX (20-min RF-exposure/NAC). Protein oxidation (PCO), advanced oxidation protein products (AOPP) and antioxidant enzyme activities of superoxide dismutase (SOD) were evaluated after the exposure and the treatments with N-acetylcysteine (NAC) and (-)-epigallocatechin-3-gallate (EGCG). **RESULTS and CONCLUSIONS:** Significant decreases in the activities of SOD were observed in the liver of guinea pigs after RFR exposure. Protein damage did not change due to RFR exposure. On the other hand, only NAC treatment induces increase PCO levels, whereas EGCG treatment alone elevated the level of AOPP. Due to antioxidants have pro-oxidant behavior, the well decided doses and treatment time tables of NAC and EGCG is needed.

Ozgur E, Güler G, Seyhan N. Mobile phone radiation-induced free radical damage in the liver is inhibited by the antioxidants n-acetyl cysteine and epigallocatechin-gallate. *Int J Radiat Biol.* 86(11):935-945, 2010.

Purpose: To investigate oxidative damage and antioxidant enzyme status in the liver of guinea pigs exposed to mobile phone-like radiofrequency radiation (RFR) and the potential protective effects of N-acetyl cysteine (NAC) and epigallocatechin-gallate (EGCG) on the oxidative damage. **Materials and methods:** Nine groups of guinea pigs were used to study the effects of exposure to an 1800-MHz Global System for Mobile Communications (GSM)-modulated signal (average whole body Specific Absorption Rate

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(SAR) of 0.38 W/kg, 10 or 20 min per day for seven days) and treatment with antioxidants. Results: Significant increases in malondialdehyde (MDA) and total nitric oxide (NO(x)) levels and decreases in activities of superoxide dismutase (SOD), myeloperoxidase (MPO) and glutathione peroxidase (GSH-Px) were observed in the liver of guinea pigs after RFR exposure. Only NAC treatment induces increase in hepatic GSH-Px activities, whereas EGCG treatment alone attenuated MDA level. Extent of oxidative damage was found to be proportional to the duration of exposure ($P < 0.05$).

Conclusion: Mobile phone-like radiation induces oxidative damage and changes the activities of antioxidant enzymes in the liver. The adverse effect of RFR may be related to the duration of mobile phone use. NAC and EGCG protect the liver tissue against the RFR-induced oxidative damage and enhance antioxidant enzyme activities.

Devrim E, Ergüder IB, Kılıçoğlu B, Yaykaşlı E, Cetin R, Durak I. Effects of electromagnetic radiation use on oxidant/antioxidant status and dna turn-over enzyme activities in erythrocytes and heart, kidney, liver, and ovary tissues from rats: possible protective role of Vitamin C. Toxicol Mech Methods.18(9):679-683, 2008.

ABSTRACT In this study, the aim was to investigate possible effects of Electromagnetic Radiation (EMR) use on oxidant and antioxidant status in erythrocytes and kidney, heart, liver, and ovary tissues from rats, and possible protective role of vitamin C. For this aim, 40 Wistar albino female rats were used throughout the study. The treatment group was exposed to EMR in a frequency of 900 MHz, the EMR plus vitamin C group was exposed to the same EMR frequency and given vitamin C (250 mg/kg/day) orally for 4 weeks. There were 10 animals in each group including control and vitamin C groups. At the end of the study period, blood samples were obtained from the animals to get erythrocyte sediments. Then the animals were sacrificed and heart, kidney, liver, and ovary tissues were removed. Malondialdehyde (MDA) levels and superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), xanthine oxidase (XO), and adenosine deaminase (ADA) enzyme activities were measured in the tissues and erythrocytes. It was observed that MDA level, XO, and GSH-Px activities significantly increased in the EMR group as compared with those of the control group in the erythrocytes. In the kidney tissues, it was found that MDA level and CAT activity significantly increased, whereas XO and ADA activities decreased in the cellular phone group as compared with those of the control group. However, in the heart tissues it was observed that MDA level, ADA, and XO activities significantly decreased in the cellular phone group as compared with those of the control group. The results suggest that EMR at the frequency generated by a cell phone causes oxidative stress and peroxidation in the erythrocytes and kidney tissues from rats. In the erythrocytes, vitamin C seems to make partial protection against the oxidant stress.

Ozguner F, Oktem F, Armagan A, Yilmaz R, Koyu A, Demirel R, Vural H, Uz E. Comparative analysis of the protective effects of melatonin and caffeic acid phenethyl ester (CAPE) on mobile phone-induced renal impairment in rat. Mol Cell Biochem. 276(1-2):31-37, 2005.

Melatonin and caffeic acid phenethyl ester (CAPE), a component of honeybee propolis,

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were recently found to be potent free radical scavengers and antioxidants. There are a number of reports on the effects induced by electromagnetic radiation (EMR) in various cellular systems. Mechanisms of adverse effects of EMR indicate that reactive oxygen species may play a role in the biological effects of this radiation. The present study was carried out to compare the protective effects of melatonin and CAPE against 900 MHz EMR emitted mobile phone-induced renal tubular injury. Melatonin was administered whereas CAPE was given for 10 days before the exposure. Urinary N-acetyl-beta-D-glucosaminidase (NAG, a marker of renal tubular injury) and malondialdehyde (MDA, an index of lipid peroxidation), were used as markers of oxidative stress-induced renal impairment in rats exposed to EMR. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate the changes of antioxidant status in renal tissue. Urinary NAG and renal MDA were increased in EMR exposed rats while both melatonin and CAPE caused a significant reduction in the levels of these parameters. Likewise, renal SOD and GSH-Px activities were decreased in EMR exposed animals while melatonin caused a significant increase in the activities of these antioxidant enzymes but CAPE did not. Melatonin caused a significant decrease in urinary NAG activity and MDA levels which were increased because of EMR exposure. CAPE also reduced elevated MDA levels in EMR exposed renal tissue, but the effect of melatonin was more potent than that of CAPE. Furthermore, treatment of EMR exposed rats with melatonin increased activities of SOD and GSH-Px to higher levels than those of control rats. In conclusion, melatonin and CAPE prevent renal tubular injury by reducing oxidative stress and protect the kidney from oxidative damage induced by 900 MHz mobile phone. Nevertheless, melatonin seems to be a more potent antioxidant compared with CAPE in kidney.

Ozguner F, Oktem F, Ayata A, Koyu A, Yilmaz HR. A novel antioxidant agent caffeic acid phenethyl ester prevents long-term mobile phone exposure-induced renal impairment in rat. Prognostic value of malondialdehyde, N-acetyl-beta-D-glucosaminidase and nitric oxide determination. Mol Cell Biochem. 277(1-2):73-80, 2005.

Caffeic acid phenethyl ester (CAPE), a flavonoid like compound, is one of the major components of honeybee propolis. It has been used in folk medicine for many years in Middle East countries. It was found to be a potent free radical scavenger and antioxidant recently. The aim of this study was to examine long-term applied 900 MHz emitting mobile phone-induced oxidative stress that promotes production of reactive oxygen species (ROS) and, was to investigate the role of CAPE on kidney tissue against the possible electromagnetic radiation (EMR)-induced renal impairment in rats. In particular, the ROS such as superoxide and nitric oxide (NO) may contribute to the pathophysiology of EMR-induced renal impairment. Malondialdehyde (MDA, an index of lipid peroxidation) levels, urinary N-acetyl-beta-D-glucosaminidase (NAG, a marker of renal tubular injury) and nitric oxide (NO, an oxidant product) levels were used as markers of oxidative stress-induced renal impairment and the success of CAPE treatment. The activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) in renal tissue were determined to evaluate the changes of antioxidant status. The rats used in the study were randomly grouped (10 each) as

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follows: i) Control group (without stress and EMR), ii) Sham-operated rats stayed without exposure to EMR (exposure device off), iii) Rats exposed to 900 MHz EMR (EMR group), and iv) A 900 MHz EMR exposed + CAPE treated group (EMR + CAPE group). In the EMR exposed group, while tissue MDA, NO levels and urinary NAG levels increased ($p < 0.0001$), the activities of SOD, CAT, and GSH-Px in renal tissue were reduced ($p < 0.001$). CAPE treatment reversed these effects as well ($p < 0.0001$, $p < 0.001$ respectively). In conclusion, the increase in NO and MDA levels of renal tissue, and in urinary NAG with the decrease in renal SOD, CAT, GSH-Px activities demonstrate the role of oxidative mechanisms in 900 MHz mobile phone-induced renal tissue damage, and CAPE, via its free radical scavenging and antioxidant properties, ameliorates oxidative renal damage. These results strongly suggest that CAPE exhibits a protective effect on mobile phone-induced and free radical mediated oxidative renal impairment in rats.

Oktem F, Ozguner F, Mollaoglu H, Koyu A, Uz E. Oxidative damage in the kidney induced by 900-MHz-emitted mobile phone: protection by melatonin. Arch Med Res.36(4):350-355, 2005.

BACKGROUND: The mobile phones emitting 900-MHz electromagnetic radiation (EMR) may be mainly absorbed by kidneys because they are often carried in belts. Melatonin, the chief secretory product of the pineal gland, was recently found to be a potent free radical scavenger and antioxidant. The aim of this study was to examine 900-MHz mobile phone-induced oxidative stress that promotes production of reactive oxygen species (ROS) on renal tubular damage and the role of melatonin on kidney tissue against possible oxidative damage in rats. METHODS: The animals were randomly grouped as follows: 1) sham-operated control group and 2) study groups: i) 900-MHz EMR exposed (30 min/day for 10 days) group and ii) 900-MHz EMR exposed+melatonin (100 $\mu\text{g kg}^{-1}$) s.c. before the daily EMR exposure) treated group. Malondialdehyde (MDA), an index of lipid peroxidation, and urine N-acetyl-beta-d-glucosaminidase (NAG), a marker of renal tubular damage were used as markers of oxidative stress-induced renal impairment. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate the changes of antioxidant status. RESULTS: In the EMR-exposed group, while tissue MDA and urine NAG levels increased, SOD, CAT, and GSH-Px activities were reduced. Melatonin treatment reversed these effects as well. In this study, the increase in MDA levels of renal tissue and in urine NAG and also the decrease in renal SOD, CAT, GSH-Px activities demonstrated the role of oxidative mechanism induced by 900-MHz mobile phone exposure, and melatonin, via its free radical scavenging and antioxidant properties, ameliorated oxidative tissue injury in rat kidney. CONCLUSIONS: These results show that melatonin may exhibit a protective effect on mobile phone-induced renal impairment in rats.

Mugunthan N, Anbalagan J, Meenachi S, Samy AS. EXPOSURE OF MICE TO 900 - 1900 MHZ RADIATIONS FROM CELL PHONE RESULTING IN MICROSCOPIC CHANGES IN THE KIDNEY. IJCRR. 6(16): 44-49, 2014

Objective: The study was to evaluate possible effects of chronic exposure to 900 - 1900

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MHz radiations emitted from 2G cell phone on kidney of mice at the histological level. Methods: Mice were exposed to 2G ultra-high frequency radiation, 48 minutes per day for a period of 30 to 180 days. The amount of electromagnetic field (EMF) exposed was measured by radiation frequency meter. The sham control mice were subject to similar conditions without 2G exposure. Six animals each were sacrificed at the end of 30, 60, 90,120,150 and 180 days of exposure in the experimental group after 24 hours of last exposure. Same numbers of control animals were sacrificed on similar period. Both kidneys were harvested and processed for histomorphometric study. Kidneys size, weight and volume were measured and analysed. Kidney sections were analysed under the light microscope and structural changes were studied. Results: In 2G exposed group the kidney weight and volume was significantly reduced in the first month. Kidney weight alone was significantly increased in the fifth month. Glomerulus showed dilated capillaries and increased urinary space. Proximal convoluted tubule showed wider lumen with reduced cell size. Brush border interrupted at places and vacuolated cytoplasm and pyknotic nuclei. Wider lumen with decreased cell size and marked basal striations were found in the distal convoluted tubule. Conclusion: Chronic exposure to ultra-high frequency radiation from 2G cell phone could cause microscopic changes in glomerulus, proximal and distal convoluted tubules of the kidney.

Luo YP, Ma HR, Chen JW, Li JJ, Li CX. [Effect of American Ginseng Capsule on the liver oxidative injury and the Nrf2 protein expression in rats exposed by electromagnetic radiation of frequency of cell phone.] [Article in Chinese]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 34(5):575-580, 2014. (In Chinese)

OBJECTIVE: To observe the effect of American Ginseng Capsule (AGC) on the liver oxidative injury and the Nrf2 protein expression in the liver tissue of rats exposed by 900 MHz cell phone electromagnetic radiation. METHODS: Totally 40 male SD rats were randomly divided into the normal control group, the model group, the Shuifei Jibin Capsule (SJC) group, and the AGC group,10 in each group. Rats in the normal control group were not irradiated. Rats in the rest three groups were exposed by imitated 900 MHz cellular phone for 4 h in 12 consecutive days. Meanwhile, rats in the SJC group and the AGC group were intragastrically administrated with suspension of SJC and AGC (1 mL/200 g body weight) respectively. Normal saline was administered to rats in the normal control group and the model group. The histomorphological changes of the liver tissue were observed by HE staining. Contents of malonic dialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH), and glutathione peroxidase (GSH-PX) were detected by colorimetry. The Nrf2 protein expression of hepatocytes was detected by immunohistochemical assay and Western blot. RESULTS: Compared with the normal control group, hepatocyte nucleus was atrophied or partially disappeared, the contents of liver MDA and Nrf2 protein obviously increased ($P < 0.05$, $P < 0.01$); contents of liver SOD and GSH decreased ($P < 0.05$) in the model group. Compared with the model group, karyopyknosis was obviously attenuated and approached to the normal level in the SJC group and the AGC group. The contents of liver MDA and Nrf2 protein expression decreased ($P < 0.05$), and the contents of liver SOD, GSH, and GSH-PX

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obviously increased ($P < 0.05$) in the SJC group. The contents of liver MDA and the Nrf2 protein expression decreased ($P < 0.05$), and contents of SOD and GSH obviously increased in the AGC group ($P < 0.01$, $P < 0.05$). CONCLUSIONS: The electromagnetic radiation induced by 900 MHz cell phone could affect the expression of Nrf2 protein, induce oxidative injury, and induce abnormal morphology of liver cells. SJC and AGC could promote the morphological recovery of the liver cells. Its mechanism might be related to affecting the expression of Nrf2 protein and attenuating oxidative damage of liver cells.

Koca O, Gökçe AM, Oztürk MI, Ercan F, Yurdakul N, Karaman MI. Effects of intensive cell phone (philips genic 900) use on the rat kidney tissue. Urol J. 10(2):886-891. 2013.
 PURPOSE: To investigate effects of electromagnetic radiation (EMR) emitted by cell phones on the rat kidney tissue. MATERIALS AND METHODS: Twenty-one male Albino rats were divided into 3 groups, each comprising 7 rats. Group 1 was exposed to a cell phone in speech mode for 8 hours/day for 20 days and their kidneys were removed. Group 2 was exposed to EMR for 20 days and then their kidneys were removed after an interval of 20 days. Cell phone used in the present study was Philips Genie 900, which has the highest specific absorption rate on the market. RESULTS: Light microscopic examination of the kidney tissues obtained from the first group of rats revealed glomerular damage, dilatation of Bowman's capsule, formation of large spaces between the tubules, tubular damage, perivascular edema, and inflammatory cell infiltration. The mean severity score was 4.64 ± 1.7 in group 1, 4.50 ± 0.8 in group 2, and 0 in group 3. While there was no significant difference between group 1 and group 2 ($P > .05$), the mean severity scores of groups 1 and 2 were significantly higher than that of the control group ($P = .001$ for each). CONCLUSION: Considering the damage in rat kidney tissue caused by EMR-emitting cell phones, high-risk individuals should take protective measures.

Koca O, Gokce AM, Akyuz M, Ercan F, Yurdakul N, Karaman MI. A new problem in inflammatory bladder diseases: Use of mobile phones! Int Braz J Urol. 40(4):520-525, 2014.
 PURPOSE: Technological developments provide a lot of conveniences to our lives. This issue is one of the risks that arise along with these conveniences. In our study we tried to understand the impact of electromagnetic waves from mobile phones on bladder tissue. MATERIALS AND METHODS: Twenty-one adult male albino rats were divided into three equal groups. Group 1 was exposed to electromagnetic wave for 8 hours per day for 20 days and then their bladders were taken off immediately. Group 2 was firstly exposed to electromagnetic wave for 8 hours per day for 20 days then secondly another for 20 days without exposition to electromagnetic wave and then their bladders were taken off. Group 3 was the control group and they were not exposed to electromagnetic wave. RESULTS: Under microscopic examination of bladder tissue, in the first group severe inflammatory cell infiltration was seen in lamina propria and muscle layer in contrast to intact urothelium. In the second group mild inflammatory cell infiltration was seen in lamina propria and muscle layer. The mean scores for the three groups were 5.5 ± 2.5 , 0.8 ± 1.3 and 1.2 ± 1.5 respectively. Mean score of group 1 was

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statistically higher than others ($p = 0.001$). CONCLUSION: Intensive use of mobile phones has negative impact on bladder tissue as well as the other organs. Keeping a minimum level of mobile phone use makes it easy to be kept under control of diseases in which inflammation is an etiologic factor.

Mercury Release in Dental Amalgams

Mortazavi SM, Daiee E, Yazdi A, Khiabani K, Kavousi A, Vazirinejad R, Behnejad B, Ghasemi M, Mood MB. Mercury release from dental amalgam restorations after magnetic resonance imaging and following mobile phone use. Pak J Biol Sci. 11(8):1142-1146, 2008.

In the 1st phase of this study, thirty patients were investigated. Five milliliter stimulated saliva was collected just before and after MRI. The magnetic flux density was 0.23 T and the duration of exposure of patients to magnetic field was 30 minutes. In the 2nd phase, fourteen female healthy University students who had not used mobile phones before the study and did not have any previous amalgam restorations were investigated. Dental amalgam restoration was performed for all 14 students. Their urine samples were collected before amalgam restoration and at days 1, 2, 3 and 4 after restoration. The mean \pm SD saliva Hg concentrations of the patients before and after MRI were 8.6 \pm 3.0 and 11.3 \pm 5.3 microg L(-1), respectively ($p < 0.01$). A statistical significant ($p < 0.05$) higher concentration was observed in the students used mobile phone. The mean \pm SE urinary Hg concentrations of the students who used mobile phones were 2.43 \pm 0.25, 2.71 \pm 0.27, 3.79 \pm 0.25, 4.8 \pm 0.27 and 4.5 \pm 0.32 microg L(-1) before the amalgam restoration and at days 1, 2, 3 and 4, respectively. Whereas the respective Hg concentrations in the controls, were 2.07 \pm 0.22, 2.34 \pm 0.30, 2.51 \pm 0.25, 2.66 \pm 0.24 and 2.76 \pm 0.32 microg L(-1). It appears that MRI and microwave radiation emitted from mobile phones significantly release mercury from dental amalgam restoration. Further research is needed to clarify whether other common sources of electromagnetic field exposure may cause alterations in dental amalgam and accelerate the release of mercury.

Effects on Other Living Things

Panagopoulos DJ, Chavdoula ED, Karabarbounis A, Margaritis LH. Comparison of bioactivity between GSM 900 MHz and DCS 1800 MHz mobile telephony radiation. Electromagn Biol Med. 26(1):33-44, 2007.

An increasing number of studies find that pulsed Radio Frequency (RF), electromagnetic radiation of both systems of digital mobile telephony, established and commonly used in Europe during the last years, GSM 900 MHz (Global System for Mobile telecommunications) and DCS 1800 MHz (Digital Cellular System), exert intense biological action on different organisms and cells (Hardell et al., 2006; Hyland, 2000; Kundi, 2004; Panagopoulos et al., 2004, 2007). The two types of cellular telephony

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radiation use different carrier frequencies and give different frequency spectra, but they usually also differ in intensity, as GSM 900 MHz antennas operate at about double the power output than the corresponding DCS 1800 MHz ones. In our present experiments, we used a model biological system, the reproductive capacity of *Drosophila melanogaster*, to compare the biological activity between the two systems of cellular mobile telephony radiation. Both types of radiation were found to decrease significantly and non thermally the insect's reproductive capacity, but GSM 900 MHz seems to be even more bioactive than DCS 1800 MHz. The difference seems to be dependent mostly on field intensity and less on carrier frequency.

Zareen N, Khan MY, Minhas LA. Dose related shifts in the developmental progress of chick embryos exposed to mobile phone induced electromagnetic fields. *J Ayub Med Coll Abbottabad*.21(1):130-134, 2009.

BACKGROUND: The possible adverse effects of Electromagnetic Fields (EMFs) emitted from mobile phones present a major public concern today. Some studies indicate EMFs effects on genes, free radical production, immunological and carcinogenic effects. On the other hand there are studies which do not support the hypothesis of any biological impacts of EMFs. This study was designed to observe the effects of mobile phone induced EMFs on survival and general growth and development of chick embryo, investigating dose-response relationship if any. METHODS: This was an experimental study in which developing chick embryos were exposed to different doses of mobile phone induced EMFs. For this purpose a mobile phone was placed in the incubator in the centre of fertilised eggs in silent ringing mode and was 'rung' upon from any other line or cell phone. After incubation for 10 or 15 days the eggs were opened and the developmental mile-stones of the surviving embryos were compared with the non exposed subgroup. RESULTS: EMFs exposure significantly decreased the survivability of the chick embryos. The lower doses of EMFs caused growth retardation. However, this effect of growth retardation reallocated to partial growth enhancement on increasing the dose of EMFs and shifted over to definite growth enhancement on further raising the dose. CONCLUSION: There is an adverse effect of EMFs exposure on embryo survivability. Chick embryos developmental process is influenced by EMFs. However, these effects are variable depending upon the dose of EMFs exposure.

Zareen N, Khan MY, Minhas LA. Derangement of chick embryo retinal differentiation caused by radiofrequency electromagnetic fields. *Congenit Anom (Kyoto)*. 49(1):15-19, 2009.

The possible adverse effects of radiofrequency electromagnetic fields (EMF) emitted from mobile phones present a major public concern. Biological electrical activities of the human body are vulnerable to interference from oscillatory aspects of EMF, which affect fundamental cellular activities, in particular, the highly active development process of embryos. Some studies highlight the possible health hazards of EMF, while others contest the hypothesis of biological impact of EMF. The present study was designed to observe the histomorphological effects of EMF emitted by a mobile phone on the retinae of developing chicken embryos. Fertilized chicken eggs were exposed to a ringing mobile set on silent tone placed in the incubator at different ages of

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development. After exposure for the scheduled duration the retinae of the embryos were dissected out and processed for histological examination. The control and experimental embryos were statistically compared for retinal thickness and epithelial pigmentation grades. Contrasting effects of EMF on the retinal histomorphology were noticed, depending on the duration of exposure. The embryos exposed for 10 post-incubation days exhibited decreased retinal growth and mild pigmentation of the epithelium. Growth retardation reallocated to growth enhancement on increasing EMF exposure for 15 post-incubation days, with a shift of pigmentation grade from mild to intense. We conclude that EMF emitted by a mobile phone cause derangement of chicken embryo retinal differentiation.

Soran ML, Stan M, Niinemets U, Copolovici L. Influence of microwave frequency electromagnetic radiation on terpene emission and content in aromatic plants. *J Plant Physiol.* 171(15):1436-1443, 2014

Influence of environmental stress factors on both crop and wild plants of nutritional value is an important research topic. The past research has focused on rising temperatures, drought, soil salinity and toxicity, but the potential effects of increased environmental contamination by human-generated electromagnetic radiation on plants have little been studied. Here we studied the influence of microwave irradiation at bands corresponding to wireless router (WLAN) and mobile devices (GSM) on leaf anatomy, essential oil content and volatile emissions in *Petroselinum crispum*, *Apium graveolens* and *Anethum graveolens*. Microwave irradiation resulted in thinner cell walls, smaller chloroplasts and mitochondria, and enhanced emissions of volatile compounds, in particular, monoterpenes and green leaf volatiles (GLV). These effects were stronger for WLAN-frequency microwaves. Essential oil content was enhanced by GSM-frequency microwaves, but the effect of WLAN-frequency microwaves was inhibitory. There was a direct relationship between microwave-induced structural and chemical modifications of the three plant species studied. These data collectively demonstrate that human-generated microwave pollution can potentially constitute a stress to the plants.

Tkalec M, Malaric K, Pevalek-Kozlina B. Influence of 400, 900, and 1900 MHz electromagnetic fields on *Lemna minor* growth and peroxidase activity. *Bioelectromagnetics.* 26(3):185-193, 2005.

Increased use of radio and microwave frequencies requires investigations of their effects on living organisms. Duckweed (*Lemna minor* L.) has been commonly used as a model plant for environmental monitoring. In the present study, duckweed growth and peroxidase activity was evaluated after exposure in a Gigahertz Transversal Electromagnetic (GTEM) cell to electric fields of frequencies 400, 900, and 1900 MHz. The growth of plants exposed for 2 h to the 23 V/m electric field of 900 MHz significantly decreased in comparison with the control, while an electric field of the same strength but at 400 MHz did not have such effect. A modulated field at 900 MHz strongly inhibited the growth, while at 400 MHz modulation did not influence the growth significantly. At both frequencies a longer exposure mostly decreased the

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growth and the highest electric field (390 V/m) strongly inhibited the growth. Exposure of plants to lower field strength (10 V/m) for 14 h caused significant decrease at 400 and 1900 MHz while 900 MHz did not influence the growth. Peroxidase activity in exposed plants varied, depending on the exposure characteristics. Observed changes were mostly small, except in plants exposed for 2 h to 41 V/m at 900 MHz where a significant increase (41%) was found. Our results suggest that investigated electromagnetic fields (EMFs) might influence plant growth and, to some extent, peroxidase activity. However, the effects of EMFs strongly depended on the characteristics of the field exposure.

Singh HP, Sharma VP, Batish DR, Kohli RK. Cell phone electromagnetic field radiations affect rhizogenesis through impairment of biochemical processes. *Environ Monit Assess.* 184(4):1813-1821, 2012.

Indiscriminate adoption and use of cell phone technology has tremendously increased the levels of electromagnetic field radiations (EMFr) in the natural environment. It has raised the concerns among the scientists regarding the possible risks of EMFr to living organisms. However, not much has been done to assess the damage caused to plants that are continuously exposed to EMFr present in the environment. The present study investigated the biochemical mechanism of interference of 900 MHz cell phone EMFr with root formation in mung bean (*Vigna radiata* syn. *Phaseolus aureus*) hypocotyls, a model system to study rhizogenesis in plants. Cell phone EMFr enhanced the activities of proteases (by 1.52 to 2.33 times), polyphenol oxidases (by 1.5 to 4.3 times), and peroxidases (by 1.5 to 2.0 times) in mung bean hypocotyls over control. Further, EMFr enhanced malondialdehyde (an indicator of lipid peroxidation), hydrogen peroxide, and proline content, indicating a reactive oxygen species-mediated oxidative damage in hypocotyls. It was confirmed by the upregulation in the activities of antioxidant enzymes (superoxide dismutase, ascorbate peroxidase, guaiacol peroxidase, catalase, and glutathione reductase) suggesting their possible role in providing protection against EMFr-induced oxidative damage. The study concluded that cell phone radiations affect the process of rhizogenesis through biochemical alterations that manifest as oxidative damage resulting in root impairment.

Tkalec M, Malarić K, Pavlica M, Pevalek-Kozlina B, Vidaković-Cifrek Z. Effects of radiofrequency electromagnetic fields on seed germination and root meristematic cells of *Allium cepa* L. *Mutat Res.* 672(2):76-81, 2009.

The effects of exposure to radiofrequency electromagnetic fields (RF-EMFs) on seed germination, primary root growth as well as mitotic activity and mitotic aberrations in root meristematic cells were examined in *Allium cepa* L. cv. Srebrnjak Majski. Seeds were exposed for 2h to EMFs of 400 and 900MHz at field strengths of 10, 23, 41 and 120Vm(-1). The effect of longer exposure time (4h) and field modulation was investigated at 23Vm(-1) as well. Germination rate and root length did not change significantly after exposure to radiofrequency fields under any of the treatment conditions. At 900MHz, exposures to EMFs of higher field strengths (41 and 120Vm(-1)) or to modulated fields showed a significant increase of the mitotic index compared with corresponding controls, while the percentage of mitotic abnormalities increased after all

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exposure treatments. On the other hand, at 400MHz the mitotic index increased only after exposure to modulated EMF. At this frequency, compared with the control higher numbers of mitotic abnormalities were found after exposure to modulated EMF as well as after exposure to EMFs of higher strengths (41 and 120Vm(-1)). The types of aberration induced by the EMFs of both frequencies were quite similar, mainly consisting of lagging chromosomes, vagrants, disturbed anaphases and chromosome stickiness. Our results show that non-thermal exposure to the radiofrequency fields investigated here can induce mitotic aberrations in root meristematic cells of A. cepa. The observed effects were markedly dependent on the field frequencies applied as well as on field strength and modulation. Our findings also indicate that mitotic effects of RF-EMF could be due to impairment of the mitotic spindle.

Sharma VP, Singh HP, Batish DR, Kohli RK. Cell phone radiations affect early growth of Vigna radiata (mung bean) through biochemical alterations. *Z Naturforsch C.* 65(1-2):66-72, 2010.

The indiscriminate use of wireless technologies, particularly of cell phones, has increased the health risks among living organisms including plants. We investigated the impact of cell phone electromagnetic field (EMF) radiations (power density, 8.55 microW cm(-2)) on germination, early growth, proteins and carbohydrate contents, and activities of some enzymes in Vigna radiata. Cell phone EMF radiations significantly reduced the seedling length and dry weight of V radiata after exposure for 0.5, 1, 2, and 4 h. Furthermore, the contents of proteins and carbohydrates were reduced in EMF-exposed plants. However, the activities of proteases, alpha-amylases, beta-amylases, polyphenol oxidases, and peroxidases were enhanced in EMF-exposed radicles indicating their role in providing protection against EMF-induced stress. The study concludes that cell phone EMFs impair early growth of V radiata seedlings by inducing biochemical changes.

Sharma VP, Singh HP, Kohli RK, Batish DR. Mobile phone radiation inhibits Vigna radiata (mung bean) root growth by inducing oxidative stress. *Sci Total Environ.* 407(21):5543-7, 2009.

During the last couple of decades, there has been a tremendous increase in the use of cell phones. It has significantly added to the rapidly increasing EMF smog, an unprecedented type of pollution consisting of radiation in the environment, thereby prompting the scientists to study the effects on humans. However, not many studies have been conducted to explore the effects of cell **phone** EMFr on growth and biochemical changes in plants. We investigated whether EMFr from cell phones inhibit growth of Vigna radiata (mung bean) through induction of conventional stress responses. Effects of cell **phone** EMFr (power density: 8.55 microW cm(-2); 900 MHz band width; for 1/2, 1, 2, and 4 h) were determined by measuring the generation of reactive oxygen species (ROS) in terms of malondialdehyde and hydrogen peroxide (H₂O₂) content, root oxidizability and changes in levels of antioxidant enzymes. Our results showed that cell **phone** EMFr significantly inhibited the germination (at > or =2 h), and radicle and plumule growths (> or =1 h) in mung bean in a time-dependent

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manner. Further, cell **phone** EMFr enhanced MDA content (indicating lipid peroxidation), and increased H₂O₂ accumulation and root oxidizability in mung bean roots, thereby inducing oxidative stress and **cellular** damage. In response to EMFr, there was a significant upregulation in the activities of scavenging enzymes, such as superoxide dismutases, ascorbate peroxidases, guaiacol peroxidases, catalases and glutathione reductases, in mung bean roots. The study concluded that cell **phone** EMFr inhibit root growth of mung bean by inducing ROS-generated oxidative stress despite increased activities of antioxidant enzymes.

Roux D, Faure C, Bonnet P, Girard S, Ledoigt G, Davies E, Gendraud M, Paladian F, Vian A. A possible role for extra-cellular ATP in plant responses to high frequency, low amplitude electromagnetic field. to the reports of health hazards among mobile-phone users. *Plant Signal Behav.* 3(6):383-385, 2008.

In parallel to evoking the accumulation of stress-related transcripts, exposure to low level 900 MHz EMF affected the levels of ATP, the main energy molecule of the cell. Its concentration dropped rapidly (27% after 30 min) in response to EMF exposure, along with a 18% decrease in the adenylate energy charge (AEC), a good marker of cell energy status. One could interpret this decrease in ATP and AEC in a classical way, i.e., as the result of an increase in cellular energy usage, but recent work brings exciting new insights in pointing out a signalling function for ATP, especially in the stress physiology context where it could trigger both reactive oxygen species and calcium movement (this latter being involved in plant responses to EMF exposure). In this addendum, we discuss our results within this new perspective for ATP function

Roux D, Vian A, Girard S, Bonnet P, Paladian F, Davies E, Ledoigt G. High frequency (900 MHz) low amplitude (5 V m⁻¹) electromagnetic field: a genuine environmental stimulus that affects transcription, translation, calcium and energy charge in tomato. *Planta.* 227(4):883-891, 2008.

Using an especially-designed facility, the Mode Stirred Reverberation Chamber, we exposed tomato plants (*Lycopersicon esculentum* Mill. VFN8) to low level (900 MHz, 5 V m⁻¹) electromagnetic fields for a short period (10 min) and measured changes in abundance of three specific mRNA soon after exposure. Within minutes of electromagnetic stimulation, stress-related mRNA (calmodulin, calcium-dependent protein kinase and proteinase inhibitor) accumulated in a rapid, large and 3-phase manner typical of an environmental stress response. Accumulation of these transcripts into the polysomal RNA also took place (indicating that the encoded proteins were translated) but was delayed (indicating that newly-synthesized mRNA was not immediately recruited into polysomes). Transcript accumulation was maximal at normal Ca²⁺ levels and was depressed at higher Ca²⁺, especially for those encoding calcium-binding proteins. Removal of Ca²⁺ (by addition of chelating agents or Ca²⁺ channel blocker) led to total suppression of mRNA accumulation. Finally, 30 min after the electromagnetic treatment, ATP concentration and adenylate energy charge were transiently decreased, while transcript accumulation was totally prevented by application of the uncoupling reagent, CCCP. These responses occur very soon after

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exposure, strongly suggesting that they are the direct consequence of application of radio-frequency fields and their similarities to wound responses strongly suggests that this radiation is perceived by plants as an injurious stimulus.

Tsybulin O, Sidorik E, Brieieva O , Buchynska L, Kyrylenko S, Henshel D, IYakymenko I. GSM 900 MHz cellular phone radiation can either stimulate or depress early embryogenesis in Japanese quails depending on the duration of exposure. Int J Rad Biol. Posted online on April 11, 2013. (doi:10.3109/09553002.2013.791408)

Purpose: Our study was designed to assess the effects of low intensity radiation of a GSM (Global System for Mobile communication) 900 MHz cellular phone on early embryogenesis in dependence on the duration of exposure. *Materials and methods:* Embryos of Japanese Quails were exposed *in ovo* to GSM 900 MHz cellular phone radiation during initial 38 h of brooding or alternatively during 158 h (120 h before brooding plus initial 38 h of brooding) discontinuously with 48 sec ON (average power density $0.25 \mu\text{W}/\text{cm}^2$, specific absorption rate $3 \mu\text{W}/\text{kg}$) followed by 12 sec OFF intervals. A number of differentiated somites was assessed microscopically. Possible DNA damage evoked by irradiation was assessed by an alkaline comet assay. *Results:* Exposure to radiation from a GSM 900 MHz cellular phone led to a significantly altered number of differentiated somites. In embryos irradiated during 38 h the number of differentiated somites increased ($p < 0.001$), while in embryos irradiated during 158 h this number decreased ($p < 0.05$). The lower duration of exposure led to a significant ($p < 0.001$) decrease in a level of DNA strand breaks in cells of 38-hour embryos, while the higher duration of exposure resulted in a significant ($p < 0.001$) increase in DNA damage as compared to the control. *Conclusion:* Effects of GSM 900 MHz cellular phone radiation on early embryogenesis can be either stimulating or deleterious depending on the duration of exposure.

Tsybulin O, Sidorik E, Kyrylenko S, Henshel D, Yakymenko I. GSM 900 MHz microwave radiation affects embryo development of Japanese quails. *Electromagn Biol Med.* 31(1):75-86, 2012.

A wide range of non thermal biological effects of microwave radiation (MW) was revealed during the last decades. A number of reports showed evident hazardous effects of MW on embryo development in chicken. In this study, we aimed at elucidating the effects of MW emitted by a commercial model of GSM 900 MHz cell phone on embryo development in quails (*Coturnix coturnix japonica*) during both short and prolonged exposure. For that, fresh fertilized eggs were irradiated during the first 38 h or 14 days of incubation by a cell phone in "connecting" mode activated continuously through a computer system. Maximum intensity of incident radiation on the egg's surface was $0.2 \mu\text{W}/\text{cm}^2$. The irradiation led to a significant ($p < 0.001$) increase in numbers of differentiated somites in 38-hour exposed embryos and to a significant ($p < 0.05$) increase in total survival of embryos from exposed eggs after 14 days exposure. We hypothesized that observed facilitating effect was due to enhancement of metabolism in exposed embryos provoked via peroxidation mechanisms. Indeed, a level of thiobarbituric acid (TBA) reactive substances was significantly ($p < 0.05-0.001$) higher

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in brains and livers of hatchlings from exposed embryos. Thus, observed effects of radiation from commercial GSM 900 MHz cell phone on developing quail embryos signify a possibility for non-thermal impact of MW on embryogenesis. We suggest that the facilitating effect of low doses of irradiation on embryo development can be explained by a hormesis effect induced by reactive oxygen species (ROS). Future studies need to be done to clarify this assumption.

Tafforeau M, Verdus M-C, Norris V, White G, Demarty M, Thellier M, Ripoll C. SIMS study of the calcium-deprivation step related to epidermal meristem production induced in flax by cold shock or radiation from a GSM telephone. J Trace Microprobe Tech 20(4):611-623, 2002.

Exposing seedlings of the flax, *Linum usitatissimum* L., to a variety of weak environmental stresses plus a 2-day calcium deprivation triggers the common response of production of epidermal meristems in the hypocotyls. Here, we show that the same response was induced by a 1 min cold shock. Epidermal meristem production was also induced by a single 2-h exposure to radiation emitted at 0.9 GHz at non-thermal levels by a GSM telephone. This flax-based system is therefore well suited to studying the effects of low intensity stimuli, including those of electromagnetic radiation. To begin to determine the underlying mechanisms, in which calcium is implicated, it is desirable to analyse the changes in ions in the tissues affected. We therefore performed a Secondary Ion Mass Spectrometry (SIMS) study of the distribution of the main inorganic cations in the hypocotyl of control and calcium-deprived seedlings. This showed decreases in calcium, sodium and potassium and an increase in magnesium that did not alter substantially the overall ratio of divalent to monovalent cations.

Bastide M, Youbibier-Simoa BJ, Lebecq JC, Giaimis J. Toxicologic study of electromagnetic radiation emitted by television and video display screens and cellular telephones on chickens and mice. Indoor Built Environ 10:291-298, 2001.

The effects of continuous exposure of chick embryos and young chickens to the electromagnetic fields (EMFs) emitted by video display units (VDUs) and GSM cell phone radiation, either the whole spectrum emitted or attenuated by a copper gauze, were investigated. Permanent exposure to the EMFs radiated by a VDU was associated with significantly increased fetal loss (47-68%) and markedly depressed levels of circulating specific antibodies (IgG), corticosterone and melatonin. We have also shown that under chronic exposure conditions, GSM cell phone radiation was harmful to chick embryos, stressful for healthy mice and, in this species, synergistic with cancer insofar as it depleted stress hormones. The same pathological results were observed after substantial reduction of the microwaves radiated from the cell phone by attenuating them with a copper gauze.

Vian A, Roux D, Girard S, Bonnet P, Paladian F, Davies E, Ledoigt G. Microwave irradiation affects gene expression in plants. *Plant Signal Behav.* 1(2):67-70, 2006.

The physiological impact of nonionizing radiation has long been considered negligible. However, here we use a carefully calibrated stimulation system that mimics the

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characteristics (isotropy and homogeneity) of electromagnetic fields present in the environment to measure changes in a molecular marker (mRNA encoding the stress-related bZIP transcription factor), and show that low amplitude, short duration, 900 MHz EMF evokes the accumulation of this mRNA. Accumulation is rapid (peaking 5-15 min after stimulation) and strong (3.5-fold), and is similar to that evoked by mechanical stimulations.

Panagopoulos DJ, Chavdoula ED, Nezis IP, Margaritis LH Cell death induced by GSM 900-MHz and DCS 1800-MHz mobile telephony radiation. Mutat Res.626(1-2):69-78, 2007.

In the present study, the TUNEL (Terminal deoxynucleotide transferase dUTP Nick End Labeling) assay - a well known technique widely used for detecting fragmented DNA in various types of cells - was used to detect cell death (DNA fragmentation) in a biological model, the early and mid stages of oogenesis of the insect *Drosophila melanogaster*. The flies were exposed in vivo to either GSM 900-MHz (Global System for Mobile telecommunications) or DCS 1800-MHz (Digital Cellular System) radiation from a common digital mobile phone, for few minutes per day during the first 6 days of their adult life. The exposure conditions were similar to those to which a mobile phone user is exposed, and were determined according to previous studies of ours [D.J.

Panagopoulos, A. Karabarbounis, L.H. Margaritis, Effect of GSM 900-MHz mobile phone radiation on the reproductive capacity of *D. melanogaster*, *Electromagn. Biol. Med.* 23 (1) (2004) 29-43; D.J. Panagopoulos, N. Messini, A. Karabarbounis, A.L. Philippetis, L.H. Margaritis, Radio frequency electromagnetic radiation within "safety levels" alters the physiological function of insects, in: P. Kostarakis, P. Stavroulakis (Eds.), *Proceedings of the Millennium International Workshop on Biological Effects of Electromagnetic Fields*, Heraklion, Crete, Greece, October 17-20, 2000, pp. 169-175, ISBN: 960-86733-0-5; D.J. Panagopoulos, L.H. Margaritis, Effects of electromagnetic fields on the reproductive capacity of *D. melanogaster*, in: P. Stavroulakis (Ed.), *Biological Effects of Electromagnetic Fields*, Springer, 2003, pp. 545-578], which had shown a large decrease in the oviposition of the same insect caused by GSM radiation. Our present results suggest that the decrease in oviposition previously reported, is due to degeneration of large numbers of egg chambers after DNA fragmentation of their constituent cells, induced by both types of mobile telephony radiation. Induced cell death is recorded for the first time, in all types of cells constituting an egg chamber (follicle cells, nurse cells and the oocyte) and in all stages of the early and mid-oogenesis, from germarium to stage 10, during which programmed cell death does not physiologically occur. Germarium and stages 7-8 were found to be the most sensitive developmental stages also in response to electromagnetic stress induced by the GSM and DCS fields and, moreover, germarium was found to be even more sensitive than stages 7-8.

Panagopoulos DJ, Karabarbounis A, Margaritis LH. Effect of gsm 900-mhz mobile phone radiation on the reproductive capacity of drosophila melanogaster. Electromag Biol Med 23:29-43, 2004.

Pulsed radio frequency, (RF), electromagnetic radiation from common GSM mobile

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phones, (Global System for Mobile Telecommunications) with a carrier frequency at 900 MHz, “modulated” by human voice, (speaking emission) decreases the reproductive capacity of the insect *Drosophila melanogaster* by 50%–60%, whereas the corresponding “nonmodulated” field (nonspeaking emission) decreases the reproductive capacity by 15%–20%. The insects were exposed to the near field of the mobile phone antenna for 6 min per day during the first 2–5 days of their adult lives. The GSM field is found to affect both females and males. Our results suggest that this field-radiation decreases the rate of cellular processes during gonad development in insects.

Nittby H, Moghadam MK, Sun W, Malmgren L, Eberhardt J, Persson BR, Salford LG. Analgetic effects of non-thermal GSM-1900 radiofrequency electromagnetic fields in the land snail *Helix pomatia*. *Int J Radiat Biol.* ;88(3):245-252, 2012

Abstract. Abstract Purpose: To investigate whether mobile phone radiation might affect snail nociception, employing radiofrequency (RF) electromagnetic fields (EMF) which, to our knowledge, have hitherto not been studied in a snail model. Exposure to extremely low frequency (ELF) magnetic fields has however been shown to significantly affect nociceptive responses. Materials and methods: In the present study, we exposed 29 land snails of the strain *Helix pomatia* to global system for mobile communications (GSM) EMF at 1900 MHz at the non-thermal level 48 mW/kg for 1 hour each and 29 snails were sham controls. The experiments took place during the onset of summer, with all snails being well out of hibernation. Before and after GSM or sham exposure, the snails were subjected to thermal pain by being placed on a hot plate. The reaction time for retraction from the hot plate was measured by two blinded observers. Results: Comparing the reaction pattern of each snail before and after exposure, the GSM exposed snails were less sensitive to thermal pain as compared to the sham controls, indicating that RF exposure induces a significant analgesia (Mann-Whitney $p < 0.001$). Conclusion: This study might support earlier findings, describing beneficial effects of EMF exposure upon nociception.

Markkanen A, Penttinen P, Naarala J, Pelkonen J, Sihvonen A-P, Juutilainen J. Apoptosis induced by ultraviolet radiation is enhanced by amplitude modulated radiofrequency radiation in mutant yeast cells *Bioelectromagnetics* 25:127-133, 2004.

The aim of this study was to investigate whether radiofrequency (RF) electromagnetic field (EMF) exposure affects cell death processes of yeast cells. *Saccharomyces cerevisiae* yeast cells of the strains KFY417 (wild-type) and KFY437 (*cdc48*-mutant) were exposed to 900 or 872 MHz RF fields, with or without exposure to ultraviolet (UV) radiation, and incubated simultaneously with elevated temperature (+37°C) to induce apoptosis in the *cdc48*-mutated strain. The RF exposure was carried out in a special waveguide exposure chamber where the temperature of the cell cultures can be precisely controlled. Apoptosis was analyzed using the annexin V-FITC method utilizing flow cytometry. Amplitude modulated (217 pulses per second) RF exposure significantly enhanced UV induced apoptosis in *cdc48*-mutated cells, but no effect was observed in cells exposed to unmodulated fields at identical time-average specific absorption rates

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(SAR, 0.4 or 3.0 W/kg). The findings suggest that amplitude modulated RF fields, together with known damaging agents, can affect the cell death process in mutated yeast cells.

Kumar NR, Sangwan S, Badotra P. Exposure to cell phone radiations produces biochemical changes in worker honey bees. Toxicol Int. 18(1):70-72, 2011.

The present study was carried out to find the effect of cell phone radiations on various biomolecules in the adult workers of *Apis mellifera* L. The results of the treated adults were analyzed and compared with the control. Radiation from the cell phone influences honey bees' behavior and physiology. There was reduced motor activity of the worker bees on the comb initially, followed by en masse migration and movement toward "talk mode" cell phone. The initial quiet period was characterized by rise in concentration of biomolecules including proteins, carbohydrates and lipids, perhaps due to stimulation of body mechanism to fight the stressful condition created by the radiations. At later stages of exposure, there was a slight decline in the concentration of biomolecules probably because the body had adapted to the stimulus

Geronikolou S, Zimeras S, Davos CH, Michalopoulos I, Tsitomeneas S. Diverse Radiofrequency Sensitivity and Radiofrequency Effects of Mobile or Cordless Phone near Fields Exposure in *Drosophila melanogaster*. PLoS One. 2014 Nov 17;9(11):e112139. doi: 10.1371/journal.pone.0112139. eCollection 2014.

INTRODUCTION: The impact of electromagnetic fields on health is of increasing scientific interest. The aim of this study was to examine how the *Drosophila melanogaster* animal model is affected when exposed to portable or mobile phone fields. **METHODS/RESULTS:** Two experiments have been designed and performed in the same laboratory conditions. Insect cultures were exposed to the near field of a 2G mobile phone (the GSM 2G networks support and complement in parallel the 3G wide band or in other words the transmission of information via voice signals is served by the 2G technology in both mobile phones generations) and a 1880 MHz cordless phone both digitally modulated by human voice. Comparison with advanced statistics of the egg laying of the second generation exposed and non-exposed cultures showed limited statistical significance for the cordless phone exposed culture and statistical significance for the 900 MHz exposed insects. We calculated by physics, simulated and illustrated in three dimensional figures the calculated near fields of radiation inside the experimenting vials and their difference. Comparison of the power of the two fields showed that the difference between them becomes null when the experimental cylinder radius and the height of the antenna increase. **CONCLUSIONS/SIGNIFICANCE:** Our results suggest a possible radiofrequency sensitivity difference in insects which may be due to the distance from the antenna or to unexplored intimate factors. Comparing the near fields of the two frequencies bands, we see similar not identical geometry in length and height from the antenna and that lower frequencies tend to drive to increased radiofrequency effects.

Grigor'ev IuG. [Biological effects of mobile phone electromagnetic field on chick

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embryo (risk assessment using the mortality rate)] Radiats Biol Radioecol. 43(5):541-543, 2003. [Article in Russian]

Chicken embryos were exposed to EMF from GSM mobile phone during the embryonic development (21 days). As a result the embryo mortality rate in the incubation period increased to 75% (versus 16% in control group).

Favre D. Mobile phone-induced honeybee worker piping Apidologie 42:270–279, 2011.

The worldwide maintenance of the honeybee has major ecological, economic, and political implications. In the present study, electromagnetic waves originating from mobile phones were tested for potential effects on honeybee behavior. Mobile phone handsets were placed in the close vicinity of honeybees. The sound made by the bees was recorded and analyzed. The audiograms and spectrograms revealed that active mobile phone handsets have a dramatic impact on the behavior of the bees, namely by inducing the worker piping signal. In natural conditions, worker piping either announces the swarming process of the bee colony or is a signal of a disturbed bee colony.

Chen G, Lu D, Chiang H, Leszczynski D, Xu Z. Using model organism *Saccharomyces cerevisiae* to evaluate the effects of ELF-MF and RF-EMF exposure on global gene expression. Bioelectromagnetics. 33(7):550-560, 2012.

The potential health hazard of exposure to electromagnetic fields (EMF) continues to cause public concern. However, the possibility of biological and health effects of exposure to EMF remains controversial and their biophysical mechanisms are unknown. In the present study, we used *Saccharomyces cerevisiae* to identify genes responding to extremely low frequency magnetic fields (ELF-MF) and to radiofrequency EMF (RF-EMF) exposures. The yeast cells were exposed for 6 h to either 0.4 mT 50 Hz ELF-MF or 1800 MHz RF-EMF at a specific absorption rate of 4.7 W/kg. Gene expression was analyzed by microarray screening and confirmed using real-time reverse transcription-polymerase chain reaction (RT-PCR). We were unable to confirm microarray-detected changes in three of the ELF-MF responsive candidate genes using RT-PCR ($P > 0.05$). On the other hand, out of the 40 potential RF-EMF responsive genes, only the expressions of structural maintenance of chromosomes 3 (SMC3) and aquaporin 2 (AQY2 (m)) were confirmed, while three other genes, that is, halotolerance protein 9 (HAL9), yet another kinase 1 (YAK1) and one function-unknown gene (open reading frame: YJL171C), showed opposite changes in expression compared to the microarray data ($P < 0.05$). In conclusion, the results of this study suggest that the yeast cells did not alter gene expression in response to 50 Hz ELF-MF and that the response to RF-EMF is limited to only a very small number of genes. The possible biological consequences of the gene expression changes induced by RF-EMF await further investigation.

Aksoy U, Sahin S, Ozkoc S, Ergor G. The effect of electromagnetic waves on the growth of *Entamoeba histolytica* and *Entamoeba dispar*. Saudi Med J. 26(9):1388-1390, 2005.

OBJECTIVE: The aim of this study was to investigate the influence of electromagnetic radiation of a digital Global System for Mobile Communication mobile telephone (900

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MHz) on *Entamoeba histolytica* (*E. histolytica*) and *Entamoeba dispar* (*E. dispar*) (cysts or trophozoites, or both) in a 24-hour period. **METHODS:** This study was carried out from April 2004 to May 2004 at the Department of Parasitology, Medical Faculty of Dokuz Eylul University in Izmir, Turkey. The cultivated isolate tubes, which were exposed to electromagnetic field at 37OC, were evaluated as study group, whereas the tubes without exposure were assessed as control group. Finally, only living parasites in all tubes were counted using a hemacytometer. The effect of the temperature was evaluated for both control and study groups. **RESULTS:** The influence of electromagnetic field and temperature was assessed separately for the study group. The parasite number of *E. histolytica* decreased after exposure at 37OC and room temperature ($p=0.009$) compared to the decrease in the control group ($p=0.009$). The parasite number of *E. dispar* also decreased after exposure at 37OC and room temperature ($p=0.009$). In comparison to control tubes, this was a significant decrease ($p=0.008$). In the case of exposure of *E. histolytica* the results did not reveal any significant difference between temperature degrees to magnetic field ($p=0.459$) and *E. dispar* ($p=0.172$). **CONCLUSION:** Our findings show that exposure to electromagnetic field for a certain period of time may cause damage that can lead to death in single-cell organisms.

Cammaerts MC, Debeir O, Cammaerts R. Changes in *Paramecium caudatum* (protozoa) near a switched-on GSM telephone. *Electromagn Biol Med.* 30(1):57-66, 2011.

The protozoan *Paramecium caudatum* was examined under normal conditions versus aside a switched-on GSM telephone (900 MHz; 2 Watts). Exposed individuals moved more slowly and more sinuously than usual. Their physiology was affected: they became broader, their cytopharynx appeared broader, their pulse vesicles had difficult in expelling their content outside the cell, their cilia less efficiently moved, and trichocysts became more visible. All these effects might result from some bad functioning or damage of the cellular membrane. The first target of communication electromagnetic waves might thus be the cellular membrane.

Cammaerts MC, Rachidi Z, Bellens F, De Doncker P. Food collection and response to pheromones in an ant species exposed to electromagnetic radiation. *Electromagn Biol Med.* 2013 Jan 15. [Epub ahead of print]

We used the ant species *Myrmica sabuleti* as a model to study the impact of electromagnetic waves on social insects' response to their pheromones and their food collection. We quantified *M. sabuleti* workers' response to their trail, area marking and alarm pheromone under normal conditions. Then, we quantified the same responses while under the influence of electromagnetic waves. Under such an influence, ants followed trails for only short distances, no longer arrived at marked areas and no longer orientated themselves to a source of alarm pheromone. Also when exposed to electromagnetic waves, ants became unable to return to their nest and recruit congeners; therefore, the number of ants collecting food increases only slightly and slowly. After 180 h of exposure, their colonies deteriorated. Electromagnetic radiation obviously affects social insects' behavior and physiology.

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Cammaerts M-C, Vandenbosch GAE, Volski V. Effect of short-term GSM radiation at representative levels in society on a biological model: the ant *Myrmica sabuleti*. J Insect Beh. 27(4):514-526. 2014.

Well-controlled electromagnetic exposure conditions were set up at a representative societal GSM radiation intensity level, 1.5 V/m, which is the legally allowed level in Brussels. Two nests of the ant species *Myrmica sabuleti* were repeatedly irradiated during 10 min. before their behavior was observed, based on the analysis of the ant trajectories. Under these exposure conditions, behavioral effects were detected. The ants' locomotion slightly changed. The ants' orientation towards their attractive alarm pheromone statistically became of lower quality. The ants still presented their trail following behavior but less efficiently. In this controversial issue, ants could be considered as possible bioindicators.

Miscellaneous Effects

Yariktas M, Doner F, Ozguner F, Gokalp O, Dogru H, Delibas N. Nitric oxide level in the nasal and sinus mucosa after exposure to electromagnetic field. Otolaryngol Head Neck Surg. 132(5):713-716, 2005.

OBJECTIVE: The purpose of this study was to examine the changes in nitric oxide (NO) level in the nasal and paranasal sinus mucosa after exposure radiofrequency electromagnetic fields (EMF). **STUDY DESIGN AND SETTING:** Thirty male Sprague-Dawley rats were randomly grouped as follows: EMF group (group I; n, 10), EMF group in which melatonin received (group II; n, 10) and the control (sham operated) group (group III; n, 10). Groups I and II were exposed to a 900 MHz. Oral melatonin was given in group II. Control rats (group III) were also placed in the tube as the exposure groups, but without exposure to EMF. At the end of 2 weeks, the rats were sacrificed, and the nasal and paranasal sinus mucosa dissected. NO was measured in nasal and paranasal mucosa. **RESULTS:** The nasal and paranasal sinus mucosa NO levels of group I were significantly higher than those of the control group (group III) ($P < 0.05$). However, there was no statistically significant difference between group II and the control group (group III) regarding NO output ($P > 0.05$). **CONCLUSION:** Exposure to EMF released by mobile phones (900 MHz) increase NO levels in the sinus and nasal mucosa. **SIGNIFICANCE:** Increased NO levels may act as a defense mechanism and presumably related to tissue damage. In addition, melatonin may have beneficial effect to prevent these changes in the mucosa.

Taberski K, Kloze M, Grote K, El Ouardi A, Streckert J, Hansen VW, Lerchl A. Noninvasive Assessment of Metabolic Effects of Exposure to 900 MHz Electromagnetic Fields on Djungarian Hamsters (*Phodopus sungorus*). Radiat Res. 181(6):617-622, 2014.

Sixteen male Djungarian hamsters, serving as their own controls, were individually exposed to RF-EMF (900 MHz, GSM modulation) at 0 (sham), 0.08, 0.4 or 4 W/kg specific absorption rate (SAR) in specially constructed rectangular waveguides. Exposure

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duration was one week per condition, followed by one week without exposure. Once per day, the temperatures of the hamsters' back fur (a surrogate for skin temperature) and the cornea of the eye (a surrogate for body temperature), were measured by infrared thermography. Oxygen, carbon dioxide and humidity were measured continuously in the ambient and exhaled air. Food and water consumption, as well as body weight were recorded once per week. Only at the highest SAR level were the following effects observed: fur temperatures were elevated by approximately 0.5°C (P < 0.001), while the temperatures of the eyes' surface were not affected; food consumption was lowered (P < 0.05), while water consumption and body weight were not affected; the production of carbon dioxide was lowered during the day (P < 0.01) and unaffected during the night, while oxygen consumption levels remained unaffected and finally the respiratory quotient (carbon dioxide production divided by oxygen consumption) was lower during the day (P < 0.05) and also somewhat lower during the night (not significant). The results demonstrate the usefulness of our methods for experiments dealing with metabolic effects of RF-EMF exposure in rodents. They also confirm the assumption that even though the metabolism is reduced at high SAR levels, the body core temperature is being kept constant by the energy uptake from the RF-EMF exposure which is able to physiologically compensate for the reduced metabolism.

Urbinello D, Rösli M. Impact of one's own mobile phone in stand-by mode on personal radiofrequency electromagnetic field exposure. J Expo Sci Environ Epidemiol. 23:545-548, 2013.

When moving around, mobile phones in stand-by mode periodically send data about their positions. The aim of this paper is to evaluate how personal radiofrequency electromagnetic field (RF-EMF) measurements are affected by such location updates. Exposure from a mobile phone handset (uplink) was measured during commuting by using a randomized cross-over study with three different scenarios: disabled mobile phone (reference), an activated dual-band phone and a quad-band phone. In the reference scenario, uplink exposure was highest during train rides (1.19 mW/m²) and lowest during car rides in rural areas (0.001 mW/m²). In public transports, the impact of one's own mobile phone on personal RF-EMF measurements was not observable because of high background uplink radiation from other people's mobile phone. In a car, uplink exposure with an activated phone was orders of magnitude higher compared with the reference scenario. This study demonstrates that personal RF-EMF exposure is affected by one's own mobile phone in stand-by mode because of its regular location update. Further dosimetric studies should quantify the contribution of location updates to the total RF-EMF exposure in order to clarify whether the duration of mobile phone use, the most common exposure surrogate in the epidemiological RF-EMF research, is actually an adequate exposure proxy.

Weisbrot D, Lin H, Ye L, Blank M, Goodman R. Effects of mobile phone radiation on reproduction and development in *Drosophila melanogaster*. J Cell Biochem 89(1):48-55, 2003.

In this report we examined the effects of a discontinuous radio frequency (RF) signal

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produced by a GSM multiband mobile phone (900/1,900 MHz; SAR approximately 1.4 W/kg) on *Drosophila melanogaster*, during the 10-day developmental period from egg laying through pupation. As found earlier with low frequency exposures, the non-thermal radiation from the GSM mobile phone increased numbers of offspring, elevated hsp70 levels, increased serum response element (SRE) DNA-binding and induced the phosphorylation of the nuclear transcription factor, ELK-1. The rapid induction of hsp70 within minutes, by a non-thermal stress, together with identified components of signal transduction pathways, provide sensitive and reliable biomarkers that could serve as the basis for realistic mobile phone safety guidelines.

Paredi P, Kharitonov SA, Hanazawa T, Barnes PJ, Local vasodilator response to mobile phones. *Laryngoscope* 111(1):159-162, 2001.

OBJECTIVES: The use of mobile phones with the resulting generation of potentially harmful electromagnetic fields (EMF) is the focus of public interest. Heat generation and the activation of the inducible form of nitric oxide (NO) synthase may be possible causes of the biological effects of EMF exposure. We investigated if a mobile telephone conversation can modify skin temperature, NO, and nasal resistance. METHODS: We studied the effect of an EMF (900 MHz) generated by a commercially available cellular phone during a 30-minute telephone conversation on skin temperature, nasal NO measured by chemiluminescence, and nasal minimal cross-sectional area (MCA) measured by rhinometry. Eleven normal subjects (mean age +/- standard error of mean [SEM], 32 +/- 5 y; 10 male) were studied. RESULTS: There was a similar and significant increase in skin temperature of the nostril and occipital area on the same side as the telephone (maximal increase 2.3 +/- 0.2 degrees C at 6 min) as well as a tendency for higher nasal NO levels (maximal increase 12.9 +/- 4.9% at 10 min), whereas the MCA was significantly reduced (maximal decrease -27 +/- 6% at 15 min). Such changes were not recorded when an earpiece was used to avoid the direct exposure to the electromagnetic field. There were no changes in the skin temperature and nasal NO measured on the opposite side to the mobile phone, whereas the MCA was significantly increased (38 +/- 10%). CONCLUSIONS: Exposure to EMF produced by a mobile phone produces biological effects that can be easily measured. Microwaves may increase skin temperature and therefore cause vasodilation and reduce MCA. Further studies are needed to study the long-term effects of mobile phone use and the relation among NO production, vasodilation, and temperature.

Panagopoulos, D. J., Johansson O. & Carlo G.L. Polarization: A Key Difference between Man-made and Natural Electromagnetic Fields, in regard to Biological Activity. *Sci. Rep.* 5, 14914; doi: 10.1038/srep14914 (2015). Published online Oct 12, 2015.

In the present study we analyze the role of polarization in the biological activity of Electromagnetic Fields (EMFs)/Electromagnetic Radiation (EMR). All types of man-made EMFs/EMR - in contrast to natural EMFs/EMR - are polarized. Polarized EMFs/EMR can have increased biological activity, due to: 1) Ability to produce constructive interference effects and amplify their intensities at many locations. 2) Ability to force all charged/polar molecules and especially free ions within and around all living cells to

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oscillate on parallel planes and in phase with the applied polarized field. Such ionic forced-oscillations exert additive electrostatic forces on the sensors of cell membrane electro-sensitive ion channels, resulting in their irregular gating and consequent disruption of the cell's electrochemical balance. These features render man-made EMFs/EMR more bioactive than natural non-ionizing EMFs/EMR. This explains the increasing number of biological effects discovered during the past few decades to be induced by man-made EMFs, in contrast to natural EMFs in the terrestrial environment which have always been present throughout evolution, although human exposure to the latter ones is normally of significantly higher intensities/energy and longer durations. Thus, polarization seems to be a trigger that significantly increases the probability for the initiation of biological/health effects.

Lepp A, Barkley JE, Sanders GJ, Rebold M, Gates P. The relationship between cell phone use, physical and sedentary activity, and cardiorespiratory fitness in a sample of U.S. college students. *Int J Behav Nutr Phys Act.* 2013 Jun 21;10:79. doi: 10.1186/1479-5868-10-79.

BACKGROUND: Today's cell phones increase opportunities for activities traditionally defined as sedentary behaviors (e.g., surfing the internet, playing video games). People who participate in large amounts of sedentary behaviors, relative to those who do not, tend to be less physically active, less physically fit, and at greater risk for health problems. However, cell phone use does not have to be a sedentary behavior as these devices are portable. It can occur while standing or during mild-to-moderate intensity physical activity. Thus, the relationship between cell phone use, physical and sedentary activity, and physical fitness is unclear. The purpose of this study was to investigate these relationships among a sample of healthy college students. METHODS: Participants were first interviewed about their physical activity behavior and cell phone use. Then body composition was assessed and the validated self-efficacy survey for exercise behaviors completed. This was followed by a progressive exercise test on a treadmill to exhaustion. Peak oxygen consumption (VO₂ peak) during exercise was used to measure cardiorespiratory fitness. Hierarchical regression was used to assess the relationship between cell phone use and cardiorespiratory fitness after controlling for sex, self-efficacy, and percent body fat. Interview data was transcribed, coded, and Chi-square analysis was used to compare the responses of low and high frequency cell phone users. RESULTS: Cell phone use was significantly ($p = 0.047$) and negatively ($\beta = -0.25$) related to cardio respiratory fitness independent of sex, self-efficacy, and percent fat which were also significant predictors ($p < 0.05$). Interview data offered several possible explanations for this relationship. First, high frequency users were more likely than low frequency users to report forgoing opportunities for physical activity in order to use their cell phones for sedentary behaviors. Second, low frequency users were more likely to report being connected to active peer groups through their cell phones and to cite this as a motivation for physical activity. Third, high levels of cell phone use indicated a broader pattern of sedentary behaviors apart from cell phone use, such as watching television. CONCLUSION: Cell phone use, like traditional sedentary behaviors, may disrupt physical activity and reduce cardiorespiratory fitness.

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Lee KS, Choi JS, Hong SY, Son TH, Yu K. Mobile phone electromagnetic radiation activates MAPK signaling and regulates viability in Drosophila. *Bioelectromagnetics*.29(5):371-379, 2008.

Mobile phones are widely used in the modern world. However, biological effects of electromagnetic radiation produced by mobile phones are largely unknown. In this report, we show biological effects of the mobile phone 835 MHz electromagnetic field (EMF) in the Drosophila model system. When flies were exposed to the specific absorption rate (SAR) 1.6 W/kg, which is the proposed exposure limit by the American National Standards Institute (ANSI), more than 90% of the flies were viable even after the 30 h exposure. However, in the SAR 4.0 W/kg strong EMF exposure, viability dropped from the 12 h exposure. These EMF exposures triggered stress response and increased the production of reactive oxygen species. The EMF exposures also activated extracellular signal regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling, but not p38 kinase signaling. Interestingly, SAR 1.6 W/kg activated mainly ERK signaling and expression of an anti-apoptotic gene, whereas SAR 4.0 W/kg strongly activated JNK signaling and expression of apoptotic genes. In addition, SAR 4.0 W/kg amplified the number of apoptotic cells in the fly brain. These findings demonstrate that the exposure limit on electromagnetic radiation proposed by ANSI triggered ERK-survival signaling but the strong electromagnetic radiation activated JNK-apoptotic signaling in Drosophila.

Aly AA, Cheema MI, Tambawala M, Laterza R, Zhou E, Rathnabharathi K, Barnes FS. Effects of 900-MHz Radio Frequencies on the Chemotaxis of Human Neutrophils in Vitro. *IEEE Transactions on Biomedical Engineering*, 55(2): 795-797, 2008.

Summary: The effects of radio frequency (RF) fields on the ability of human neutrophils to follow concentration gradients of Cyclic Adenosine 3', 5'-Monophosphate (C-AMP) are reported. Blood from healthy adult donors was exposed in vitro to different temperatures and 900-MHz RF field at approximately 0.4 V/m. It was observed that the neutrophils' speed increased with increasing temperatures from 35 °C to 40 °C where it peaked and then decreased above 40 °C without RF exposure. When 900-MHz RF field was applied, the speed increased above the value observed at the same temperature, and the maximum speed exceeded that measured value at any temperature by approximately 50%. The calculated temperature change resulting from the RF exposure was less than one microdegree. The direction of motion changed from along the concentration gradient and the electrical field lines to motion at right angles to the concentration gradient and the electric field. The average time for the neutrophils to respond to the effect of RF radiation was about 2.5 min.

Aweda MA, Ajekigbe AT, Ibitoye AZ, Ewhierhurhoma BO, Eletu OB. Potential health risks due to telecommunications radiofrequency radiation exposures in Lagos State Nigeria. *Nig Q J Hosp Med*. 19(1):6-14, 2009.

BACKGROUND: The global system mobile telecommunications system (GSM) which was recently introduced in Nigeria is now being used by over 40 million people in Nigeria. The use of GSM is accompanied with exposure of the users to radiofrequency radiation

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(RFR), which if significant, may produce health hazards. This is the reason why many relevant national and international organizations recommended exposure limits to RFR and why it is made compulsory for GSM handsets to indicate the maximum power output as a guide to potential consumers. OBJECTIVE: This study was conducted to measure the RFR output power densities (S) from the most commonly used GSM handsets used in Lagos State and compare with the limit recommended for safety assessment. METHODS: Over 1100 most commonly used handsets of different makes and models as well as wireless phones were sampled and studied in all over the local government areas of the State. An RFR meter, Electrosmog from LESSEMF USA was used for the measurements. The handsets were assessed for health risks using the reference value of 9 Wm^{-2} as recommended by the International Commission on Non-Ionizing Radiation Protection (ICNIRP). RESULTS: The range of the S-values obtained varied from a minimum of 1.294 Wm^{-2} with Siemens model R228 to a maximum of $16.813 \pm 0.094 \text{ Wm}^{-2}$ with Samsung model C140*. The results from wireless telephones showed very low S-values ranging from a minimum of $0.024 \pm 0.001 \text{ Wm}^{-2}$ with HUAWEI and ST CDMA 1 to a maximum of $0.093 \pm 0.002 \text{ Wm}^{-2}$ with HISENSE. CONCLUSION: The results showed that the population in Lagos State may be at risk due to significant RFR exposures resulting principally from the use of GSM. Quite a number of handsets emit power above the ICNIRP recommended value. Measured RFR power close to Radio and Television masts and transmitters are within tolerable limits in most cases, only that the public should not reside or work close to RFR installations. Phone calls with GSM should be restricted to essential ones while youths and children that are more susceptible to RFR hazards should be supervised in their use of GSM. Wireless phones are quite safe.

Ayata A, Mollaoglu H, Yilmaz HR, Akturk O, Ozguner F, Altuntas I. Oxidative stress-mediated skin damage in an experimental mobile phone model can be prevented by melatonin. J Dermatol. 31(11):878-883, 2004.

Most mobile phones emit 900 MHz of radiation that is mainly absorbed by the external organs. The effects of 900 MHz of radiation on fibrosis, lipid peroxidation, and anti-oxidant enzymes and the ameliorating effects of melatonin (Mel) were evaluated in rat skin. Thirty Wistar-Albino rats were used in the study. The experimental groups were the control group, the irradiated group (IR), and the irradiated+Mel treated group (IR+Mel). A dose of 900 MHz, 2 W radiation was applied to the IR group every day for 10 days (30 min/day). The IR+Mel group received 10 mg/kg/day melatonin in tap water for 10 days before the irradiation. At the end of the 10th day, a skin specimen was excised from the thoracoabdominal area. The levels of malondialdehyde (MDA) and hydroxyproline and the activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) were studied in the skin samples. MDA and hydroxyproline levels and activities of CAT and GSH-Px were increased significantly in the IR group compared to the control group ($p < 0.05$) and decreased significantly in the IR+Mel group ($p < 0.05$). SOD activity was decreased significantly in the IR group and this decrease was not prevented by the Mel treatment. These results suggest that rats irradiated with 900 MHz suffer from increased fibrosis and lipid peroxidation (LPO). Mel

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treatment can reduce the fibrosis and LPO caused by radiation.

Barteri M, De Carolis R, Marinelli F, Tomassetti G, Montemiglio LC. Effects of microwaves (900 MHz) on peroxidase systems: a comparison between lactoperoxidase and horseradish peroxidase. Electromagn Biol Med. 2015 Jan 12:1-7. [Epub ahead of print]

This work shows the effects of exposure to an electromagnetic field at 900 MHz on the catalytic activity of the enzymes lactoperoxidase (LPO) and horseradish peroxidase (HRP). Experimental evidence that irradiation causes conformational changes of the active sites and influences the formation and stability of the intermediate free radicals is documented by measurements of enzyme kinetics, circular dichroism spectroscopy (CD) and cyclic voltammetry.

Driving Impairment Using a Cell Phone

Violanti JM, Cellular phones and traffic accidents. Public Health 111(6):423-428, 1997.

Cellular phone use in motor vehicles is becoming an increasing world-wide phenomenon. Using data obtained from traffic accidents reported between 1992 and 1995 in the state of Oklahoma, USA, this study examined statistical rate-ratios of accident characteristics between drivers with or without cellular phones. Rates were calculated between cellular phone involvement and reported accident causes, types of collision, driver actions immediately prior to the accident, location of the accident, the extent of fatalities, and age and gender of drivers. Results indicated a significant increased rate among drivers with cellular phones for inattention, unsafe speed, driving on wrong side of road, striking a fixed object, overturning their vehicle, swerving prior to the accident, and running off the roadway. People with phones stood an increased risk of being killed in an accident over persons without phones. Males with phones had a significantly higher rate than females for many of accident characteristics mentioned above. Rate-ratios of some accident characteristics and fatalities increased as age increased, with the exception of drivers under age 20 yrs, who had the highest fatality rate. *Limitations* of the study and possible prevention alternatives are discussed.

Violanti JM, Marshall JR, Cellular phones and traffic accidents: an epidemiological approach. Accid Anal Prev 28(2):265-270, 1996.

Using epidemiological case-control design and logistic regression techniques, this study examined the association of cellular phone use in motor vehicles and traffic accident risk. The amount of time per month spent talking on a cellular phone and 18 other driver inattention factors were examined. Data were obtained from: (1) a case group of 100 randomly selected drivers involved in accidents within the past 2 years, and (2) a control group of 100 randomly selected

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licensed drivers not involved in accidents within the past 10 years. Groups were matched on geographic residence. Approximately 13% (N = 7) of the accident and 9% (N = 7) of the non-accident group reported use of cellular phones while driving. Data was obtained from Department of Motor Vehicles accident reports and survey information from study subjects. We hypothesized that increased use of cellular phones while driving was associated with increased odds of a traffic accident. Results indicated that talking more than 50 minutes per month on cellular phones in a vehicle was associated with a 5.59-fold increased risk in a traffic accident. The combined use of cellular phones and motor and cognitive activities while driving were also associated with increased traffic accident risk. Readers should be cautioned that this study: (1) consists of a small sample, (2) reveals statistical associations and not causal relationships, and (3) does not conclude that talking on cellular phones while driving is inherently dangerous.

Violanti JM, Cellular phones and fatal traffic collisions. *Accid Anal Prev* 30(4):519-524, 1998.

A case-control study was conducted to determine statistical associations between traffic fatalities and the use or presence of a cellular phone, given involvement in a collision. The hypothesis of this study does not imply that cellular phones directly affect fatalities, but that phones increase the risk of certain accident characteristics in fatal collisions more than those same characteristics in non-fatal collisions. Analysis employed data from 223,137 traffic accidents occurring between 1992 and 1995. Information on collision characteristics and cellular phone involvement for each fatality was compared with the same information for each non-fatality (controls). Statistically adjusting for other collision variables (age, gender, alcohol use, speed, inattention and driving left of center), an approximate nine-fold increased risk was found for a fatality given the use of a cellular phone. An approximate two-fold increased risk for a fatality was found given the presence of a cellular phone in the vehicle. Combined effects of reported phone use, driving to the left of center and inattention increased the risk of a fatal collision more than phone use did by itself. This analysis implies a statistical, but not necessarily a causal, relationship. A multitude of factors are involved in any traffic collision, and the exact cause of an accident and its severity level is difficult to disentangle.

Strayer DL, Johnston WA. Driven to distraction: dual-Task studies of simulated driving and conversing on a cellular telephone. *Psychol Sci* 12(6):462-466, 2001.

Dual-task studies assessed the effects of cellular-phone conversations on performance of a simulated driving task. Performance was not disrupted by listening to radio broadcasts or listening to a book on tape. Nor was it disrupted by a continuous shadowing task using a handheld phone, ruling out, in this case, dual-task interpretations associated with holding the phone, listening, or speaking. However

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significant interference was observed in a word-generation variant of the shadowing task, and this deficit increased with the difficulty of driving. Moreover unconstrained conversations using either a handheld or a hands-free cell phone resulted in a twofold increase in the failure to detect simulated traffic signals and slower reactions to those signals that were detected. We suggest that cellular-phone use disrupts performance by diverting attention to an engaging cognitive context other than the one immediately associated with driving.

Strayer DL, Drews FA, Johnston WA. Cell phone-induced failures of visual attention during simulated driving. J Exp Psychol Appl 9(1):23-32, 2003.

This research examined the effects of hands-free cell phone conversations on simulated driving. The authors found that these conversations impaired driver's reactions to vehicles braking in front of them. The authors assessed whether this impairment could be attributed to a withdrawal of attention from the visual scene, yielding a form of inattention blindness. Cell phone conversations impaired explicit recognition memory for roadside billboards. Eye-tracking data indicated that this was due to reduced attention to foveal information. This interpretation was bolstered by data showing that cell phone conversations impaired implicit perceptual memory for items presented at fixation. The data suggest that the impairment of driving performance produced by cell phone conversations is mediated, at least in part, by reduced attention to visual inputs.

Jeness JW, Lattanzio RJ, O'Toole M, Taylor N, Pax C. Effects of manual versus voice-activated dialing during simulated driving. Percept Mot Skills 94(2):363-379, 2002.

We measured driving performance (lane-keeping errors, driving times, and glances away from the road scene) in a video driving simulator for 24 volunteers who each drove alone on a 10.6-km multicurved course while simultaneously placing calls on a mobile phone subscribed to a voice-activated dialing system. Driving performance also was measured for the same distance while participants manually dialed phone numbers and while they drove without dialing. There were 22% fewer lane-keeping errors ($p < .01$) and 56% fewer glances away from the road scene ($p < .01$) when they used voice-activated dialing as compared to manual dialing. Significantly longer driving times in both of the dialing conditions as compared to the No Dialing condition are discussed in terms of the hypothesis that drivers decrease driving speed to compensate for the demands of the secondary phone tasks.

Zajdel R, Zajdel J, Zwolińska A, Smigielski J, Beling P, Cegliński T, Nowak D. The sound of a mobile phone ringing affects the complex reaction time of its owner. Arch Med Sci. 8(5):892-898, 2012.

INTRODUCTION: Mobile phone conversation decreases the ability to concentrate and impairs the attention necessary to perform complex activities, such as driving a car. Does the ringing sound of a mobile phone affect the driver's ability to perform complex sensory-motor activities? We compared a subject's reaction time while performing a test either with a mobile phone ringing or without. MATERIAL AND METHODS: The examination was performed on a PC-based reaction time self-constructed system

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Reactor. The study group consisted of 42 healthy students. The protocol included instruction, control without phone and a proper session with subject's mobile phone ringing. The terms of the study were standardised. RESULTS: There were significant differences ($p < 0.001$) in reaction time in control (597 ms), mobile (633 ms) and instruction session (673 ms). The differences in female subpopulation were also significant ($p < 0.01$). Women revealed the longest reaction time in instruction session (707 ms), were significantly quicker in mobile (657 ms, $p < 0.01$) and in control session (612 ms, $p < 0.001$). In men, the significant difference was recorded only between instruction (622 ms) and control session (573 ms, $p < 0.01$). The other differences were not significant ($p > 0.08$). Men proved to complete significantly quicker than women in instruction ($p < 0.01$) and in mobile session ($p < 0.05$). Differences amongst the genders in control session was not significant ($p > 0.05$). CONCLUSIONS: The results obtained proofed the ringing of a phone exerts a significant influence on complex reaction time and quality of performed task.

Strayer DL, Drews FA. Profiles in driver distraction: effects of cell phone conversations on younger and older drivers. Hum Factors. 46(4):640-649, 2004.

Our research examined the effects of hands-free cell phone conversations on simulated driving. We found that driving performance of both younger and older adults was influenced by cell phone conversations. Compared with single-task (i.e., driving-only) conditions, when drivers used cell phones their reactions were 18% slower, their following distance was 12% greater, and they took 17% longer to recover the speed that was lost following braking. There was also a twofold increase in the number of rear-end collisions when drivers were conversing on a cell phone. These cell-phone-induced effects were equivalent for younger and older adults, suggesting that older adults do not suffer a significantly greater penalty for talking on a cell phone while driving than compared with their younger counterparts. Interestingly, the net effect of having younger drivers converse on a cell phone was to make their average reactions equivalent to those of older drivers who were not using a cell phone. Actual or potential applications of this research include providing guidance for recommendations and regulations concerning the use of mobile technology while driving.

Redelmeier DA, Tibshirani RJ, Association between cellular-telephone calls and motor vehicle collisions. N Engl J Med 13;336(7):453-458, 1997.

BACKGROUND: Because of a belief that the use of cellular telephones while driving may cause collisions, several countries have restricted their use in motor vehicles, and others are considering such regulations. We used an epidemiologic method, the case-crossover design, to study whether using a cellular telephone while driving increases the risk of a motor vehicle collision. METHODS: We studied 699 drivers who had cellular telephones and who were involved in motor vehicle collisions resulting in substantial property damage but no personal injury. Each person's cellular-telephone calls on the day of the collision and during the previous week were analyzed through the use of detailed billing records. RESULTS: A total of 26,798 cellular-telephone calls were made during the 14-month study period. The risk of a collision when using a cellular telephone was four

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times higher than the risk when a cellular telephone was not being used (relative risk, 4.3; 95 percent confidence interval, 3.0 to 6.5). The relative risk was similar for drivers who differed in personal characteristics such as age and driving experience; calls close to the time of the collision were particularly hazardous (relative risk, 4.8 for calls placed within 5 minutes of the accident, as compared with 1.3 for calls placed more than 15 minutes before the accident; $P < 0.001$); and units that allowed the hands to be free (relative risk, 5.9) offered no safety advantage over hand-held units (relative risk, 3.9; P not significant). Thirty-nine percent of the drivers called emergency services after the collision, suggesting that having a cellular telephone may have had advantages in the aftermath of an event. CONCLUSIONS: The use of cellular telephones in motor vehicles is associated with a quadrupling of the risk of a collision during the brief time interval involving a call. Decisions about regulation of such telephones, however, need to take into account the benefits of the technology and the role of individual responsibility.

Tornros JE, Bolling AK. Mobile phone use-Effects of handheld and handsfree phones on driving performance. *Accid Anal Prev.* 37(5):902-909, 2005.

The study was concerned with effects of handsfree and handheld mobile phone dialling and conversation in simulated driving. In the main experiment dealing with conversation, 48 participants drove a distance of about 70km on a route which led through urban and rural environments. In the dialling experiment, the participants drove a distance of 15km on a rural two-lane road. The experimental design was mixed with phone mode as a between-subjects factor and phone use (yes/no) as a within-subjects factor. Performance on a peripheral detection task (PDT) while driving was impaired by dialling and conversation for both phone modes, interpreted as an increase in mental workload. Driving performance was impaired by dialling-lateral position deviation increased in a similar way for both phone modes. Conversation had, however, opposite effects-lateral position deviation decreased in a similar way for both phone modes. Driving speed decreased as an effect of dialling with the greatest effect for handsfree phone mode. Conversation also caused reduced speed, but only for handheld phone mode. The effects on speed can be interpreted as a compensatory effort for the increased mental workload. In spite of the compensatory behaviour, mental workload was still markedly increased by phone use. Subjective effects of dialling and conversation were also analysed. Most participants reported a speed decrease but no effect on lateral position deviation as an effect of dialling or conversation. In the conversation experiment, driving performance was rated better for handsfree than for handheld mode. In the dialling experiment, no difference between the two phone modes appeared.

Oommen BS, Stahl JS. Inhibited head movements: A risk of combining phoning with other activities? *Neurology* 65(5):754-756, 2005.

Abstract-- Studies of cellular phone use while driving have attributed impaired performance to the distractions of conversation. We determined that holding an inactive phone to the ear reduces the probability of eccentric head positions, potentially indicating reduced ability to monitor the visual surround. This effect may constitute a

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risk of cellular phone use independent of conversation and peculiar to handheld models.

Miller G, Zhu G, Wright MJ, Hansell NK, Martin, NG. The Heritability and Genetic Correlates of Mobile Phone Use: A Twin Study of Consumer Behavior. Twin Research and Human Genetics / Volume 15 / Issue 01 / February 2012, pp 97-106.

There has been almost no overlap between behavior genetics and consumer behavior research, despite each field's importance in understanding society. In particular, both have neglected to study genetic influences on consumer adoption and usage of new technologies — even technologies as important as the mobile phone, now used by 5.8 out of 7.0 billion people on earth. To start filling this gap, we analyzed self-reported mobile phone use, intelligence, and personality traits in two samples of Australian teenaged twins (mean ages 14.2 and 15.6 years), totaling 1,036 individuals.

ACE modeling using Mx software showed substantial heritabilities for how often teens make voice calls (.60 and .34 in samples 1 and 2, respectively) and for how often they send text messages (.53 and .50). Shared family environment — including neighborhood, social class, parental education, and parental income (i.e., the generosity of calling plans that parents can afford for their teens) — had much weaker effects. Multivariate modeling based on cross-twin, cross-trait correlations showed negative genetic correlations between talking/texting frequency and intelligence (around $-.17$), and positive genetic correlations between talking/texting frequency and extraversion (about $.20$ to $.40$).

Our results have implications for assessing the risks of mobile phone use such as radiofrequency field (RF) exposure and driving accidents, for studying adoption and use of other emerging technologies, for understanding the genetic architecture of the cognitive and personality traits that predict consumer behavior, and for challenging the common assumption that consumer behavior is shaped entirely by culture, media, and family environment.

McEvoy SP, Stevenson MR, McCartt AT, Woodward M, Haworth C, Palamara P, Cercarelli R. Role of mobile phones in motor vehicle crashes resulting in hospital attendance: a case-crossover study. BMJ 331(7514):428, 2005.

OBJECTIVES: To explore the effect of drivers' use of mobile (cell) phones on road safety. DESIGN: A case-crossover study. SETTING: Perth, Western Australia. PARTICIPANTS: 456 drivers aged ≥ 17 years who owned or used mobile phones and had been involved in road crashes necessitating hospital attendance between April 2002 and July 2004. MAIN OUTCOME MEASURE: Driver's use of mobile phone at estimated time of crash and on trips at the same time of day in the week before the crash. Interviews with drivers in hospital and phone company's records of phone use. RESULTS: Driver's use of a mobile phone up to 10 minutes before a crash was associated with a fourfold increased likelihood of crashing (odds ratio 4.1, 95% confidence interval 2.2 to 7.7, $P < 0.001$). Risk was raised irrespective of whether or not a hands-free device was used (hands-free: 3.8, 1.8 to 8.0, $P < 0.001$; hand held: 4.9, 1.6 to 15.5, $P = 0.003$). Increased risk was similar in

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men and women and in drivers aged ≥ 30 and < 30 years. A third ($n=21$) of calls before crashes and on trips during the previous week were reportedly on hand held phones.
CONCLUSIONS: When drivers use a mobile phone there is an increased likelihood of a crash resulting in injury. Using a hands-free phone is not any safer.

Matthews R, Legg S, Charlton S. The effect of cell phone type on drivers subjective workload during concurrent driving and conversing. *Accid Anal Prev* 35(4):451-457, 2003.

The effect of three types of cell phones (hand held, hands free with an external speaker and personal hands free) on total subjective workload (including its constituent components; mental demand, physical demand, temporal demand, performance, effort and frustration) and intelligibility was measured using the NASA-task load index (TLX) and the modified rhyme test (MRT), respectively in 13 experienced drivers (nine male, four female, age range 28-65 years), whilst driving on a rural highway. The drivers rated all components of workload for each type of cell phone to be significantly higher than for a control condition in which no cell phone was used. The mean (standard deviation) total workload was lowest for the personal hands free cell phone (7.1(3.65)) and highest for the hands free speaker phone (10.8 (3.63)) ($P<0.001$). The mean (standard deviation) intelligibility score was highest for the personal hands free cell phone (74.1 (7.9)) and lowest for the hands free speaker phone (55.0 (10.4)) ($P<0.001$). Frustration was significantly correlated with total workload (0.60, $P<0.001$) and intelligibility was significantly correlated with frustration (-0.35, $P<0.05$). Physical demand was not a high contributor to total workload. It is concluded that a personal hands free cell phone would interfere least with the cognitive demands of driving.

Lesch MF, Hancock PA. Driving performance during concurrent cell-phone use: are drivers aware of their performance decrements? *Accid Anal Prev.* 36(3):471-480, 2004.

Prior research has documented the manner in which a variety of driving performance measures are impacted by concurrent cell-phone use as well as the influence of age and gender of the driver. This current study examined the extent to which different driver groups are aware of their associated performance decrements. Subjects' confidence in dealing with distractors while driving and their ratings of task performance and demand were compared with their actual driving performance in the presence of a cell-phone task. While high confidence ratings appeared to be predictive of better driving performance for male drivers (as confidence increased, the size of the distraction effects decreased), this relationship did not hold for females; in fact, for older females, as confidence increased, performance decreased. Additionally, when drivers were matched in terms of confidence level, brake responses of older females were slowed to a much greater extent (0.38s) than were brake responses of any other group (0.10s for younger males and females and 0.07s for older males). Finally, females also rated the driving task as less demanding than males, even though their performance was more greatly affected by distraction. These results suggest that many drivers may not be aware of their decreased performance while using cell-phones and that it may be particularly important to target educational campaigns on driver distraction towards female drivers

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for whom there tended to be a greater discrepancy between driver perceptions and actual performance.

Lam LT. Distractions and the risk of car crash injury: the effect of drivers' age. J Safety Res 33(3):411-419, 2002.

PROBLEM: Motor-vehicle accidents are one of the major causes of injury in most motorized countries. Driver distractions have been suggested as a contributor to traffic accidents. Moreover, age of the driver seems to have a role in the relationship between distractions and car crashes. But very few studies have investigated the effect of driver's age on this relationship. This exploratory study investigated the association between distractions, both inside and outside the vehicle, and the increased risk of car crash injury among drivers across different ages. METHOD: This study used a case series design to analyze data routinely collected by the NSW police in Australia. A special focus of this study was on how drivers' age affects the risk of car crash injury, which was determined by using a well-documented risk estimation methodology. RESULTS: The results obtained indicated that drivers of all ages, on the whole, are more susceptible to distractions inside the vehicle than distractions coming from outside. Age was shown to affect the relationship between in-vehicle distraction and the risk of car crash injury. A separate analysis was also conducted on hand-held phone usage while driving with results supplementing previous findings reported in the literature. IMPACT TO INDUSTRY: Safety strategies to countermeasure in-vehicle distractions have been suggested and discussed.

Lamble D, Kauranen T, Laakso M, Summala H, Cognitive load and detection thresholds in car following situations: safety implications for using mobile (cellular) telephones while driving. Accid Anal Pre 31(6):617-623, 1999.

This study was aimed at investigating drivers' ability to detect a car ahead decelerating, while doing mobile phone related tasks. Nineteen participants aged between 20 and 29 years, (2000-125000 km driving experience) drove at 80 km/h, 50 m behind a lead car, on a 30 km section of motorway in normal traffic. During each trial the lead car started to decelerate at an average of 0.47 m/s² while the participant either looked at the car in front (control), continuously dialed series of three random integers on a numeric keypad (divided visual attention), or performed a memory and addition task (non-visual attention). The results indicated that drivers' detection ability was impaired by about 0.5 s in terms of brake reaction time and almost 1 s in terms of time-to-collision, when they were doing the non-visual task whilst driving. This impairment was similar to when the drivers were dividing their visual attention between the road ahead and dialing numbers on the keypad. It was concluded that neither a hands-free option nor a voice controlled interface removes the safety problems associated with the use of mobile phones in a car.

Laberge-Nadeau C, Maag U, Bellavance F, Lapierre SD, Desjardins D, Messier S, Sai;di A. Wireless telephones and the risk of road crashes. Accid Anal Prev. 35(5):649-660, 2003.

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In light of the rapidly increasing development of the cell phone market, the use of such equipment while driving raises the question of whether it is associated with an increased accident risk; and if so, what is its magnitude. This research is an epidemiological study on two large cohorts, namely users and non-users of cell phones, with the objective of verifying whether an association exists between cell phone use and road crashes, separating those with injuries. The Societe de l'Assurance Automobile du Quebec (SAAQ) mailed a questionnaire and letter of consent to 175000 licence holders for passenger vehicles. The questionnaire asked about exposure to risk, driving habits, opinions about activities likely to be detrimental to driving and accidents within the last 24 months. For cell phone users, questions pertaining to the use of the telephone were added. We received 36078 completed questionnaires, with a signed letter of consent. Four wireless phone companies provided the files on cell phone activity, and the SAAQ the files for 4 years of drivers' records and police reports. The three data sources were merged using an anonymized identification number. The statistical methods include logistic-normal regression models to estimate the strength of the links between the explanatory variables and crashes. The relative risk of all accidents and of accidents with injuries is higher for users of cell phones than for non-users. The relative risks (RR) for injury collisions and also for all collisions is 38% higher for men and women cell phone users. These risks diminish to 1.1 for men and 1.2 for women if other variables, such as the kilometres driven and driving habits are incorporated into the models. Similar results hold for several sub-groups. The most significant finding is a dose-response relationship between the frequency of cell phone use, and crash risks. The adjusted relative risks for heavy users are at least two compared to those making minimal use of cell phones; the latter show similar collision rates as do the non-users.

Korpinen L, Pääkkönen R. Accidents and close call situations connected to the use of mobile phones. *Accid Anal Prev.* 45(2):75-82, 2012.

Abstract. The aim of our work was to study the accidents and close call situations connected to the use of mobile phones. We have analyzed how the accidents/close call situations are connected to background information, in particular age, gender and self-reported symptoms. The study was carried out as a cross-sectional study by posting the questionnaire to 15,000 working-age Finns. The responses (6121) were analyzed using the logistic regression models. Altogether 13.7% of respondents had close call situations and 2.4% had accidents at leisure, in which the mobile phone had a partial effect, and at work the amounts were 4.5% and 0.4% respectively, during the last 12 months. Essentially, we found that: (1) men tend to have more close calls and accidents while on a mobile phone, (2) younger people tend to have more accidents and close calls while on a mobile phone, but it does not appear to be large enough to warrant intervention, (3) employed people tend to have more problems with mobile phone usage and accidents/close calls, and (4) there was a slight increase in mobile-phone-related accidents/close calls if the respondent also reported sleep disturbances and minor aches and pains. In the future, it is important to take into account and study how symptoms can increase the risk of accidents or close call situations in which a mobile phone has a partial effect.

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Hunton J, Rose JM. Cellular telephones and driving performance: the effects of attentional demands on motor vehicle crash risk. Risk Anal. 25(4):855-866, 2005.

This study examines the effects of conversation mode and split-attention communication training on driving performance. The study is based on an experiment where drivers with and without communication training (pilots vs. nonpilots) completed a simulated driving course while involved in one of three conversation modes: no conversation, conversation with passenger, or conversation on a hands-free cellular telephone. Results indicate that cellular telephone conversations consume more attention and interfere more with driving than passenger conversations. Cell phone conversations lack the nonverbal cues available during close-contact conversations and conversation participants expend significant cognitive resources to compensate for the lack of such cues. The results also demonstrate that communication training may reduce the hazardous effects of cell phone conversations on driving performance.

Hladky, A, Musil, J, Roth, Z, Urban, P, Blazkova, V, Acute effects of using a mobile phone on CNS functions. Cent Eur J Public Health 7(4):165-167. 1999.

Twenty volunteers participated in two experiments exploring the acute effects of using the mobile phone Motorola GSM 8700 on the functions of the CNS. When speaking (5 minutes reading a text from daily newspapers) the electromagnetic fields from the mobile apparatus did not affect the visual evoked potentials. Also a 6-min exposure did not reveal any effect of electromagnetic fields on the results in two tests (memory and attention) performed while speaking into the mobile. On the other hand the phone call itself strongly influenced the performance in a secondary task applying a test of switching attention which is a good model for driving a car. The response and decision speed were significantly worse. This is a proof that even a slight psychological stress involved in calling while driving can be a great risk.

Horberry T, Anderson J, Regan MA, Triggs TJ, Brown J. Driver distraction: The effects of concurrent in-vehicle tasks, road environment complexity and age on driving performance. Accid Anal Prev. 38(1):185-191. 2006.

This paper presents the findings of a simulator study that examined the effects of distraction upon driving performance for drivers in three age groups. There were two in-vehicle distracter tasks: operating the vehicle entertainment system and conducting a simulated hands-free mobile phone conversation. The effect of visual clutter was examined by requiring participants to drive in simple and complex road environments. Overall measures of driving performance were collected, together with responses to roadway hazards and subjective measures of driver perceived workload. The two in-vehicle distraction tasks degraded overall driving performance, degraded responses to hazards and increased subjective workload. The performance decrements that occurred as a result of in-vehicle distraction were observed in both the simple and complex highway environments and for drivers in different age groups. One key difference was that older drivers traveled at lower mean speeds in the complex highway environment compared with younger drivers. The conclusions of the research are that both in-vehicle tasks impaired several aspects of driving performance, with the entertainment system

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distracter having the greatest negative impact on performance, and that these findings were relatively stable across different driver age groups and different environmental complexities.

Jenness JW, Lattanzio RJ, O'Toole M, Taylor N, Pax C. Effects of manual versus voice-activated dialing during simulated driving. Percept Mot Skills 94(2):363-379, 2002.

We measured driving performance (lane-keeping errors, driving times, and glances away from the road scene) in a video driving simulator for 24 volunteers who each drove alone on a 10.6-km multicurved course while simultaneously placing calls on a mobile phone subscribed to a voice-activated dialing system. Driving performance also was measured for the same distance while participants manually dialed phone numbers and while they drove without dialing. There were 22% fewer lane-keeping errors ($p < .01$) and 56% fewer glances away from the road scene ($p < .01$) when they used voice-activated dialing as compared to manual dialing. Significantly longer driving times in both of the dialing conditions as compared to the No Dialing condition are discussed in terms of the hypothesis that drivers decrease driving speed to compensate for the demands of the secondary phone tasks.

Dreyer NA, Loughlin JE, Rothman KJ, Cause-specific mortality in cellular telephone users. JAMA 282(19):1814-1816, 1999.

A survey of standardized mortality rates (from cancer, circulatory diseases, and motor vehicle collisions) of 285,561 analog telephone users with known age, sex, and telephone type, showed that the only category of cause of death for which there was an indication of increasing risk with increasing minutes of phone use was motor vehicle collisions. Similar results were found for number of telephone calls per day. collisions were particularly hazardous (relative risk, 4.8 for calls placed within 5 minutes of the accident, as compared with 1.3 for calls placed more than 15 minutes before the accident; $P < 0.001$); and units that allowed the hands to be free (relative risk, 5.9) offered no safety advantage over hand-held units (relative risk, 3.9; P not significant). Thirty-nine percent of the drivers called emergency services after the collision, suggesting that having a cellular telephone may have had advantages in the aftermath of an event. CONCLUSIONS: The use of cellular telephones in motor vehicles is associated with a quadrupling of the risk of a collision during the brief time interval involving a call. Decisions about regulation of such telephones, however, need to take into account the benefits of the technology and the role of individual responsibility.

Cooper PJ, Zheng Y. Turning gap acceptance decision-making: the impact of driver distraction. J Safety Res 33(3):321-335, 2002.

PROBLEM: A number of studies have found that use of in-car phones by drivers can interfere with the cognitive processing necessary for making appropriate and timely vehicle control decisions. However, the specific linkage between communication-based distraction and unsafe decision-making has not been sufficiently explored. **METHOD:** In a closed-course driving experiment, 39 subjects were exposed to approximately 100 gaps each in a circulating traffic stream of eight vehicles on an instrumented test track

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that was wet about half the time. The subjects were at the controls of an instrumented car, which was oriented in a typical left-turn configuration (traffic-crossing situation in North America) and with parking brake on and the transmission in neutral. The subjects were instructed to press on the accelerator pedal when they felt that a gap was safe to accept. Their performances were monitored and incentives were provided for balancing safe decision-making with expeditious completion of the task. For half of the gap exposures (randomly assigned), each subject was required to listen and respond to a complex verbal message. RESULTS: When not distracted, the subjects' gap acceptance judgment was found to be significantly influenced by their age, the gap size, the speed of the trailing vehicle, the level of "indecision," and the condition of the track surface. However, when distracted, the subjects did not factor pavement surface condition into the decision process. On wet pavement, the subjects were judged to have initiated twice the level of potential collisions when distracted by the messages that they did when not distracted. DISCUSSION: Listening/responding to verbal messages may reduce the capacity of drivers to process adequately all the important information necessary for safe decision-making. The effects of the messages in our study seemed to cause the subjects to misjudge gap size and speed information when operating under the additional disadvantage of adverse pavement condition. SUMMARY: Attention to complex messages while making decisions about turning through gaps in an on-coming vehicle stream was associated with significantly increased unsafe decision making by subjects in our experiment when the additional complexity of wet surface condition was introduced. IMPACT ON INDUSTRY: While the results reflected a somewhat artificial situation where the measure was signaled intention to act rather than the act itself, nevertheless, they do strongly suggest a scenario in which mental distraction could contribute to crash risk. With the rapid proliferation of telematics in the vehicle market, even with the laudable objectives represented by the Intelligent Transportation Systems initiative, there is a danger of the primary task of the driver being subordinated to a perceived need to enhance information flow to/from the external "world." Industry and governments need to work together to ensure that apparently desirable in-vehicle communication improvements do not compromise safety.

Consiglio W, Driscoll P, Witte M, Berg WP. Effect of cellular telephone conversations and other potential interference on reaction time in a braking response. *Accid Anal Prev* 35(4):495-500, 2003.

This experiment studied the effect of phone conversations and other potential interference on reaction time (RT) in a braking response. Using a laboratory station which simulated the foot activity in driving, 22 research participants were requested to release the accelerator pedal and depress the brake pedal as quickly as possible following the activation of a red brake lamp. Mean reaction time was determined for five conditions: (a) control, (b) listening to a radio, (c) conversing with a passenger, (d) conversing using a hand-held phone, and (e) conversing using a hands-free phone. Results indicated that conversation, whether conducted in-person or via a cellular phone caused RT to slow, whereas listening to music on the radio did not.

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Charlton SG. Perceptual and attentional effects on drivers' speed selection at curves. *Accid Anal Prev.* 36(5):877-884, 2004.

This paper describes an experiment comparing the relative effectiveness of various types of warnings on drivers' speed selection at curves. The experiment compared three types of curve warnings across three different curve types in a driving simulator. All of the warnings worked reasonably well for severe curves (45 km/h), regardless of demands from a secondary (cell phone) task. For less demanding curves, only those warnings with a strong perceptual component (i.e., implicit cues) were effective in reducing drivers' curve speeds in the presence of the cell phone task. The design implications of these data appear straightforward; curve warnings that contain perceptual components or emphasise the physical features of the curve work best, particularly in cognitively demanding situations. The cell phone task added to driver workload and drivers became less responsive to primary task demands (i.e., speeds were elevated and reaction times were longer).

Astrain I, Bernaus J, Claverol J, Escobar A, Godoy P. [Prevalence of mobile phone use while driving vehicles] *Gac Sanit* 17(1):66-69, 2003. [Article in Spanish]

Objective: To estimate the prevalence of mobile telephone use while driving vehicles in the city of Lleida (Spain). Methods: A random sample of 1536 cars passing through six intersections regulated by traffic lights in Lleida were selected (three with urban traffic and three with interurban traffic). Cyclists, motorcyclists and driving school cars were excluded. The variables studied were mobile telephone use, age, (18-40; 41-60; >61), sex, the presence of passengers, type of intersection (urban traffic/interurban traffic), day of the week (working day/weekend or holiday) and hour of the day (rush hour/non-rush hour). The prevalence of mobile telephone use was calculated in percentages with a 95% CI. The relationship among the dependent variable (mobile telephone use) and the other independent variables was studied using odds ratios (OR) and 95% CI. Results: A total of 1536 direct observations were made and mobile telephone use was detected in 50 drivers. The prevalence was 3.3 (95% CI, 2.4-4.3). The prevalence was higher in men (OR = 2.2; 95% CI, 1.0-5.7), in drivers aged more than 60 years old (OR = 2.2; 95% CI, 0.5-8.4) and in those aged 18-40 years old (OR = 1.5; 95% CI, 0.8-3.0), in unaccompanied drivers (OR = 3.0; 95% CI, 1.5-6.3), in urban intersections (OR = 2.7; 95% CI, 1.2-5.9), on workdays (OR = 2.0; 95% CI, 0.9-4.4) and at the rush hour (OR = 1.4; 95% CI, 0.8-2.4). Conclusions: The prevalence of mobile telephone use while driving vehicles can be considered high, because of the increase in car accidents. The profile of drivers using mobile telephones corresponds to men aged 18-40 years or more than 61 years, in urban intersections, without passengers, during workdays and at the rush hour. We recommend the implementation of measures to decrease the use of mobile telephones while driving

Asbridge M, Brubacher JR, Chan H. Cell phone use and traffic crash risk: a culpability analysis. *Int J Epidemiol.* 2012 Nov 18. [Epub ahead of print]

BACKGROUND: The use of a cell phone or communication device while driving is illegal in many jurisdictions, yet evidence evaluating the crash risk associated with cell phone

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use in naturalistic settings is limited. This article aims to determine whether cell phone use while driving increases motor vehicle crash culpability. **METHOD:** Drivers involved in crashes where police reported cell phone use (n = 312) and propensity matched drivers (age, sex, suspect alcohol/drug impairment, crash type, date, time of day, geographical location) without cell phone use (n = 936) were drawn from Insurance Corporation of British Columbia Traffic Accident System data. A standardized scoring tool, modified to account for Canadian driving conditions, was used to determine crash culpability from police reports on all drivers from the crashes. The association between crash culpability and cell phone use was determined, with additional subgroup analyses based on crash severity, driver characteristics and type of licence. **RESULTS:** A comparison of crashes with vs without cell phones revealed an odds ratio of 1.70 (95% confidence interval 1.22-2.36; P = 0.002). This association was consistent after adjustment for matching variables and other covariates. Subgroup analyses demonstrated an association for male drivers, unimpaired drivers, injured and non-injured drivers, and for drivers aged between 26 and 65 years. **CONCLUSIONS:** Crash culpability was found to be significantly associated with cell phone use by drivers, increasing the odds of a culpable crash by 70% compared with drivers who did not use a cell phone. This increased risk was particularly high for middle-aged drivers.

Atchley P, Dressel J. Conversation limits the functional field of view. Hum Factors. 46(4):664-673, 2004.

The purpose of these two experiments is to investigate one possible mechanism that might account for an increase in crash risk with in-car phone use: a reduction in the functional field of view. In two between-subjects experiments, college undergraduates performed a task designed to measure the functional field of view in isolation and while performing a hands-free conversational task. In both experiments, the addition of the conversational task led to large reductions in the functional field of view. Because similar reductions have been shown to increase crash risk, reductions in the functional field of view by conversation may be an important mechanism involved in increased risk for crashes with in-car phone use. Actual or potential applications of this research include improving driver performance.

Barkana Y, Zadok D, Morad Y, Avni I. Visual field attention is reduced by concomitant hands-free conversation on a cellular telephone. Am J Ophthalmol. 138(3):347-353, 2004.

PURPOSE: To quantify the central attention-diverting effect of hands-free cellular phone conversation on visual field awareness. **DESIGN:** Experimental study. **METHODS:** Twenty male and 21 female healthy participants performed a pretest and baseline Esterman visual field examinations with the Humphrey Systems Visual Field Analyzer II. During the consequent third examination, each participant engaged in a hands-free conversation using a cellular phone. The conversation was the same for all participants. Visual field performance parameters were compared between the second (baseline) examination, and the third (test) examination for each eye. **RESULTS:** During phone conversation, missed points increased from mean 1.0 +/- 1.5 to 2.6 +/- 3.4 (P <= .001) in the right eye

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and from 1.1 +/- 1.53 to 3.0 +/- 3.4 (P <.001) in the left eye. Fixation loss increased from mean 7.8% to 27.4% (P <.0001) and from 7.2% to 34.8% (P <.0001) for the right and left eyes, respectively. Test duration increased by a mean of 0.28 seconds (15%) per stimulus (P <.0001). Approximately half of missed points were inside the central 30 degrees. There was no significant difference in the performance of male and female participants. CONCLUSION: We describe a new model for the quantification of the attention-diverting effect of cellular-phone conversation on the visual field. In the current study, cellular hands-free conversation caused some subjects to miss significantly more points, react slower to each stimulus, and perform with reduced precision. Legislative restrictions on concomitant cellular-phone conversation and driving may need to be based on individual performance rather than a general ban on cellular phone usage.

Beede KE, Kass SJ. Engrossed in conversation: The impact of cell phones on simulated driving performance. Accid Anal Prev38(2):415-21, 2006.

The current study examined the effects of cognitively distracting tasks on various measures of driving performance. Thirty-six college students with a median of 6 years of driving experience completed a driving history questionnaire and four simulated driving scenarios. The distraction tasks consisted of responding to a signal detection task and engaging in a simulated cell phone conversation. Driving performance was measured in terms of four categories of behavior: traffic violations (e.g., speeding, running stop signs), driving maintenance (e.g., standard deviation of lane position), attention lapses (e.g., stops at green lights, failure to visually scan for intersection traffic), and response time (e.g., time to step on brake in response to a pop-up event). Performance was significantly impacted in all four categories when drivers were concurrently talking on a hands-free phone. Performance on the signal detection task was poor and not significantly impacted by the phone task, suggesting that considerably less attention was paid to detecting these peripheral signals. However, the signal detection task did interact with the phone task on measures of average speed, speed variability, attention lapses, and reaction time. The findings lend further empirical support of the dangers of drivers being distracted by cell phone conversations.

Overlooked Health Effects in Science

Marino AA, Carrubba S. The effects of mobile-phone electromagnetic fields on brain electrical activity: a critical analysis of the literature. Electromagn Biol Med. 28(3):250-274, 2009.

We analyzed the reports in which human brain electrical activity was compared between the presence and absence of radio-frequency and low-frequency electromagnetic fields (EMFs) from mobile phones, or between pre- and post-exposure to the EMFs. Of 55 reports, 37 claimed and 18 denied an EMF-induced effect on either the baseline electroencephalogram (EEG), or on cognitive processing of visual or auditory stimuli as reflected in changes in event-related potentials. The positive reports

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did not adequately consider the family-wise error rate, the presence of spike artifacts in the EEG, or the confounding role of the two different EMFs. The negative reports contained neither positive controls nor power analyses. Almost all reports were based on the incorrect assumption that the brain was in equilibrium with its surroundings. Overall, the doubt regarding the existence of reproducible mobile-phone EMFs on brain activity created by the reports appeared to legitimate the knowledge claims of the mobile-phone industry. However, it funded, partly or wholly, at least 87% of the reports. From an analysis of their cognitive framework, the common use of disclaimers, the absence of information concerning conflicts of interest, and the industry's donations to the principal EMF journal, we inferred that the doubt was manufactured by the industry. The crucial scientific question of the pathophysiology of mobile-phone EMFs as reflected in measurements of brain electrical activity remains unanswered, and essentially unaddressed.

Wilen J, Sandstrom M, Hansson Mild K. Subjective symptoms among mobile phone users-A consequence of absorption of radiofrequency fields? *Bioelectromagnetics* 24(3):152-159, 2003.

In a previous epidemiological study, where we studied the prevalence of subjective symptoms among mobile phone (MP) users, we found as an interesting side finding that the prevalence of many of the subjective symptoms increased with increasing calling time and number of calls per day. In this extrapolative study, we have selected 2402 people from the epidemiological study who used any of the four most common GSM MP. We used the information about the prevalence of symptoms, calling time per day, and number of calls per day and combined it with measurements of the Specific Absorption Rate (SAR). We defined three volumes in the head and measured the maximum SAR averaged over a cube of 1 g tissue (SAR(1g)) in each volume. Two new exposure parameters Specific Absorption per Day (SAD) and Specific Absorption per Call (SAC) have been devised and are obtained as combinations of SAR, calling time per day, and number of calls per day, respectively. The results indicates that SAR values >0.5 W/kg may be an important factor for the prevalence of some of the symptoms, especially in combination with long calling times per day.

Marjanović AM, Pavičić I, Trošić I Biological indicators in response to radiofrequency/microwave exposure. *Arh Hig Rada Toksikol.* 2012 Sep 25;63(3):407-416, 2012.

Over the years, due to rapid technological progress, radiation from man-made sources exceeded that of natural origin. There is a general concern regarding a growing number of appliances that use radiofrequency/ microwave (RF/MW) radiation with particular emphasis on mobile communication systems. Since nonthermal biological effects and mechanisms of RF/MW radiation are still uncertain, laboratory studies on animal models, tissues, cells, and cell free system are of extraordinary importance in bioelectromagnetic research. We believe that such investigations play a supporting role in public risk assessment. Cellular systems with the potential for a clear response to RF/MW exposures should be used in those studies. It is known that organism is a

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complex electrochemical system where processes of oxidation and reduction regularly occur. One of the plausible mechanisms is connected with generation of reactive oxygen species (ROS). Depending on concentration, ROS can have both beneficial and deleterious effects. Positive effects are connected with cell signalling, defence against infectious agents, and proliferative cell ability. On the other hand, excessive production, which overloads antioxidant defence mechanism, leads to cellular damage with serious potential for disease development. ROS concentration increase within the cell caused by RF/MW radiation seems to be a biologically relevant hypothesis to give clear insight into the RF/MW action at non-thermal level of radiation. In order to better understand the exact mechanism of action and its consequences, further research is needed in the field. We would like to present current knowledge on possible biological mechanisms of RF/MW actions.

Lauer O, Frei P, Gosselin MC, Joseph W, Rösli M, Fröhlich J. Combining near- and far-field exposure for an organ-specific and whole-body RF-EMF proxy for epidemiological research: A reference case. *Bioelectromagnetics*. 2013 Feb 15. doi: 10.1002/bem.21782. [Epub ahead of print]

A framework for the combination of near-field (NF) and far-field (FF) radio frequency electromagnetic exposure sources to the average organ and whole-body specific absorption rates (SARs) is presented. As a reference case, values based on numerically derived SARs for whole-body and individual organs and tissues are combined with realistic exposure data, which have been collected using personal exposure meters during the Swiss Qualifex study. The framework presented can be applied to any study region where exposure data is collected by appropriate measurement equipment. Based on results derived from the data for the region of Basel, Switzerland, the relative importance of NF and FF sources to the personal exposure is examined for three different study groups. The results show that a 24-h whole-body averaged exposure of a typical mobile phone user is dominated by the use of his or her own mobile phone when a Global System for Mobile Communications (GSM) 900 or GSM 1800 phone is used. If only Universal Mobile Telecommunications System (UMTS) phones are used, the user would experience a lower exposure level on average caused by the lower average output power of UMTS phones. Data presented clearly indicate the necessity of collecting band-selective exposure data in epidemiological studies related to electromagnetic fields.

Huss A, Egger M, Hug K, Huwiler-Müntener K, Rösli M, Gomes D, Da Ros MA Source of funding and results of studies of health effects of mobile phone use: systematic review of experimental studies. *Cien Saude Colet*. 13(3):1005-1012, 2008.

There is concern regarding the possible health effects of cellular telephone use. We conducted a systematic review of studies of controlled exposure to radiofrequency radiation with health-related outcomes (electroencephalogram, cognitive or cardiovascular function, hormone levels, symptoms, and subjective well-being). We searched Embase, Medline, and a specialist database in February 2005 and scrutinized reference lists from relevant publications. Data on the source of funding, study design,

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methodologic quality, and other study characteristics were extracted. The primary outcome was the reporting of at least one statistically significant association between the exposure and a health-related outcome. Data were analyzed using logistic regression models. Of 59 studies, 12 (20%) were funded exclusively by the telecommunications industry, 11 (19%) were funded by public agencies or charities, 14 (24%) had mixed funding (including industry), and in 22 (37%) the source of funding was not reported. Studies funded exclusively by industry reported the largest number of outcomes, but were least likely to report a statistically significant result. The interpretation of results from studies of health effects of radiofrequency radiation should take sponsorship into account.

Hutter HP, Moshammer H, Wallner P, Kundi M. Public perception of risk concerning cell towers and mobile phones. *Soz Praventivmed.* 49(1):62-66, 2004.

OBJECTIVE: The controversy about health risks of electromagnetic fields (EMF) has contributed in raising fears concerning emissions from celltowers. The study was to examine whether or not neighbours of celltowers are particularly concerned about adverse health effects of mobile phones and their base stations. METHODS: Prior to information delivered by medical doctors of the Institute of Environmental Health at public hearings a questionnaire was handed out to participants asking for their personal rating of several environmental health risks including those of mobile telecommunication (n = 123, response rate approx. 48%). Medical students (n = 366) served as a contrast group. RESULTS: Participants rated health risk for both, mobile phones and celltowers higher as students. A trend for higher ratings was also seen with older subjects and female sex. The risk ratings of both exposures correlated well with each other. The magnitude of the perceived risks, however, resembled that of other ubiquitous exposures like traffic noise and air pollution. CONCLUSION: Contrary to the claims of the telecommunication industry, opponents of celltowers generally do not express unusual fears concerning electromagnetic field exposure. The outcome of our study indicates that the risk rating is comparable with other perceived common hazards of the civilised world. It is hypothesised that offering information and participation to the concerned population will be efficient in reducing exaggerated fears.

Redmayne M, Inyang I, Dimitriadis C, Benke G, Abramson MJ. Cordless telephone use: implications for mobile phone research. *J Environ Monit.* 12(4):809-812, 2010.

Cordless and mobile (cellular) telephone use has increased substantially in recent years causing concerns about possible health effects. This has led to much epidemiological research, but the usual focus is on mobile telephone radiofrequency (RF) exposure only despite cordless RF being very similar. Access to and use of cordless phones were included in the Mobile Radiofrequency Phone Exposed Users Study (MoRPhEUS) of 317 Year 7 students recruited from Melbourne, Australia. Participants completed an exposure questionnaire-87% had a cordless phone at home and 77% owned a mobile phone. There was a statistically significant positive relationship ($r = 0.38, p < 0.01$) between cordless and mobile phone use. Taken together, this increases total RF exposure and its ratio in high-to-low mobile users. Therefore, the design and analysis of

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future epidemiological telecommunication studies need to assess cordless phone exposure to accurately evaluate total RF telephone exposure effects.

Cancer - Brain Tumors; Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with the use of mobile and cordless phones. Rev Environ Health. (Hardell and Carlsberg); 2013

Lennart Hardell* and Michael Carlberg

Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with use of mobile and cordless phones¹⁾

Abstract

Background: Wireless phones, i.e., mobile phones and cordless phones, emit radiofrequency electromagnetic fields (RF-EMF) when used. An increased risk of brain tumors is a major concern. The International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) evaluated the carcinogenic effect to humans from RF-EMF in May 2011. It was concluded that RF-EMF is a group 2B, i.e., a “possible”, human carcinogen. Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 on the association or causation that provides a helpful framework for evaluation of the brain tumor risk from RF-EMF.

Methods: All nine issues on causation according to Hill were evaluated. Regarding wireless phones, only studies with long-term use were included. In addition, laboratory studies and data on the incidence of brain tumors were considered.

Results: The criteria on strength, consistency, specificity, temporality, and biologic gradient for evidence of increased risk for glioma and acoustic neuroma were fulfilled. Additional evidence came from plausibility and analogy based on laboratory studies. Regarding coherence, several studies show increasing incidence of brain tumors, especially in the most exposed area. Support for the experiment came from antioxidants that can alleviate the generation of reactive oxygen species involved in biologic effects, although a direct mechanism for brain tumor carcinogenesis has not been shown. In addition, the finding of no increased risk for brain tumors in subjects using the mobile phone only in a car with an external antenna is supportive evidence. Hill did not consider all the needed nine viewpoints to be essential requirements.

Conclusion: Based on the Hill criteria, glioma and acoustic neuroma should be considered to be caused by RF-EMF emissions from wireless phones and regarded as carcinogenic to humans, classifying it as group 1 according to the IARC classification. Current guidelines for exposure need to be urgently revised.

Keywords: acoustic neuroma; causation; glioma; Hill criteria; wireless phones.

¹⁾Based on a presentation at the Corporate Interference with Science and Health: Fracking, Food and Wireless, Scandinavia House, New York City, March 13 and 14, 2013.

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Background

Mobile phones have been used since the early 1980s, and the Scandinavian countries were among the first in the world to adopt this technology. At first, analog phones [Nordic Mobile Telephone System (NMT)] were used, but in the early 1990s, the digital system [Global System for Mobile Communication (GSM)] was introduced. The analog system was definitely closed down in Sweden on December 31, 2007. Nowadays, mobile phones are used more than landline phones in Sweden (1). Worldwide, estimates of 5.9 billion mobile phone subscriptions were reported at the end of 2011 by the International Telecommunication Union (2).

Desktop cordless telephones have been used in Sweden since the end of the 1980s, first using the analog system, but since the 1990s, the digital variant was used. They are very common both in homes and at workplaces, overtaking telephones connected to landlines.

Wireless phones, i.e., mobile phones and cordless phones, emit radiofrequency electromagnetic fields (RF-EMF) when used. Cordless phones should be given an equal consideration as mobile phones when this type of exposure is assessed. In fact, this has not been the case except for the Hardell group studies in Sweden (3–8). When used, the handheld mobile phones gives exposure

to RF-EMF to the brain, especially to the temporal lobe on the same side where the phone is used, i.e., ipsilateral exposure (9, 10). This has given concern of an increased risk of brain tumors, although other potential health effects from RF-EMF cannot be excluded.

Few studies exist with data on long-term (i.e., >10 years) use of wireless phones and health risks. Regarding brain tumors, only case-control studies from the Hardell group in Sweden (3–8) and the Interphone Study Group (11, 12) give such results. However, Interphone presented results only for mobile phone use. The cases in the Hardell group studies were diagnosed during 1997–2003, whereas Interphone included 16 research centers in 13 countries during varying periods between 2000 and 2004. There was no overlap of included subjects in the Hardell group studies and the Swedish part of Interphone. A Danish cohort study on mobile users (13) has been evaluated to be inconclusive due to serious methodologic problems (14–16).

Because of the widespread use of wireless technology, even a small risk increase would have serious public health consequences. In May 2011, the International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) evaluated the carcinogenic effect of RF-EMF to humans. It included radiation from mobile phones and from other devices that emit similar nonionizing EMFs in the frequency range 30 kHz–300 GHz. It was concluded that RF-EMF is a group 2B, i.e., a “possible”, human carcinogen (14, 16).

This conclusion was mainly based on epidemiologic studies from the Hardell group in Sweden and the IARC Interphone study. These studies showed an association between two types of brain tumors, glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones. There was no consistent pattern of an association within the studied latency period (time since first exposure), with the most common benign brain tumor, meningioma, suggesting specificity for these other tumor types.

To further evaluate strengths of evidence, Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 that appeared afterward as an article in the *Proceedings of the Royal Society of Medicine* at the height of the tobacco and lung cancer controversy (17). That article on causation provides a helpful framework for assessing the brain tumor risk from wireless phones and offers some very insightful comments that are useful in this context. In the article “The environment and disease: association or causation”, Hill offered a list of nine aspects of an association to be considered when deciding if an association is causal. He did not intend to give a list of necessary conditions but warned that he did not believe “that we can usefully lay down some – hard-and-fast rules of evidence that

must be obeyed before we can accept cause and effect”. He wrote, “None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non* (essential requirement)”. In fact, temporality (no. 4 in his list) is required for, e.g., infectious diseases; a cause must precede an effect, as noted later (18). However, Hill was correct that in many cases, it is impossible to define the point in time when the disease covertly started. This holds for virtually all chronic diseases and especially for cancer. Meanwhile, an agent may act as a promoter and an existing tumor is stimulated to grow. Tumor promoters are not able to cause a tumor.

Methods

We used the Hill viewpoints to evaluate the causality on brain tumor risk from RF-EMF emitted from wireless phones. The evaluation was based on studies from the Hardell group (3–8) and Interphone (11, 12), the only studies with results on phone use for more than one decade. Other investigations with relevant data on, e.g., laboratory studies, and the incidence of brain tumors were included. More recent comprehensive reviews on this field of research than the IARC evaluation were also considered (8, 19, 20). Furthermore, some data are presented from a new case-control study on brain tumors by the Hardell group, including the time period 2007–2009 (21–23). For statistical methods used to calculate odds ratios (OR) and 95% confidence intervals (CIs), see previous publications from the Hardell group (3–8, 21–23) and Interphone (11, 12). Random-effects model was used for all meta-analyses using StataSE 12.1 (Stata/SE 12.1 for Windows; Stata Corp., College Station, TX, USA). Restricted cubic splines were used to visualize the relationship between latency and cumulative use of wireless phones and the risk of acoustic neuroma and malignant brain tumors, respectively. Adjustment was made for the same variables as in the logistic regression analysis. Four knots were used at the 5th, 35th, 65th, and 95th percentiles.

Results

Strength

The first criterion discussed by Hill is the strength of the association. The highest risk was found for ipsilateral glioma and acoustic neuroma in the highest exposure category based on cumulative use of mobile phones both in Hardell et al. (7, 8) and Interphone (11, 12) (Table 1). Thus, the meta-analysis yielded in total for ipsilateral glioma OR=1.22, 95% CI=0.58–2.55, which increases with cumulative mobile phone use of >1640 h to OR=2.29, 95% CI=1.56–3.37. In addition, regarding acoustic neuroma, the OR was highest for ipsilateral mobile phone use.

Table 1 OR and 95% CI for glioma and acoustic neuroma based on publications from the Hardell group (7, 8) and Interphone (11, 12).

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Glioma						
Ipsilateral						
All	279/374	1.78 (1.40–2.25)	677/753	0.84 (0.69–1.04)	956/1127	1.22 (0.58–2.55)
≥1640 h	29/21	2.94 (1.60–5.41)	100/62	1.96 (1.22–3.16)	129/83	2.29 (1.56–3.37)
Acoustic neuroma						
Ipsilateral						
All	80/374	1.78 (1.23–2.59)	271/471	0.77 (0.59–1.02)	351/845	1.16 (0.51–2.64)
≥1640 h	7/21	3.10 (1.21–7.95)	47/46	2.33 (1.23–4.40)	54/67	2.55 (1.50–4.40)

The numbers of exposed cases (Ca) and controls (Co) are given. The use of mobile phones and the risk for glioma and acoustic neuroma are localized on the same side of the brain (ipsilateral) where the mobile phone was mostly used. Results are presented for all use and cumulative use ≥1640 h.

Consistency

Similar results have been found in different studies. As can be seen in Table 2, the results for glioma are similar in Hardell et al. (7) and Interphone (11) when the same

inclusion criteria were used. The results by Hardell et al. (4) were recalculated using the same age group, 30–59 years, as in the Interphone study. Cordless phone use was excluded, and such use was included in the “unexposed” group as in the Interphone study. Note that the handheld

Table 2 OR and 95% CI for glioma in the Interphone study (11) compared with the Hardell group (4, 7).

	Hardell group				Interphone	
	20–80 (All)	20–59	30–59	30–59, Cordless among unexposed	30–59	30–59, Appendix 2
Latency ≥10 years						
Ca/Co	88/99	57/74	56/74	56/74	252/232	190/150
OR	2.26	2.15	1.96	1.79	0.98	2.18
95% CI	1.60–3.19	1.41–3.29	1.27–3.01	1.19–2.70	0.76–1.26	1.43–3.31
Latency ≥10 years, ipsilateral						
Ca/Co	57/45	36/30	35/30	35/30	108/82	NR
OR	2.84	2.70	2.48	2.29	1.21	
95% CI	1.82–4.44	1.54–4.73	1.40–4.38	1.33–3.97	0.82–1.80	
Latency ≥10 years, contralateral						
Ca/Co	29/29	20/24	20/24	20/24	49/56	NR
OR	2.18	2.04	1.96	1.71	0.70	
95% CI	1.24–3.85	1.04–4.00	0.995–3.87	0.89–3.28	0.42–1.15	
Cumulative use ≥1640 h						
Ca/Co	42/43	32/37	29/37	29/37	210/154	160/113
OR	2.31	2.23	1.89	1.75	1.40	1.82
95% CI	1.44–3.70	1.30–3.82	1.08–3.30	1.02–3.00	1.03–1.89	1.15–2.89
Cumulative use ≥1640 h, ipsilateral						
Ca/Co	29/21	22/18	20/18	20/18	100/62	NR
OR	2.94	2.71	2.32	2.18	1.96	
95% CI	1.60–5.41	1.36–5.42	1.14–4.73	1.09–4.35	1.22–3.16	
Cumulative use ≥1640 h, contralateral						
Ca/Co	12/12	9/11	8/11	8/11	39/31	NR
OR	2.10	1.99	1.73	1.48	1.25	
95% CI	0.90–4.90	0.77–5.16	0.65–4.63	0.57–3.87	0.64–2.42	

The numbers of cases (Ca) and controls (Co) are given. NR, not reported. Note that >10-year latency were used in the Hardell group studies and contralateral was defined as <50% use of tumor side. Unexposed in the Interphone study (Appendix 2): latency 1–1.9 years; unexposed in Hardell et al.: no use or latency ≤1 year.

cordless phone emits RF-EMF when used, which cannot be neglected (24). The risk would be biased toward unity by including the use of cordless phones in the “unexposed” category. Also excluding the youngest and oldest age groups, as in the Interphone study, may preclude the possibility to find an increased risk (8). The youngest persons may be more sensitive than older ones; in fact, we found the highest risk for glioma and acoustic neuroma in cases with first use of a wireless phone before 20 years old (8). The prevalence of mobile phone use is highest in the age group 30–59 years according to our findings. Excluding older cases diminishes the possibility to find an increased risk, assuming a reasonable latency time. The peak incidence of most brain tumors is at an older age, between 45 and 75 years of age, with median survival of <1 year for glioblastoma (25). In a case series from Canada, all brain tumors showed a bimodal age distribution with one peak in the 0–4 age group and the other in the 60–69 age group (26). It is concluded that, using the same criteria, there is consistency between the Hardell group and Interphone results.

Specificity

The anatomic areas of the brain that absorb the highest wireless phone radiation, e.g., the temporal lobe (9, 10), have the highest risk. Thus, in the latency group ≥10 years, the meta-analyses of Hardell et al. (5, 7) and Interphone (11, 12) gave in total OR=1.48, 95% CI=0.65–3.35, increasing to OR=1.71, 95% CI=1.04–2.26, for glioma in the temporal lobe

(Table 3). The meta-analysis gave for acoustic neuroma with latency ≥10 years OR=1.46, 95% CI=0.39–5.47, in total and OR=1.81, 95% CI=0.73–4.45, for ipsilateral use of mobile phones. For ipsilateral acoustic neuroma and cumulative use of mobile phones ≥1640 h, the meta-analysis gave OR=2.55, 95% CI=1.50–4.40 [data not in table, see Hardell et al. (8)]. Regarding acoustic neuroma, reversed causality might be possible. In some of the earlier Interphone studies of the relationship between mobile phone use and acoustic neuroma, there were some indications that because of hearing problems, there is a switching of the ear usually used, thus reducing ipsilateral risk.

Furthermore, there is specificity regarding tumor type. Both the Hardell group and Interphone found increased risk for glioma and acoustic neuroma but not for meningioma in the same sets of studies (3, 4, 11, 12, 21–23).

Temporality

Those with most years since first use have the highest risk, i.e., an effect of time since first use (latency). This is illustrated in Table 4 in studies from the Hardell group. For the study period 2007–2009, OR=1.7, 95% CI=1.04–2.8, was calculated in total for malignant brain tumors, increasing to OR=2.2, 95% CI=1.3–3.8 with latency >20 years (see also Figure 1) (21). The results for acoustic neuroma were based on the study periods 1997–2003 and 2007–2009 (22). Highest risk was calculated in the >20-year-latency group, yielding OR=4.4, 95% CI=2.2–9.0 (see Figure 2). An increased risk with increasing latency may support temporality. It should

Table 3 OR and 95% CI for glioma and acoustic neuroma and mobile phone use in Hardell et al. (5, 7) and Interphone (11, 12).

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Glioma						
Latency ≥1 year						
All	432/900	1.32 (1.09–1.61)	1666/1894	0.81 (0.70–0.94)	2098/2794	1.03 (0.64–1.66)
Temporal lobe	116/900	1.30 (0.92–1.83)	509/568	0.86 (0.66–1.13)	625/1468	1.04 (0.70–1.56)
Latency ≥10 years						
All	88/99	2.26 (1.60–3.19)	252/232	0.98 (0.76–1.26)	340/331	1.48 (0.65–3.35)
Temporal lobe	28/99	2.26 (1.32–3.86)	94/69	1.36 (0.88–2.11)	122/168	1.71 (1.04–2.81)
Acoustic neuroma						
Latency ≥1 year						
All	130/900	1.66 (1.20–2.28)	643/1308	0.85 (0.69–1.04)	773/2208	1.17 (0.61–2.26)
Ipsilateral	80/374	1.78 (1.23–2.59)	271/471	0.77 (0.59–1.02)	351/845	1.16 (0.51–2.64)
Latency ≥10 years						
All	20/99	2.93 (1.57–5.46)	68/141	0.76 (0.52–1.11)	88/240	1.46 (0.39–5.47)
Ipsilateral	13/45	2.97 (1.42–6.21)	44/52	1.18 (0.69–2.04)	57/97	1.81 (0.73–4.45)

The numbers of cases (Ca) and controls (Co) are given.

Table 4 OR and 95% CI for malignant brain tumors (n=593; 1368 controls) and acoustic neuroma (n=316; 3530 controls): Hardell group studies (21, 22).

Wireless phones	All		>20-Year latency	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Malignant brain tumors	571/1261	1.7 (1.04–2.8)	82/125	2.2 (1.3–3.8)
Acoustic neuroma	227/2472	1.5 (1.1–2.0)	14/126	4.4 (2.2–9.0)

The numbers of cases (Ca) and controls (Co) are given.

be noted that Interphone did find only weak evidence for increased risks with increased latency.

Biologic gradient

There is a clear dose-response effect, i.e., higher cumulative use in hours of wireless phones gives a higher risk with statistically significant trend in the Hardell group studies. In the recent study on malignant brain tumors (21), the highest risk was calculated in the fourth quartile, >2376 h, of mobile phone and cordless phone use (Table 5). This amount of time corresponds to about 40 min of wireless phone use per day for 10 years. For mobile phone use, OR=2.8, 95% CI=1.6–4.8 (p, trend=0.0001), and for cordless phone use, OR=3.1, 95% CI=1.8–5.5 (p, trend <0.0001) were calculated in the fourth quartile. Figure 3 illustrates the dose-response effect. Also, for acoustic neuroma, the

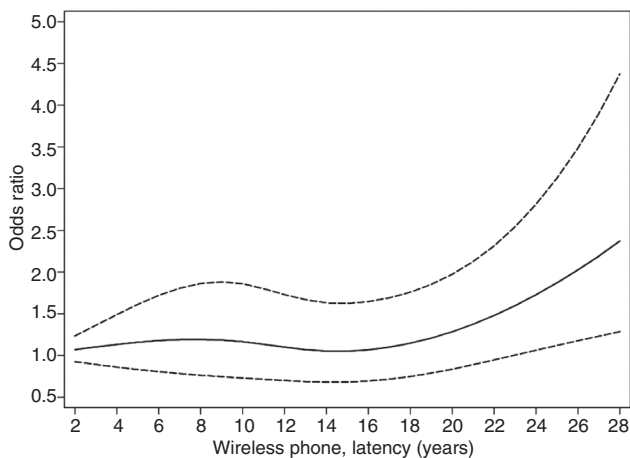


Figure 1 Restricted cubic spline plot of the relationship between latency of wireless phone use and malignant brain tumors (21). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

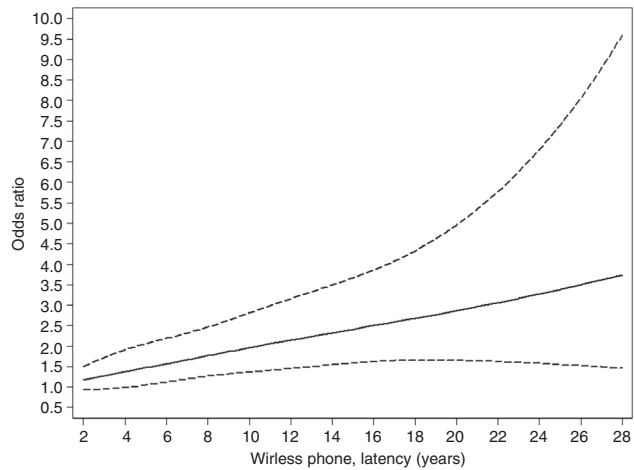


Figure 2 Restricted cubic spline plot of the relationship between latency of wireless phone use and acoustic neuroma (22). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

highest risk was found in the fourth quartile of cumulative use (>1486 h), yielding OR=2.2, 95% CI=1.5–3.4 in total (p, trend=0.03) [see Hardell et al. (22) and Figure 4].

In contrast, Interphone, although reporting a significant OR for the highest decile of hours of use, did not find a dose-response relationship for glioma (11). However, it should be noted that according to Appendix 2, with few exceptions, all ORs were >1.0 for glioma in contrast to meningioma. The highest ORs for glioma were found in one of the two highest exposure categories for time since the start of regular use, cumulative call time, and cumulative number of calls. The greatest increase was with increasing time since the start of use of mobile phone. A risk of brain tumors in relation to estimated RF dose from mobile phones in joules per kilogram was reported from five Interphone countries (27). A dose-response relationship for exposure 7+ years ago was reported.

Plausibility

An increase in both single- and/or double-strand breaks of DNA has been detected in humans (28), animal models (29–31), and cell cultures (32, 33). RF-EMF may stimulate reactive oxygen species (ROS) generation both in vivo (34) and in vitro (35). The formation of ROS is considered to be one of the primary mechanisms that are involved in the bio-effects that are mediated by RF-EMF exposure (36).

In a study using a mouse spermatocyte-derived cell line, it was demonstrated that RF-EMF exposure can

Table 5 OR and 95% CI for malignant brain tumors (n=593, 1368 controls) based on Hardell et al. (21).

Quartile	Mobile phone, total			Cordless phone			Wireless phone		
	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co
First quartile	1.4	0.8–2.3	190/587	1.3	0.8–2.2	164/434	1.5	0.9–2.5	108/317
Second quartile	1.7	1.02–3.0	126/261	1.7	1.01–3.0	120/278	1.4	0.8–2.4	110/314
Third quartile	1.5	0.9–2.7	95/210	2.1	1.2–3.7	98/194	1.7	1.003–2.9	137/315
Fourth quartile	2.8	1.6–4.8	137/159	3.1	1.8–5.5	79/109	2.5	1.5–4.2	216/315
p, Trend	0.0001			<0.0001			0.0001		

The numbers of exposed cases (Ca) and controls (Co) are given. First quartile, >39–405 h; second quartile, 406–1091 h; third quartile, 1092–2376 h; fourth quartile, >2376 h according to cumulative use among controls.

increase ROS production and subsequently induce the formation of oxidative base damage as evaluated by FPG-comet assay and 8-oxoG formation (37). To further elucidate the central role of ROS in RF-EMF exposure-induced DNA base damage, the authors used α -tocopherol pretreatment to antagonize the oxidation of ROS; α -tocopherol is an important lipophilic antioxidant that can inactivate harmful ROS. The protective role of α -tocopherol pretreatment confirmed that ROS are involved in RF exposure-induced DNA base damage (37).

However, these studies do not provide a biologic mechanism behind the influence of RF-EMF on brain tumors. Hill pointed out that biologic plausibility cannot be demanded because of the dependency on the limited knowledge of the day. Causality would be strongly supported if rather specific mutations should be demonstrated. Unfortunately, there are currently no studies that address this issue.

Coherence

Brain and nervous system cancer rates, potential confounders, and environmental risk factors were studied in 165 of 208 countries using ecologic data (38). The only exogenous risk factor consistently associated with higher incidence was the penetration of rate of mobile/cellular telecommunication subscriptions. According to these ecologic results, the latency period is at least 11–12 years but probably more than 20 years.

The incidence of brain tumor has been studied in different countries. An increasing incidence of brain tumors, especially of the type that would be expected based on epidemiologic results (glioblastoma multiforme), in the most exposed parts of the brain (temporal and adjacent lobes) has been shown. Such studies are listed below and are more discussed elsewhere (8).

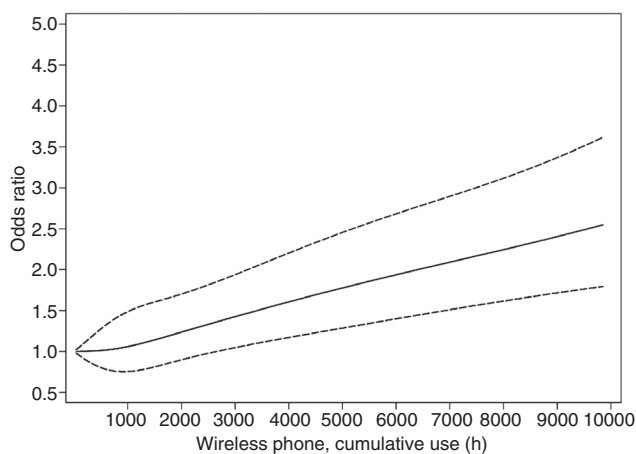


Figure 3 Restricted cubic spline plot of the relationship between cumulative use of wireless phones and malignant brain tumors (21). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

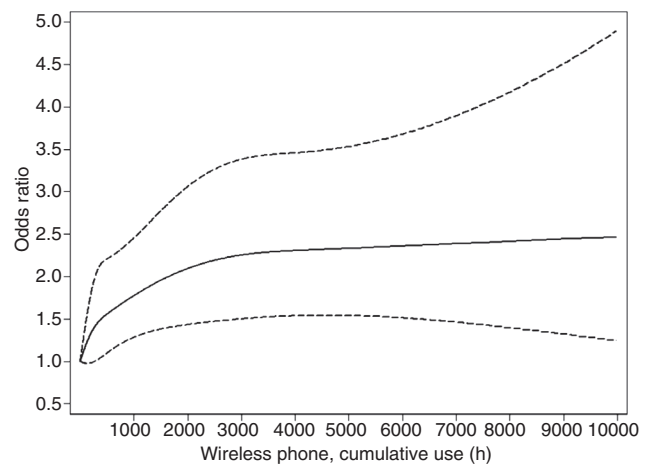


Figure 4 Restricted cubic spline plot of the relationship between cumulative use of wireless phones and acoustic neuroma (22). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

- United States: High-grade glioma (1992–2008): SEER annual percentage change (APC), +0.64%, 95% CI=+0.33 to +0.95% (39) Microscopically confirmed glioblastoma multiforme (1992–2006): SEER APC, +2.4% to +3.0% ($p \leq 0.001$) (frontal lobe), +1.3% to +2.3% ($p \leq 0.027$) (temporal lobe), across all registries (40). In the parietal and occipital lobes or in overlapping lobes, no statistically significant changes in incidence were seen.
- England: Brain tumors (majority, glioma; 1998–2007): increasing incidence in the temporal lobe for men and women ($p < 0.01$) (41) Malignant brain tumors (1998–2011): the age-standardized incidence rates for frontal and temporal lobe tumors in England rose at an average annual percentage change (AAPC) of +3.7%, 95% CI=+2.9% to +4.6% ($p < 0.0001$). The overall rates for all (C71) malignant tumors increased slightly. The results show that the pattern of change in incidence over time is statistically significant different for frontal and temporal lobe tumors compared with all other brain tumors (Alasdair Philips, Powerwatch, UK, personal communication, to be published).
- Australia: Malignant brain tumors (2000–2008): APC, +3.9%, 95% CI=+2.4% to +5.4% (42).
- Denmark: Brain and central nervous system tumors (2000–2009): men: APC, +2.7%, 95% CI=+1.1% to +4.3%; women: APC, +2.9%, 95% CI=+0.7% to +5.2% (15).
- Sweden: Astrocytoma (glioma; 2000–2007): age group >19 years: APC, +2.16%, 95% CI=+0.25% to +4.10% (5).

Experiment

The RF-EMF toxic effects on DNA mediated by ROS can be prevented by antioxidants, as shown in several studies. Antioxidants like melatonin and vitamins C and E can alleviate the ROS oxidation and apoptosis that are induced by RF-EMF in an animal model (43, 44). The protective role of α -tocopherol pretreatment in RF exposure-induced DNA base damage was recently demonstrated by Liu et al. (37). However, there is no direct relationship between these findings and brain tumor development because no useful animal model has been investigated so far that shows an increased brain tumor incidence after RF-EMF exposure that could be inhibited by antioxidants.

No studies exist on the risk for brain tumors among subjects that have used a wireless phone previously but are current nonusers. However, especially in the 1980s, mobile phone use was common in cars, with a fixed external antenna as the only mode of use. Such use has been

assessed in the Hardell group studies and considered to be no exposure to RF-EMF. For the study period 1 January 1997–30 June 2000, among 1429 responding cases and 1470 controls, 73 cases and 90 controls had always used the mobile phone with fixed external antenna and 1 additional control had always used a hands-free device (45). This yielded crude OR=0.8, 95% CI=0.6–1.1. Thus, this “experiment” showed that if the RF-EMF exposure from the mobile phone was protected, no increased risk was found.

Analogy

Animal carcinogenicity of RF-EMF was evaluated by the IARC Working Group in May 2011 (14, 16). There was limited evidence of carcinogenicity in experimental animals. Four classes of cancer bioassays in animals were reviewed. Although an increased cancer risk was found in some studies, it was concluded that there was no consistent pattern of increased risk in seven 2-year cancer bioassays, 12 studies that used different tumor-prone animal models and 16 studies of promotion and initiation. Of six co-carcinogenesis studies involving five different animal models, four responses were reported (16). It should be mentioned that, for example, increased risk (initiation) or earlier development (promotion) of total cancer including malignant lymphoma (46), mammary tumors (47), skin cancer (48), and lymphoma (49) has been reported from RF-EMF exposure.

Discussion

Bradford Hill warned against the misuse of tests of statistical significance. He noted, “We must not be too ready to dismiss a cause-and-effect hypothesis merely on the ground that the observed association appears to be slight”. As noted by Kundi (50), the nine issues discussed by Hill were not intended to dismiss a factor as potentially causing a disease. However, the Hill criteria were used in an overall assessment of mobile phone use and brain cancer and other tumors by Repacholi et al. (51). The authors concluded, “In summary, none of the Hill criteria support a causal relationship between wireless phone use and brain cancer or other tumors in the areas of the head that most absorb the RF energy from wireless phones”. This conclusion goes far beyond what the authors studied using less reliable methods. For example, they claimed that the use of “wireless phones” was assessed, although only mobile phones were considered and not cordless desktop phones. There are several other reasons to regard this article as less

informative. For example, the Interphone study on acoustic neuroma (12) was not included, although it was available at that time, with partly the same authors. In addition, the article by Cardis et al. (27) on risk of brain tumors in relation to estimated RF dose from mobile phones was omitted despite being available on line (27). Furthermore, no analyses were performed on ipsilateral or contralateral mobile phone use. The authors used the Interphone exposure criteria for effect estimates without considering our definition that was readily available in our publications and also discussed in detail elsewhere (7, 52). The Danish cohort study on mobile phone subscribers (13) was included, although several methodologic shortcomings including the lack of individual exposure data were inherent (15).

Regarding the strength of evidence, there is clearly an increased risk for glioma and acoustic neuroma in the highest exposure category of cumulative use of mobile phones both in the Hardell group studies and Interphone.

Consistency can only be answered by a repetition of the circumstances and observations both by the same research group and other investigators. According to Table 2 and the IARC evaluation (14, 16), the results of increased risk regarding mobile phone use and risk of glioma and acoustic neuroma are similar in the Hardell group and Interphone studies. Unfortunately, Interphone has not published data on cordless phone use, although the Hardell group has published similar results as for mobile phones. Hill also gives an interesting remark that is an answer to those scientists who insist that every positive study must be replicated, "Once again looking at the obverse of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions". However, in this case, results have been repeated and we are beyond that comment.

Hill writes, "if *specificity* exists we may be able to draw conclusions without hesitation". Table 3 presents increased risk for glioma in the temporal lobe with highest risk in the ≥ 10 -year latency group. For acoustic neuroma, the ipsilateral use of the mobile phone gives the highest risk. Moreover, the increased risk is specific for glioma and acoustic neuroma, whereas no increased risk was found for meningioma in the same studies (3, 8, 11, 23).

The fourth issue discussed by Hill deals with temporality. As exemplified in Table 4 and Figures 1 and 2, the risk increases with latency with highest OR for both malignant brain tumors and acoustic neuroma in the >20 -year-latency group. This is by far the longest latency (time from first use to diagnosis) that has been published.

With a biologic gradient or a dose-response curve, "then we should look most carefully for such evidence". Clearly, in Table 5, a statistically significant biologic

gradient is demonstrated for malignant brain tumors and the use of both mobile phones and cordless phones. This is visualized for wireless phone use in Figures 3 and 4.

Regarding plausibility, Hill states to those who insist that we wait until the exact causal mechanism is established: "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day". To those who insist on more in vivo or in vitro evidence, he states: "Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agents, the lack of such evidence cannot nullify the epidemiological observations in man". Regarding plausibility, as reviewed, oxidative stress is one important mechanism for adverse health effects from RF-EMF emissions. However, it should be pointed out that the exact mechanism for RF-EMF initiation of brain tumors has not been identified.

Bradford Hill discusses coherence among cigarette smoking, lung cancer, and the temporal rise in the two variables over the last generation. No doubt, there are now studies that show an increasing incidence of brain tumors. However, considering the long latency periods of decades in brain tumor genesis, it is currently too early to predict the real incidence increase. By now, there are also studies that show different patterns of incidence for malignant brain tumors in the frontal and temporal lobes compared with the other lobes. This highlights the need of improved data quality in the cancer registries on anatomic localization of the tumors.

Experiment with prevention is one option, especially in industry. Exposure to vinyl chloride and the increased risk of angiosarcoma in the liver is one example of prevention that gave a reduced number of victims (53). Antioxidants like melatonin and vitamins C and E can alleviate the ROS oxidation and apoptosis that are induced by RF-EMF in an animal model (37, 43, 44). No risk increase for brain tumors was found in subjects using external antenna in a car during mobile phone calls without any other wireless phone use (45).

As to the ninth point, analogy, Hill wrote, "In some circumstances it would be fair to judge by analogy". Although he does not discuss this in depth, animal studies may be useful. As stated by IARC, the evidence is limited in experimental animals for carcinogenesis.

Hill noted that, "However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.... If we are wrong in

deducing causation from associations no great harm will be done... All scientific work is incomplete... That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time". These wise rules should also be considered when RF-EMF from wireless phones is evaluated as a human carcinogen.

Conclusions

Based on Hill's viewpoints and his discussion on how these issues should be used, the conclusion of this review is that glioma and acoustic neuroma are caused

by RF-EMF emissions from wireless phones. According to the IARC Preamble (54), the classification should be group 1, i.e., "the agent is carcinogenic to humans", and urgent revision of current guidelines for exposure is needed.

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Cancer - Brain Tumors; Mobile phone use and brain tumour risk: early warnings, early actions? (Gee, Hardell Carlsberg) (Chapter 21 of Report: "Late lessons from early warnings: science, precaution"); 2013

21 Mobile phone use and brain tumour risk: early warnings, early actions?

Lennart Hardell, Michael Carlberg and David Gee ⁽¹⁾

In 2011 the World Health Organization's International Agency for Research on Cancer (IARC) categorised the radiation fields from mobile phones and other devices that emit similar non-ionizing electromagnetic fields (EMFs), as a Group 2B i.e. 'possible' human carcinogen. Nine years earlier IARC gave the same classification to the magnetic fields from overhead electric power lines.

The IARC decision on mobile phones was principally based on two sets of case-control human studies of possible links between mobile phone use and brain tumours: the IARC Interphone study and the Hardell group studies from Sweden. Both provided complementary and generally mutually supportive results. This chapter gives an account of the studies by these two groups — and others coming to different conclusions — as well as reviews and discussions leading up to the IARC decision in 2011. The chapter also describes how different groups have interpreted the authoritative IARC evaluation very differently.

There are by now several meta-analyses and reviews on mobile phones and brain tumours, which describe the challenges of doing epidemiology on this issue, the methodological limitations of the major studies published so far and the difficulties of interpreting their results.

It has been suggested that national incidence data on brain tumours could be used to qualify or disqualify the association between mobile phones and brain tumours observed in the case-control studies. However, in addition to methodological shortcomings, there might be other factors that influence the overall incidence rate such as changes in exposure to other risk factors for brain tumours that are unknown in descriptive studies. Cancer incidence depends on initiation, promotion and progression of the disease. As the mechanism for radiofrequency electromagnetic fields carcinogenesis is unclear, it supports the view that descriptive data on brain tumour incidence is of limited value.

The chapter points to mobile phone industry inertia in considering the various studies and taking the IARC carcinogenic classification into account and a failings from the media in providing the public with robust and consistent information on potential health risks. The IARC carcinogenic classification also appears not to have had any significant impact on governments' perceptions of their responsibilities to protect public health from this widespread source of radiation.

The benefits of mobile telecommunications are many but such benefits need to be accompanied by consideration of the possibility of widespread harms. Precautionary actions now to reduce head exposures would limit the size and seriousness of any brain tumour risk that may exist. Reducing exposures may also help to reduce the other possible harms that are not considered in this case study.

Evidence is increasing that workers with heavy long-term use of wireless phones who develop glioma or acoustic neuroma should be compensated. The first case in the world was established on 12 October 2012. The Italian Supreme Court affirmed a previous ruling that the Insurance Body for Work (INAIL) must grant worker's compensation to a businessman who had used wireless phones for 12 years and developed a neuroma in the brain.

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21.1 Introduction

On May 31, 2011 the WHO International Agency for Research on Cancer (IARC) categorised the radiation fields from mobile phones, and from other devices that emit similar non-ionizing electromagnetic fields (EMFs), as a Group 2B i.e. a 'possible' human carcinogen. Nine years earlier IARC had also classified the magnetic fields from overhead electric power lines as a Group 2B carcinogen.

The IARC decision on mobile phones was principally based on two sets of case-control human studies: the IARC Interphone study and the Hardell group studies from Sweden. Both provided complementary but generally mutually supportive results.

But why were these case-control studies into possible brain tumours from mobile phones initiated?

21.2 The Hardell group studies – 1999–2011

Sweden, along with Israel, was one of the first countries in the world to widely adopt wireless telecommunications technology. Analogue phones (NMT; Nordic Mobile Telephone System) were introduced in the early 1980's using both 450 and 900 Megahertz (MHz) fields. NMT 450 was used in Sweden since 1981 but closed down in 31 December, 2007, whereas NMT 900 operated during 1986–2000.

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1 800 MHz, started to operate in 1991 and now dominates the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1900/2100 MHz RF fields has been introduced worldwide since a few years, in Sweden in 2003. Currently the fourth generation, 4G, operating at 800/2 600 MHz, and Trunked Radio Communication (TETRA, 380–400 MHz) are being established in Sweden and elsewhere in Europe.

Desktop cordless phones (e.g. Digital Enhanced Cordless Telecommunications; DECT) have been used in Sweden since 1988, first using analogue 800–900 MHz RF fields, but since early 1990's the digital 1900 MHz system has been used.

Nowadays mobile phones are used more than landline phones in Sweden. (<http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf>).

The real increase in use and exposures to their radiation fields has been since the end of the 1990's. Wireless phones emit radiofrequency (RF) EMFs and the brain is the main target organ during use of the handheld phone (Cardis et al., 2008).

One of the author's (LH) interest in this research area was initiated by his involvement in a Swedish committee that evaluated cancer risks from exposure to extremely low frequency (ELF) EMFs from power lines. The conclusion was that there was an increased risk for childhood leukemia based on distance to power lines (Hardell et al., 1995). In 2002 IARC concluded that ELF electric and magnetic fields from power lines etc. is a human Group 2B carcinogen (IARC, 2002).

From a review of the literature there seemed to be an increased risk for brain tumours in the electronics industry (Hardell et al., 1995). It was decided to study it further in a case-control study. However, at that time there was also some media attention to a US lawsuit against cell phone industry companies.

It was alleged that repeated use of mobile phone had caused a fatal brain tumour in a woman. The head line in Los Angeles Times was '*Suit Over Cellular Radiation Raises Hazard Questions*' (Carlo and Schram, 2001). It was therefore decided to add questions on mobile phone use in the first of 4 linked case-control studies that are briefly described below.

This is followed by the results of the other major publications with some data on long-term use, the Interphone study, and the IARC evaluation of the RF and cancer evidence, and related responses and discussions.

The aim is not to give a thorough review of this research area, nor to deal with possible other effects of RF exposures which can be found in other publications including meta-analyses of the risk of brain tumours related to use of wireless phones (Hardell et al., 2006d; 2009; Myung et al., 2009; Kundi, 2009; Cardis and Sadetzki, 2011; Levis et al., 2011; IARC Monograph, in press).

21.3 First Hardell group study on mobile phone use and brain tumours – 1999

In 1999 the Hardell group in Sweden published results from their first case-control study on brain tumours and use of mobile phones (Hardell et al.,

1999a). In total 209 (90 %) of the cases and 425 (91 %) of the controls that fulfilled the inclusion criteria answered the mailed questionnaire. Overall no association between use of mobile phones and brain tumours was found.

A slightly increased (but not statistically significant) risk was found for analogue phone (NMT) use and for a *latency* period greater than 10 years, Odds Ratio (OR) = 1.20 (95 % Confidence Interval; CI = 0.56–2.59). For tumours located in the temporal ⁽²⁾, occipital or temporoparietal lobe areas of the brain an increased risk was found for ipsilateral ⁽³⁾ exposure, OR = 2.42 (95 % CI = 0.97–6.05) (Hardell et al., 1999a, 2001). However, all results were based on low numbers of exposed subjects and different histopathological types of brain tumours so no firm conclusions could be drawn. Furthermore, in this first study use of cordless phones was not included.

Authors of an Editorial in 2001, in commenting on a 'negative' US study (Inskip et al., 2001) that was published after the first Hardell et al. (1999a) study, stated that *...the use of cellular telephones does not detectably increase the risk of brain tumors*' and that *'This study allays fears raised by alarmist reports that the use of cellular telephones causes brain tumors* (Trichopoulos and Adami, 2001). This statement goes far beyond what was scientifically defensible. For example, among the 782 patients with brain tumours only 22 had 5 years or more of mobile phone use and no data with longer latencies were presented. The Editorial illustrates a common misconception which is that a 'non-positive' study is often assumed to be a 'negative' study when in fact the data do not support this assumption.

21.4 Second and third Hardell group studies — 2002–2006

This initial study by the Hardell group gave some support for an association between use of mobile phones and brain tumours. However, the results were based on low numbers especially regarding tumour type and long-term use. The first study was thus followed by two larger studies with cases diagnosed during the time period 1997–2003. The second study encompassed cases diagnosed during 1 January 1997 to 30 June 2000 and the third study 1 July 2000 to 31 December 2003. The methods were

the same including an identical questionnaire in both studies. Results for these two study periods were published separately (Hardell et al., 2002, 2005, 2006a), but here pooled results for the whole study period 1997–2003 are presented (Hardell et al., 2006b, 2006c; Hardell and Carlberg 2009). More details can be found in the different publications.

In short, all cases were reported to a cancer registry and had histopathological verification of tumour diagnosis. Both men and women aged 20–80 years at the time of diagnosis were included. Matched controls were identified from the Swedish Population Registry. The study included use of both mobile and cordless (DECT) phones (wireless phones), the latter an exposure which most other studies ignore ⁽⁴⁾. Also questions e.g. about occupational exposures were asked. Use of wireless phones was assessed by a self-administered questionnaire. The information was supplemented over the phone, if necessary.

The ear that had mostly been used during calls with mobile phone and/or cordless phone was assessed by separate questions; more than 50 % of the time for one side, or equally both sides. This information was checked during the supplementary phone call. Moreover every person that had used a wireless phone received after that a letter asking them again to specify the ear that had been used during phone calls and to what extent that side of the head was mostly used. There was a very good agreement for the result using these three methods to assess these data.

Separately, tumour localisation was defined by using medical records, such as computer tomography (CT) and/or magnetic resonance imaging (MRI). Use of mobile and cordless phones was defined as ipsilateral (more than 50 % of the time), equally ipsi/contralateral or contralateral (less than 50 %) in relation to tumour side. Calculation of cumulative hours of use over the years was based on information on first and last year of use (time period) and average number of minutes per day during that period. Use in a car with external antenna was disregarded as well as use of a handsfree device. A minimum latency period of one year was adopted. Hence, latency period and cumulative use for the different phone types could be defined.

⁽²⁾ A review of 110 phone models showed that exposure to radiations is generally higher in the temporal lobe, which is a part of the brain that is near to the ear, (Cardis et al., 2008).

⁽³⁾ i.e. the tumour appears on the side of head at which the phone is normally used.

⁽⁴⁾ The Interphone study (see Section 20.9) had some questions on cordless phone use at least in some countries but that information has never been properly analysed or published.

Box 21.1 Some concepts and tools for identifying cancer risks in human studies

OR: Odds ratio. The odds ratio is an estimate of the relative risk, showing how much more likely it is that someone who is exposed to a factor (e.g. cell phones) will develop an outcome (e.g. brain tumour) compared to someone who is not exposed. An OR of 1 indicates no risk, OR < 1 decreased risk and OR > 1 increased risk. For example, an OR of 1.5 indicates that those who are exposed have a 1.5 times higher risk of developing a disease compared to those who are not exposed.

SIR: Standardized incidence ratio. The SIR compares the observed number of cases in a specific population (e.g. cell phone subscribers) to the number of cases expected would the same rates apply as observed in a reference population (e.g. general population). A SIR of 1 indicates no risk, SIR < 1 decreased risk and SIR > 1 increased risk.

CI: Confidence interval. A confidence interval shows the uncertainty of the statistical estimate. In the case of OR and SIR, if the corresponding CI range does not cover 1.0, the result is considered **statistically significant**. Usually 95 % confidence intervals are reported indicating the range of the true OR/SIR with 95 % statistical confidence. The absence of 'statistical significance' can often be a weak guide to the strength of evidence for a risk compared to the power of a study to detect a risk ⁽⁵⁾.

Latency period. Time between first exposure and identification of the disease. For cancer, particularly the solid tumours like brain cancers in contrast to cancers of the blood, such as leukemia, the latency period can be from 15–45 years on average, depending on age at exposure, type and intensity of exposure ⁽⁶⁾ etc. This means that any study of cancer has to be at least as long as the average latent period for the tumour being studied before there will be any clear evidence of a cancer risk.

21.5 Fourth Hardell group study — 2010

In a review commissioned by the former Swedish Radiation Protection Agency (now called the Swedish Radiation Safety Authority) it was suggested that the exclusion of deceased cases was a source of bias in the Hardell group studies (Boice and McLaughlin, 2002). The scientific reason for this suggestion was not given.

As a response to that critique a fourth study was performed. This included the cases with a malignant brain tumour who had died before inclusion in the case-control studies 1997–2003. These cases represented patients with a poor prognosis, mostly with an astrocytoma grade IV tumour. Controls were selected from the Death Registry in Sweden.

Two groups of controls were included, one group consisted of controls that had died from other types

of malignant diseases than brain tumour and one group of controls that had died from other diseases than cancer. Relatives to both cases and controls were identified through the Swedish Population Registry at the Swedish Tax Agency. The study encompassed 464 cases and 464 controls that had died from a malignant disease and 463 controls with other causes of death. A similar questionnaire as in previous studies was used and exposure was assessed by a questionnaire sent to the next of kin to each deceased case and control.

Replies were obtained for 346 (75 %) cases, 343 (74 %) cancer controls and 276 (60 %) controls with other diseases. Use of mobile phones gave an increased risk, highest in the >10 years latency group yielding an OR of 2.4 (95 % CI = 1.4–4.1). The risk increased with cumulative number of life-time hours of use, being highest in the more than 2000 hours group who had an OR of 3.4 (95 % CI = 1.6–7.1).

- ⁽⁵⁾ See Sir Bradford Hill's classic epidemiology paper, 'The Environment and Disease: Association or Causation?' (Proceedings of the Royal Society of Medicine, 1965) where he warned not to overrate the value of statistical significance since it often led people to 'grasp the shadow and lose the substance' of what was in the data. See Chapter 26 on science for precautionary decision-making.
- ⁽⁶⁾ Stein, Y., Levy-Nativ, O., Richter, E.D., 'A sentinel case series of cancer patients with occupational exposures to electromagnetic non-ionising radiation and other agents', *Eur. J. Oncol.*, 2011, (16/1) 21–54. It has taken almost 50 years to be sure that the atomic bomb dropped on Japan in 1945 also caused brain cancers: the data before then were not clear or robust enough. (Shibata, Y. et al., 'Intercranial meningiomas among Nagasaki atomic bomb survivors', *Lancet*, 1994, (344) 1 770).

No clear association was found for use of cordless phones, although an OR of 1.7 (95 % CI = 0.8–3.4) was found in the group with more than 2000 hours cumulative use. This investigation confirmed the previous results of an association between mobile phones and malignant brain tumours (Hardell et al., 2010). It was concluded that the critique made by Boice and McLaughlin (2002) was scientifically unfounded.

21.6 Some Swedish responses to the Hardell group studies

The first publication on mobile phone use and brain tumour risk (Hardell et al., 1999a) was quickly followed by a letter to the journal (Ahlbom and Feychting, 1999). They suggested that selection bias of cases might have created the high response rate in the Hardell study. However, the critique was unfounded and easy to rebut (Hardell et al., 1999b). In all of the Hardell et al. studies there has usually been a high response rate to the oncologists who have been trained in cancer epidemiology. This applies as well to studies not related to mobile phone use.

Interestingly in the Swedish part of the Interphone studies, one of the authors (Anders Ahlbom) had stated, even before the study started, that an association between cellular telephones and brain tumours was *biologically bizarre* in an 'opinion' letter (Adami et al., 2001). Ahlbom's own work provided evidence for an association between exposure to magnetic fields from overhead power lines and childhood leukemia: an association that would also have to be regarded as *biologically bizarre* (Feychting and Ahlbom, 1993).

Maria Feychting, who participated in the Swedish part of the Interphone studies, queried whether '*the questions really were placed in the same way to cases and controls*' (Björkstén, 2006). Indeed they were in the Hardell studies, however, different methods do seem to have been used for the interviews with cases and controls in the Interphone study, for example, when bed-side interviews were done of cases only.

Meanwhile, the Hardell studies and other evidence of possible health risks from EMF inspired a group of scientists to summarise this evidence in their BioInitiative Report (BioInitiative Working Group, 2007). This had considerable impact in alerting many people to the emerging evidence of risks and to the presence of a small but growing minority

of experts who did not agree with the WHO EMF Project statements and other reports that there was no evidence of risk (e.g. of SCENIHR 2007).

The European Environment Agency (EEA), having produced a report *Late lessons from early warnings* (EEA, 2001) was invited by the Bioinitiative group to submit a chapter about the relevance of the 14 well known 'Late lessons' case studies to the emerging issue of EMF. Having considered the published evidence, the EEA decided it was timely to issue a guarded early warning about the possible risk of brain tumours from mobile phones in September 2007 (see Box 21.2).

21.7 A pooled analysis of the Hardell group studies

Pooled analysis of the two case-control studies on brain tumour cases (glioma, meningioma and acoustic neuroma (?), Table 21.1) diagnosed for the whole time period 1997–2003 was made and results were reported for both malignant (Hardell et al., 2006b) and benign (Hardell, 2006c) tumours. This was possible since the same methods were used in both studies with an identical questionnaire. In this presentation results for glioma in the fourth study were added (Hardell et al., 2010; Hardell et al., 2011a).

Latency was divided in three categories, > 1–5 year, > 5–10 year, and > 10 year from first use of a wireless phone until diagnosis. Both use of mobile and cordless phones gave an increased risk overall for **glioma**, highest in the latency group > 10 years, increasing further for *ipsilateral* use; mobile phone OR of 2.9 (95 % CI = 1.8–4.7) and cordless phone OR of 3.8 (95 % CI = 1.8–8.1). Highest OR was found in the > 10 year latency group for total wireless phone use as well.

Table 21.1 gives the same calculations for **meningioma** (n = 916). There was no consistent pattern of an increased risk, although highest risk was found for *ipsilateral* exposure in the > 10 year latency period, mobile phone OR = 1.6 (95 % CI = 0.9–2.9). Also ipsilateral use of cordless phone in the same latency category yielded an increased risk, OR = 3.0 (95 % CI = 1.3–7.2).

Regarding **acoustic neuroma** (n = 243) wireless phone use gave OR = 2.2 (95 % CI = 1.3–3.7) in the > 10 y latency period. *Ipsilateral* use gave higher risks than contralateral use for both mobile phone and cordless phone use.

(?) Studying especially long-term use and laterality.

21.8 Risks to children

Use of wireless phones is widespread among children and adolescents (Söderqvist et al., 2007, 2008). Children's brain absorbs higher radiation from RF-EMF emissions than adults (Cardis et al., 2008; Christ et al., 2010; Gandhi et al., 2012). This is due to the smaller head, thinner skull bone and higher conductivity of the brain tissue. The developing brain is more sensitive to toxins (Kheifets et al., 2005) and the brain is still developing until about 20 years of age (Dosenbach et al., 2010). The greater absorption of RF energy per unit of time, the greater sensitivity of their brain, and the longer lifetimes within which to develop a brain tumour leaves children at a higher risk than adults from mobile phone radiations.

Analyses of the Hardell group results revealed that first use before age of 20 is associated with the highest risk for glioma and acoustic neuroma, see Table 21.2 (Hardell, Carlberg, 2009).

Three age groups for first use of a wireless phone were used; < 20 years, 20–49 years and 50–80 years. For glioma, first use of a mobile phone < 20 y of age gave OR = 3.1 (95 % CI = 1.4–6.7). A similar pattern was found also for cordless phone use (data not shown). Also for acoustic neuroma the risk was highest in the youngest age group; OR = 5.0 (95 % CI = 1.5–16), but no conclusions could be drawn regarding cordless phones since only 1 case had first use before the age of 20 years. These ORs increased further for *ipsilateral* mobile phone use in the youngest age group; glioma OR = 4.4 (95 % CI = 1.3–15), acoustic neuroma OR = 6.8 (95 % CI = 1.4–3.4). No clear age dependent pattern of increased risk was found for meningioma.

There have been very few other studies of children and mobile phone use except the CEFALO study (Aydin et al., 2011) and that of the EU, Mobikids⁽⁶⁾, which is ongoing.

The multi-centre case-control study CEFALO, conducted in Denmark, Sweden, Norway, and Switzerland has been commented in detail by Söderqvist et al. (2011) since serious methodological problems exist as exemplified below.

In the summary of the study the authors wrote that they *did not observe that regular use of a mobile phone increased the risk for brain tumors*. This conclusion was accompanied by an editorial stating that the study

showed *no increased risk of brain tumors* (Boice and Tarone, 2011) as well as by a news release from the Karolinska Institute in Stockholm that the results of no increased risk were 'reassuring' (Karolinska Institute, 2011). However, the statements go far beyond what the study really showed.

For example the data collection and analyses of use of cordless phones was not valid. Use of cordless phones was assessed only *in the first 3 years* of use, a most peculiar definition for which the authors gave no explanation for or reference to. Furthermore, the study never considered wireless phone use, including both mobile and cordless phones, as an exposure category. IARC categorised wireless phone use as a relevant exposure group (Baan et al., 2011). Instead, Aydin et al. (2011) included use of cordless phones in the 'unexposed' category, so risk estimates for mobile phone use might therefore be underestimated. Similarly mobile phone use was included among the 'unexposed' when considering use of cordless phones and thereby potentially concealing an increased risk.

The study yielded a statistically non-significant increased risk for brain tumours among regular users of mobile phones, OR = 1.36 (95 % CI = 0.92–2.02). This OR increased somewhat with cumulative duration of subscriptions and duration of calls (Aydin et al., 2011). Only latency time of 5 years or more was presented with very few cases within this category. Further support of a true association was found in the results based on operator-recorded use for 62 cases and 101 controls, which for time since first subscription > 2.8 years yielded a statistically significant OR of 2.15 (95 % CI = 1.07–4.29) with a statistically significant trend ($p = 0.001$).

Although the authors do not emphasize that the results yielded an increased risk, the data indicate a moderately increased risk, in spite of low exposure, short latency period and limitations in study design and analyses. Certainly it cannot be used as reassuring evidence *against* an association, as discussed in the commentary (Söderqvist et al., 2011).

Unfortunately, the CEFALO study (Aydin et al., 2011) was published after the IARC meeting in May 2011. Had it been available at the IARC meeting it would have provided additional evidence to support the IARC conclusion that human exposure to RF-EMF is a group 2B carcinogen.

⁽⁶⁾ Contact: ecardis@creal.cat for details.

Box 21.2 The EEA early warnings on brain tumour from mobile phones, 2007–2011

'There are many examples of the failure to use the precautionary principle in the past, which have resulted in serious and often irreversible damage to health and environments. Appropriate, precautionary and proportionate actions taken now to avoid plausible and potentially serious threats to health from EMF are likely to be seen as prudent and wise from future perspectives' (EEA, 2007).

This early warning was updated in 2009 to include:

'The evidence for a head tumour risk from mobile phones, although still very limited, and much contested, is, unfortunately, stronger than two years ago when we first issued our early warning'.

The evidence is now strong enough, using the precautionary principle, to justify the following steps (EEA, 2009):

1. For governments, the mobile phone industry, and the public to take all **reasonable measures to reduce exposures to EMF, especially to radio frequencies from mobile phones, and particularly the exposures to children and young adults who seem to be most at risk from head tumours**. Such measures would include stopping the use of a mobile phone by placing it next to the brain. This can be achieved by the use of texting; hands free sets; and by the use of phones of an improved design which could generate less radiation and make it convenient to use hands free sets ⁽⁹⁾.
2. **To reconsider the scientific basis for the present EMF exposure standards which have serious limitations** such as reliance on the contested thermal effects paradigm; and simplistic assumptions about the complexities of radio frequency exposures.
3. To provide **effective labelling and warnings** about potential risks for users of mobile phones. Across the European Union, the vast majority (80 %) of citizens do not feel that they are informed on the existing protection framework relating to potential health risks of electromagnetic fields. 65 % of citizens say that they are not satisfied with the information they receive concerning the potential health risks linked to EMF. (Special Euro barometer report on EMF, Fieldwork Oct/Nov 2006, published 2007).
4. To **generate the funds needed to finance and organise the urgently needed research** into the health effects of phones and associated masts (base stations). **Such funds could include grants from industry and possibly a small levy on the purchase and or use of mobile phones**. This idea of a research levy is a practice that we think the US pioneered in the rubber industry with a research levy on rubber industry activities in the 1970s when lung and stomach cancer was an emerging problem for that industry. The research funds would be used by independent bodies ⁽¹⁰⁾ (http://latelessons.ew.eea.europa.eu/foi572324/statements/Benefits_of_mobile_phones_and_potential_hazards_of_EMF.doc).

This was updated in 2011 when evidence was presented to the Council of Europe hearing on mobile phones, February 2011 (EEA, 2011a).

⁽⁹⁾ The EEA has since noted, with some relief, what appears to be an increased use of hands free devices, particularly in the younger generation, due to enhanced applications.

⁽¹⁰⁾ The EEA has noted the increasing evidence of 'funding bias' in scientific research whereby results outcomes are strongly linked to source of funding. This observation is based on evidence from pharmaceuticals, tobacco, lead, asbestos, BPA and EMF, as well as on evidence from other fields such as cost-benefit analysis and transport construction project cost estimations.

Table 21.1 Odds ratio (OR) and 95 % confidence interval (CI) for glioma, meningioma and acoustic neuroma and use of wireless phones (mobile phones and/or cordless phones)

	Ipsilateral, > 10 year latency OR, CI	> 10 year latency OR, CI	Total, > 1 year latency OR, CI
Glioma (n = 1148)			
Wireless phone	-	2.1 1.6–2.8	1.3 1.1–1.5
Mobile phone	2.9 1.8–4.7	2.5 1.8–3.3	1.3 1.1–1.6
Cordless phone	3.8 1.8–8.1	1.7 1.1–2.6	1.3 1.1–1.6
Meningioma (n = 916)			
Wireless phone	-	1.4 0.97–2.0	1.0 0.9–1.2
Mobile phone	1.6 0.9–2.9	1.4 0.9–2.1	1.1 0.9–1.3
Cordless phone	3.0 1.3–7.2	1.6 0.9–2.8	1.1 0.9–1.4
Acoustic neuroma (n = 243)			
Wireless phone	-	2.2 1.3–3.7	1.5 1.1–2.0
Mobile phone	3.0 1.4–6.2	2.6 1.5–4.6	1.7 1.2–2.3
Cordless phone	2.3 0.6–8.8	1.0 0.3–2.9	1.5 1.04–2.0

Note: Bold = statistically significant. Number of controls = 2438 in analyses of glioma (living and deceased controls), 2162 for meningioma and acoustic neuroma (only living controls). Only living cases and controls included in analyses of ipsilateral use of mobile and cordless phones.

Adjustment was made for age, gender, socioeconomic-code and year of diagnosis. For glioma adjustment was also made for vital status.

Source: Hardell et al., 2006b, 2006c, 2010, 2011a.

Table 21.2 Odds ratio (OR) and 95 % confidence interval (CI) for glioma, meningioma and acoustic neuroma in different age groups for age at first use of a mobile phone

	Glioma (n = 1148) OR, (CI)	Meningioma (n = 916) OR, (CI)	Acoustic neuroma (n = 243) OR, (CI)
Mobile phone	1.3 (1.1–1.6)	1.1 (0.9–1.3)	1.7 (1.2–2.3)
< 20 years old	3.1 1.4–6.7	1.9 0.6–5.6	5.0 1.5–16
20–49 years old	1.4 1.1–1.7	1.3 0.99–1.6	2.0 1.3–2.9
≥ 50 years old	1.3 1.01–1.6	1.0 0.8–1.3	1.4 0.9–2.2

Note: Bold = statistically significant. Number of controls=2438 in analyses of glioma (living and deceased controls), 2162 for meningioma and acoustic neuroma (only living controls).

Adjustment was made for age, gender, socioeconomic-code, year of diagnosis. For glioma adjustment was also made for vital status.

Source: Hardell et al., 2006b, 2006c, 2010, 2011a.

21.9 The Interphone study 2000–2010: disagreements and delays

The Interphone study was an international collaboration on brain tumour risk and mobile phone use conducted under the guidance of IARC, which is an independent agency of WHO. The investigation was initiated by recommendations from several expert groups to study possible health effects of exposure to RF-fields (McKinlay, 1997; Cardis et al., 2007). It was conducted at 16 research centres in 13 countries during varying time periods between 2000 and 2004. It cost nearly EUR 20 million of which industry contributed 5.5 million (IARC, 2010) ⁽¹¹⁾.

Some of the separate country analyses of the Interphone study produced different results, with some being positive i.e. finding increased brain tumour risks, and some negative i.e. finding decreased risks, i.e. seemingly a 'protective' effect of the radiation.

The authors therefore found it hard to come to an agreed conclusion and there was a 4 year delay between publication of the country results and of the overall study results. One group reportedly thought that the Interphone study overall had found indications of a positive link between mobile phone use and brain tumours, especially when the results of the 10+ year exposure group were analysed separately. Another group thought that they had found no indication of a risk and that the apparent excess of brain tumour was an artifact of the study design and methodology. A third group could agree to neither position.

The publication of the overall Interphone results was finally initiated by the Director of IARC, Christopher Wild, who brokered sufficient agreement between the scientists to finally get the results published in May 2010.

No association between mobile phone use and meningioma was found in the overall Interphone results whereas subgroup analyses showed statistically significant increased risk for glioma in the highest exposure group, i.e. those who had used their mobile phones for 1 640 hours or more, which corresponds to about half an hour of use per day for ten years (Interphone Study Group, 2010), OR = 1.40 (95 % CI = 1.03–1.89). The risk increased further for ipsilateral exposure (OR = 1.96, 95 % CI = 1.22–3.16) and for tumours in

the most exposed part of the brain, the temporal lobe, (OR = 1.87, 95 % CI = 1.09–3.22) in the highest exposure group for glioma.

However, the compromise reached between the opposing scientists involved the juxtaposition of two contrasting sentences that were pointing in different directions: *There were suggestions of an increased risk of glioma, and much less so meningioma, at the highest exposure levels, for ipsilateral exposures and, for glioma, for tumours in the temporal lobe followed by ...biases and errors limit the strength of the conclusions we can draw from these analyses and prevent a causal [our emphasis] interpretation* (Interphone Study Group, 2010).

There was no explanation about how the strength of a link between a cause and an effect can vary from a 'scientific suspicion of risk' to a 'strong association' through 'reasonable certainty' and on to 'causality' which requires the strongest of evidence. This continuum in strengths of evidence, which was illustrated in Bradford Hill's paper written at the height of the tobacco and lung cancer controversy (Hill, 1965), was not explained in the Interphone paper. This meant that the media and the public could assume that 'not causal' meant 'no link' between mobile phones and brain tumours. Other epidemiologists did pick up this rather significant nuance.

In an Editorial accompanying the Interphone results (Saracci and Samet, 2010), published in the International Journal of Epidemiology, the main conclusion of the Interphone results, was described as *both elegant and oracular... (which) tolerates diametrically opposite readings*. They also pointed out several methodological reasons why the Interphone results were likely to have underestimated the risks, such as the short latency period since first exposures became widespread: less than 10 % of the Interphone cases had more than 10 years exposure.

None of the today's established carcinogens, including tobacco, could have been firmly identified as increasing risk in the first 10 years or so since first exposure.

The 'oracular' concluding sentences from the Interphone study therefore allowed the media to report opposite conclusions. For example, on 17 May, 2010 the UK Daily Telegraph reported that the Interphone study provided evidence of a brain tumour risk from mobile phones (<http://>

⁽¹¹⁾ The Hardell studies cost approximately EUR 410 000 and were financed by the Swedish Work Environment Fund, Cancer- och Allergifonden, Cancerhjälpen, Telia, Fondkistan, and the Örebro University Hospital Cancer Fund.

www.telegraph.co.uk/health/7729676/Half-an-hour-of-mobile-use-a-day-increases-brain-cancer-risk.html) whilst the BBC News reported on the same day that there was no risk (<http://news.bbc.co.uk/2/hi/health/8685839.stm>). This conflicting media reporting pattern was widely repeated elsewhere ⁽¹²⁾.

Further confusion for the public and policymakers followed as a result of the differences in the statements of the Interphone scientists reported in the media. For example, Microwave News reported on 17 May that Elisabeth Cardis, the coordinator of the Interphone study, thought that *Overall...the results show a real effect*; Bruce Armstrong, the Australian Interphone participant, thought that *It shows some indication of an increased risk of gliomas, but I cannot say this with certainty*; and Siegal Sadetzki from Israel thought the results had consistency in indicating a risk but, whilst not *strong enough for a causal* [our emphasis] *interpretation, they are sufficient to support precautionary policies* (<http://www.microwavenews.com/Interphone.Main.html>).

In contrast, another co-author, Feychting, thought, *the use of mobile phones for over ten years shows no increased risk of brain tumours* (http://www.i-sis.org.uk/EEA_Highlight_Mobile_Phone_Cancer_Risks.php) and Ahlbom, also from the Swedish Interphone part, told Chinese Television that *there is nothing in these data or in previous data, really, to indicate that there is any risk involved in this* (<http://www.youtube.com/watch?v=TllmreWZdoA>).

In later publications of Interphone data the estimated RF dose from mobile phone use in the tumour area was also associated with an increased risk for glioma in parts of the Interphone group. The OR increased with increasing total cumulative dose of specific energy (J/kg) absorbed at the estimated tumour centre for more than 7 years before diagnosis with an OR of 1.91 (95 % CI = 1.05–3.47) in the highest quintile of exposure (Cardis et al., 2011).

This important result, which for the first time linked amount of radiation absorbed (rather than just its proxy which is years of exposure/cumulative hours of use) to tumour induction, received very little media attention.

A similar study based on less sound methods was later published by another part of the Interphone study group, see below (Larjavaara et al., 2011).

Results have also now been published for **acoustic neuroma** (Interphone study group, 2011). An increased risk was found for start of *ipsilateral* mobile phone use ≥ 10 year before reference date and cumulative use ≥ 1640 h; OR = 3.74 (95 % CI = 1.58–8.83).

The total Interphone results for tumours of the parotid gland ⁽¹³⁾ have never been published. Since the IARC has now terminated the Interphone study ⁽¹⁴⁾ only the results from Sweden (Lönn et al., 2006) and Israel (Sadetzki et al., 2008) are available. Subgroup analyses that considered laterality (side of use and risk of tumour) and/or amount of use (cumulative hours) indicated increased risks. However, results from other studies do not indicate a consistent pattern of increased risk (Auvinen et al., 2002; Hardell et al., 2004; Duan et al., 2011; Söderqvist et al., 2012a). Results on long-term use are, however, scarce.

21.10 Some reviews and discussions of the Hardell group and Interphone studies

There are by now several meta-analyses and reviews on mobile phones and cancer and they describe the challenges of doing epidemiology on this issue, the methodological limitations of the major studies published so far and the difficulties of interpreting their results.

For example, several of the Interphone findings display differential misclassification of exposure due to observational and recall bias which would tend to underestimate the risk. There were low participation rates for both cases and controls in the Interphone studies, for example in some countries only about 50 % of the cases and about 40 % of the controls participated. This is to be compared with 90 % response rate for cases with malignant brain tumours, 88 % for benign and 89 % for controls in the Hardell-group studies on living subjects (Hardell et al., 2006b, 2006c). Deceased cases were included in the calculations of participation in Interphone, but in

⁽¹²⁾ The EEA had anticipated this confusion and had earlier proposed to IARC that the conflicting opinions of the different Interphone groups should be published alongside each other, with their different arguments and data interpretations clearly illustrated in the same scientific article. This would have helped the media and the public to better understand the reasons for the divergent views amongst the Interphone scientists. However, this suggestion was not adopted.

⁽¹³⁾ A tumour in a gland on the cheek in front of the ear.

⁽¹⁴⁾ According to the official website (<http://interphone.iarc.fr/>) the Interphone Study was completed in February 2012.

the Hardell studies deceased cases were included in a separate sub-study on malignant brain tumours.

About 40 % of the cases were interviewed at hospitals in the Interphone studies. Further, it was always known to the interviewer if it was a case or a control that was interviewed. Use of cordless phones was not properly assessed in the Interphone study, or at least not reported. Further discussion on these methodological points may be found elsewhere (Hardell et al., 2008; Kundi, 2009).

Myung et al. (2009) subsequently compared methods and results in all the published studies on the use of mobile phones and the risk for brain tumours. They concluded that the Hardell studies were of higher quality compared with the Interphone study based on the Interphone results from different countries that were then available.

However, one important issue was not covered in the Myung et al. (2009) review, namely that the Hardell group also assessed use of cordless phones in contrast to the Interphone study group. RF-EMF emissions from a cordless phone are of the same magnitude as that from a digital mobile phone, something that has been pointed out several times (Hardell et al., 2006d; Kundi, 2009; Redmayne et al., 2010). Moreover cordless phones are typically used for longer calls than mobile phones (Hardell et al., 2006b, 2006c). Including cordless phone use in the 'unexposed' group, as was done in the Interphone study, would bias estimates against a risk.

The use of bedside interviews of cases, as in the Interphone study, can be a major disadvantage and is ethically questionable. At that time the patient has not fully recovered from e.g. surgery, may not have been fully informed about the diagnosis, treatment and prognosis and may even be under sedation by drugs. In fact patients scored significantly lower than controls due to problems in recalling words (aphasia), problems with writing and drawing due to paralysis in the Danish part of Interphone (Christensen et al., 2005). Obviously observational bias could have been introduced thereby during these bedside interviews.

In contrast, the Hardell group cases received a postal questionnaire approximately 2 months after diagnosis and could give the answers in a relaxed manner, a situation similar to the controls. All cases and controls were later interviewed over the phone to verify and clarify different exposures. This was done blinded as to case or control status.

The possibility of recall and observational bias was investigated in the second case-control study by

Hardell et al. (2002). Use of a wireless phone was similar among cases and controls regardless if they reported a previous cancer or if a relative helped to fill in the questionnaire. Potential observational bias during phone interviews was analysed by comparing change of exposure in cases and controls after these interviews. No significant differences were found, showing that the results could not be explained by observational bias: for further details see discussion in that publication (Hardell et al., 2002). All interviews were performed by trained persons using structured instructions and protocols.

The article by Myung et al. was commented on by e.g. Rowley and Milligan (2010) representing the mobile phone industry. They claimed that the Interphone studies were independent of industry influence. However, the mobile phone industry provided 5.5 million euro for the Interphone study and additional funding was provided by the industry in some countries. Furthermore, according to the study protocol *Other parties may also be involved in the Study Group as observers or consultants. These may include representatives of industry, other concerned organisations... In addition, representatives of industry and other concerned organisations... shall be informed shortly (maximum of seven days) before publication, and before the scientific community and laymen have access to the study results (IARC, 2001).*

Rowley and Milligan claim that there is *evidence of selection, information, and recall bias, and unusually high reported participation rates* in the Hardell studies (Rowley and Milligan, 2010). These ad hoc statements are not substantiated by the authors or in their references. A high participation rate is a pre-requisite for high quality in case-control studies.

Other scientists have analysed the Hardell results more favourably (Kundi, 2009; Myung et al., 2009; Mead, 2009; Cardis and Sadetzki, 2011; Levis et al., 2011) and IARC relied mainly on the Hardell group and Interphone study group results for its evaluation of the RF evidence.

The Cardis review was particularly interesting as she was the coordinator of the Interphone study. In the review with Sadetzki, another Interphone study participant, they concluded, after a full discussion of the methodological strengths and weaknesses of the Hardell and Interphone studies, that:

It is not possible to evaluate the magnitude and direction of the different possible biases on the study results and to estimate the net effect of mobile phones on the risk of brain tumours. The overall balance of the above mentioned arguments,

however, suggest the existence of a possible association (i.e. between mobile phones and brain tumour).

They ended by concluding that:

Simple and low cost measures, such as the use of text messages, handsfree kits and/or the loudspeaker mode of the phone could substantially reduce exposure to the brain from mobile phones. Therefore, until definitive scientific answers are available, the adoption of such precautions, particularly among young people, is advisable (Cardis and Sadetzki, 2011, p. 170).

21.11 IARC evaluation of the carcinogenicity of RF-EMFs 2011

In 2011 IARC evaluated the carcinogenic effect to humans for RF-EMF emissions during a 8 days (24–31 May) meeting at Lyon in France. This included all sources of radiofrequency radiation, not only mobile and cordless phones. Regarding use of wireless phones all of the published studies by the Hardell group were included as well as overall results for Interphone (Interphone Study Group, 2010, 2011; Cardis et al., 2011). The results on glioma are similar in the Hardell group and Interphone studies if the same inclusion and exclusion criteria are used (Hardell et al., 2011b). This is in contrast to widespread claims that the results of the two sets of studies differed significantly.

The IARC Working Group consisted of 30 scientists⁽¹⁵⁾ representing four areas: 'animal cancer studies', 'epidemiology', 'exposure' and 'mechanistic and other relevant data'. The different expert groups had initially a draft written before the meeting by some of the experts. Further work was done in the expert groups and a final agreement, sentence by sentence, was obtained during plenary sessions with all experts participating.

The Working Group concluded that there is 'limited evidence in humans' for the carcinogenicity of RF-EMF, based on positive associations between glioma and acoustic neuroma and exposure to RF-EMF

from wireless phones. This conclusion was based on the Interphone study and the Hardell group studies. No conclusions could be drawn from the Danish cohort study on mobile phone subscribers due to considerable misclassification in exposure assessment (Baan et al., 2011).

The final conclusion was obtained by voting by all 30 scientists and there was a very large majority for the conclusion that RF-EMF radiation is 'possibly carcinogenic' to humans, Group 2B, based also on occupational studies.

21.12 Some responses to the IARC conclusion

It is interesting to see that even the authoritative IARC evaluation has been interpreted very differently by different groups.

*To date, no adverse health effects have been established as being caused by mobile phone use. This was stated in a fact sheet in June 2011 from WHO EMF Program after the IARC decision (<http://www.who.int/mediacentre/factsheets/fs193/en/>), and furthermore that *Tissue heating is the principal mechanism of interaction between radiofrequency energy and the human body* without acknowledging any of the non-thermal effects that could explain the evidence on brain tumours (Guiliani and Soffriti, 2010).*

Michael Milligan from the Mobile Manufacturers Forum (MMF) said:

...After reviewing the available scientific evidence, it is significant that IARC has concluded that RF electromagnetic fields are not a definite nor a probable human carcinogen... (http://www.mmfa.org/public/docs/eng/MMF_PR_310511_IARC.pdf).

Jack Rowley from GSM Association (GSMA) said:

...The IARC classification suggests that a hazard is possible but not likely... (<http://www.gsma.com/articles/gsma-statement-on-the-iarc-classification/17567/>).

⁽¹⁵⁾ David Gee of the EEA had been invited by IARC to join the group as 'a representative of your organization, rather than as an observer' (for a definition of representatives and observers, please see the Preamble: <http://monographs.iarc.fr/ENG/Preamble/currenta5participants0706.php>). However, a few days before the IARC meeting began the EEA wrote to IARC to say they were withdrawing because of further delays in publishing the full Interphone results and because of the intellectual bias of Ahlbom who was then the Chair of the epidemiology group for the meeting. The day before the meeting began Ahlbom was removed from the Chair by IARC as a result of a reported conflict of interest: and the meeting was also given part of the unpublished Interphone data. However, this was too late for the EEA to then participate.

Patrick Frostell from the Federation of Finnish Technology Industries (FFTI) said:

...IARC's classification is in line with the dominant interpretation of current research data, according to which radiofrequency electromagnetic fields are neither carcinogenic to humans nor probably carcinogenic to humans... (http://www.teknologiateollisuus.fi/en/news/announcements/2011-6/no-change-in-international-assessment-of-the-health-effects-of-mobile-phones).

Professor **Dariusz Leszczynski** from the Finnish Radiation and Nuclear Safety Authority (STUK) and member of the IARC expert panel wrote:

*Recent IARC evaluation of mobile phone radiation potential to cause cancer and classification of it as a 2B carcinogen has caused a stir of pro and contra opinions among the scientists, industry and news media. Unfortunately, the only outcome of this broad attention leads to only one — **confusion**. Regular mobile phone user, whether highly or not so highly educated, can only be **confused** by this flurry of contradictory opinions and spin-statements (http://betweenrockandhardplace.wordpress.com/2011/06/29/%e2%80%a2viva-confusion/).*

The Economist wrote:

...your correspondent thinks the whole brouhaha over mobile phones causing brain cancer is monumentally irrelevant compared with all the other things there are to worry about (http://www.economist.com/blogs/babbage/2011/06/mobile-phones-and-health).

Microwave News has followed this area for a long time. Much of the whole IARC story and the aftermath can be found at its website, for example regarding ICNIRP's standpoint:

ICNIRP is a self-perpetuating group that declines to disclose its finances. Its Standing Committee on Epidemiology, which wrote the new commentary, has only welcomed the like-minded. Its previous chairman, Anders Ahlbom, has also registered his

opinion that cell phone tumor risks are nonexistent. (He was the lead author of the last ICNIRP review of cell phones and cancer.) Another former member, Maria Blettner, was the lone dissenting voice in the final vote of the IARC working group. Both Blettner and Ahlbom worked on Interphone (http://www.microwavenews.com/ICNIRP-Interphone.html).

Perhaps even IARC has contributed to this confusion by seeming to agree with the largely non-positive but much criticized Danish cohort study, see below (http://www.microwavenews.com).

No doubt the IARC decision started a world-wide spinning machine perhaps similar to the one launched by the tobacco industry when IARC was studying and evaluating passive smoking as a carcinogen in the 1990s (Ong and Glanz, 2000) ⁽¹⁶⁾. Sowing confusion and 'manufacturing doubt' is a well known strategy used by the tobacco and other industries (Michaels, 2008; McGarity and Wagner, 2008; Oreskes and Conway, 2010).

21.13 Some further studies published since the IARC conclusion

The Nordic part of Interphone published a study relating brain tumour location to mobile phone radiation (Larjavaara et al., 2011). The results seemed to contradict the findings by Cardis et al. (2011) as discussed above, but used a different, less clear method. Only 42 cases had used the mobile phone for more than 10 years and no analysis was made of the highest exposed group with longest duration of use. Thus, this study is much less informative and less sophisticated than the one by Cardis et al. (2011).

In Denmark a cohort of mobile phone subscribers was designed and started in cooperation between The International Epidemiology Institute (IEI), Rockville, MD, USA, and the Danish Cancer Society. The cohort was established by grants from two Danish telecom operation companies (TeleDenmark Mobil and Sonafon), by IEI, and by the Danish Cancer Society. The source of money for the IEI has not been disclosed.

⁽¹⁶⁾ In the early 1990s the Philip Morris tobacco company feared that an IARC study and a possible IARC monograph on second-hand smoke would lead to increased restrictions in Europe so they spearheaded an inter-industry, three-prong strategy to subvert IARC's work. The scientific strategy attempted to undercut IARC's research and to develop industry-directed research to counter the anticipated findings. The communications strategy planned to shape opinion by manipulating the media and the public. The government strategy sought to prevent increased smoking restrictions. The IARC study cost USD 2 million over ten years; Philip Morris planned to spend USD 2 million in one year alone and up to USD 4 million on research (Ong and Glanz, 2000).

Box 21.3 IARC and its classifications of carcinogens

IARC evaluates the *hazard* from potential carcinogens, i.e. 'an agent that is capable of causing cancer under some circumstances', while a cancer *risk* is an estimate of the carcinogenic effects expected from an exposure to a cancer hazard. The IARC monographs are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title.

IARC has categorised nearly 1000 potentially carcinogenic **hazardous** agents, that it has studied over the last 40 years, into 5 classifications. These are differentiated by different strengths of evidence. In *descending order of strengths of evidence* they are: **Group 1**, which are '**established**' human carcinogens, such as asbestos, diesel engine exhaust, tobacco, and X-rays (*108 agents*); **Group 2A**, which are **probable** carcinogens, such as perchloroethylene (*64 agents*); **Group 2B**, which are **possible carcinogens**, such as other traffic fumes, lead, DDT and now radiofrequency electromagnetic fields, including mobile phones (*272 agents*); **Group 3**, where the agent is **not classifiable** because the evidence is inadequate and does not permit another classification (*508 agents*); and **Group 4**, where the agent is **probably not carcinogenic to humans**, based on fairly strong evidence *against* a cancer effect in both humans and animals (*1 agent*) (IARC, 2012).

It may be helpful to clarify the meaning of the particularly contentious groups. i.e. 2A and 2B.

IARC chooses 3 main different strengths of evidence when it is evaluating the different types of cancer evidence that may be available. The evidence evaluated comes mainly from humans; from animals; and from consideration of the biological mechanisms for cancer causation: this last can provide understanding about *how* carcinogens cause cancer, in contrast to *whether* they cause cancer.

The main strengths of evidence groups used by IARC are: 'sufficient', 'limited', and 'inadequate'. For example, while Group 1 consists of those agents where there is 'sufficient evidence of carcinogenicity' in humans; Group 2A includes those agents where there is 'limited evidence of cancer in humans' but 'sufficient evidence of cancer in animals'; and Group 2B, which is the radiofrequency EMF category, is those agents where there is 'limited evidence of cancer in humans and less than sufficient evidence in animals' and where 'chance, bias or confounding cannot be ruled out with reasonable confidence'. 'Evidence suggesting lack of carcinogenicity' is used for Group 4 (IARC, 2006, p. 19–20).

Different agents in the same classification group are evaluated on the basis of very different kinds of evidence and exposure conditions that are specific for each substance. Some 2B agents will be at the lower end of the probability range, others will be close to the nearly one in two probability and the rest are somewhere in between, depending on their very specific characteristics. By loosely lumping together several randomly chosen carcinogens from the 271 in Group 2B such as dry cleaning fumes and coffee, which invites comparison to mobile phones, journalists and others help to complicate the already difficult discussion about the likelihood of cancer risks. Each agent needs to be considered on its own evidence.

The first results from the Danish study on brain tumour risk among mobile phone subscribers were published in 2001 and updated in 2006 and 2011 (Johansen et al., 2001; Schüz et al., 2006, 2011; Frei et al., 2011). It included subjects from 1 January, 1982 until 31 December, 1995 identified from the computerized files of the two Danish operating companies, TeleDenmark Mobil and Sonafon. A total of 723 421 subscribers were identified but the initial cohort consisted of only 58 % of these subscribers.

The IARC working group's main reason for not using the Danish study as evidence for its evaluation was that it *could have resulted in considerable misclassification in exposure assessment* (Baan et al., 2011).

The authors of the Danish study have themselves pointed out the main causes of such considerable exposure misclassification (Frei et al., 2011): mobile phone subscription holders not using the phone were classified as 'exposed'; non-subscribers using the mobile phone were classified as 'unexposed'; corporate subscribers of mobile phones (200 507 people), which are likely to have been heavy users, were classified as 'unexposed'; persons with a mobile phone subscription later than 1995 (which is over 80 % of the Danish population) were classified as 'unexposed'; and many users of cordless phones, which Hardell et al. have linked to excess risks of brain cancers, were also classified as 'unexposed'.

Other limitations are the absence of analysis by laterality (the side of head where the phone is used in relation to the side of the tumour) and the complete absence of actual exposure data. These and other shortcomings in this cohort study have been discussed elsewhere in more detail (Ahlbom et al., 2007; Söderqvist et al., 2012b).

It is clear from these limitations that the authors conclusion that 'In this update of a large nationwide cohort study of mobile phone use, there were no increased risks of tumours of the central nervous system, providing little evidence for a causal association' is not soundly based (Frei et al., 2011).

21.14 Need for monitoring long term trends in country wide nervous system tumours

It has been suggested that overall incidence data on brain tumours for countries may be used to qualify or disqualify the association between mobile phones and brain tumours observed in the case-control studies (Aydin et al., 2011; Ahlbom and Feychting, 2011; Deltour et al., 2012; Little et al., 2012). In support of the findings that Frei et al. (2011) presented for Denmark, Ahlbom and Feychting (2011) refer to data on overall brain tumour incidence from the Swedish Cancer Registry (which does not show an overall increase in brain tumour incidence since the 1990s) rather than from the Danish Cancer Registry which would have been more relevant.

The quality of the Swedish Cancer Registry in reporting of central nervous system tumours, particularly high grade glioma, has been seriously questioned (Bergenheim et al., 2007; Barlow et al., 2009). In the Deltour et al. paper (2012) Sweden accounted for about 40 % of the population and cases. Thus, underreporting of brain tumour cases to the Swedish Cancer Register would make the conclusions in the Deltour et al. study less valid.

In Denmark a statistically significant increase in incidence rate per year for brain and central nervous system tumours (combined) was seen during 2000–2009, in men +2.7 % (95 % CI = 1.1 to 4.3) and in women + 2.9 % (95 % CI = 0.7 to 5.2) (NORDCAN). Recently updated results for brain and central nervous system tumours were released in Denmark. The age-standardized incidence of brain and central nervous system tumours increased by 40 % among men and by 29 % among women between 2001–2010 (Sundhedsstyrelsen, 2010).

A more recent news release based on the Danish Cancer Register states that during the last 10 years there has been an almost 4-fold increase in the incidence of the most malignant glioma type, glioblastoma (<http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftig+stigning+i+hjernesvulster.htm>). So far these incidence data are not generally available.

Little et al. (2012) studied the incidence rates of glioma during 1992–2008 in the United States and compared the results with odds ratios for glioma associated with mobile phone use in the 2010 Interphone publication (Interphone Study Group, 2010) and the Hardell group pooled results published in 2011 (Hardell et al., 2011a). However, an important methodological issue that was not stated in the abstract or in Figures, but can be found in the web appendix, is that observed rates were based on men aged 60–64 years from the Los Angeles SEER registry as the baseline category. These data were used to estimate rates in the entire dataset, men and women aged ≥ 18 years and all 12 SEER registries. Thereby numerous assumptions were made. The conclusion by Little et al. that 'Raised risk of glioma with mobile phone use, as reported by one (Swedish) study ... are not consistent with observed incidence trends in the US population data...' goes far beyond scientific evidence and what would be possible to show with the faulty methods used in the study. On the contrary, it is of interest that they in fact showed statistically significant yearly increasing incidence of high-grade glioma in the SEER data for 1992–2008, + 0.64 %, 95 % CI 0.33 to 0.95, a result not commented further by the research group.

Much care is needed when using *descriptive* data, as in Aydin et al. (2011), Deltour et al. (2012) and Little et al. (2012), to dismiss results from *analytical* epidemiology. In addition to methodological shortcomings, there might be other factors that influence the overall incidence rate such as changes in exposure to other risk factors for brain tumours that are unknown in descriptive studies. Cancer incidence depends on initiation, promotion and progression of the disease (Hazleton et al., 2005). As the mechanism for RF-EMF carcinogenesis is unclear it supports the view that descriptive data on brain tumour incidence is of limited value.

21.15 Concluding remarks

It is sometimes claimed by the telecommunications industry and others that:

- the scientific basis for the current ICNIRP limits for exposure to EMF is adequate to protect the public from cancer risks;
- that children are no more sensitive than adults to the RF from mobile phones;
- that there are no biologically significant effects from **non-thermal** levels of EMF, and
- that, if there are such effects, there are no acceptable mechanisms of action that could explain these effects.

However the recent 400-page review by the Ramazzini Institute and The International Commission for Electromagnetic Safety (ICEMS) provides a wealth of evidence on the non-thermal biological and ecological effects of EMF (Giuliani and Soffritti, 2010). The EEA summarised the main findings of this report in its evidence to the Council of Europe' hearing on RF and mobile phones in 2011 (EEA, 2011a, 2011b).

Results from the Hardell-group as well as from the Interphone group show an increased risk for glioma and acoustic neuroma associated with long term mobile phone use. Also use of cordless phones increases the risk when properly assessed and analysed. The risk is highest for ipsilateral exposure to the brain of RF-EMF emissions. Adolescents seem to be at higher risk than adults. For meningioma there is no consistent pattern of increased risk.

Furthermore, of interest is that in the same studies different results were obtained for different tumour types. This strongly argues against systematic bias as an explanation of the findings. In that case the results would have been similar regardless of tumour type.

The IARC conclusion that RF-EMF emissions overall, e.g. occupational and from wireless phones, are possibly carcinogenic to humans, Group 2B (Baan et al., 2011) has been questioned by e.g. members of ICNIRP (Swerdlow et al., 2011). That article appeared online 1 July, 2011, one month after the IARC decision, and concluded that *the trend in the accumulating evidence is increasingly against the hypotheses that mobile phone use can cause brain tumors in adults*. There has also been unfounded attacks on individual researchers as exemplified in this article, a pattern that repeats similar experiences in the asbestos, lead and tobacco histories. Published results on health effects are questioned by using obscure methods and citing single results out of context without considering the overall pattern.

There is a lack of investigating journalists who can produce nuanced reports in the media. Most journalists seem to make only reference to news reports or press releases without making their own evaluations or without seeming to have read the original articles. Many limitations of epidemiological studies are to be found in the text, but rarely in the abstract which is most often all that is read. Without accurate and reliable reporting in the media the public do not get a robust and consistent information on potential health risks to make their own judgements about how precautionary they should be.

It is remarkable that the IARC carcinogenic classification does not seem to have had any significant impact on governments' perceptions of their responsibilities to protect public health from this widespread source of radiation, especially given the ease with which exposures can be reduced (i.e. texting, handsfree devices and better phone design).

Independent research into the many unknowns about the biological and ecological effects of RF radiations are urgently needed, given the global exposure of over 5 billion people and many other species, especially those, like bees and some birds whose navigation systems are possibly being affected by such radiations (Balmori, 2005, 2009; Sharma and Kumar, 2010), and effects on breeding of wild birds (Everaert and Bauwens, 2007). Research could be in part funded by relevant industries from levies on phones and masts but used independent from their influence.

The benefits of mobile telecommunications are many, but, as with other case studies in the *Late lessons from early warnings* Volume 1 (EEA, 2001) and the present report, such benefits need not to be accompanied by the possibility of widespread harms. Precautionary actions now to reduce head exposures, as pointed out by the EEA in 2007, and many others since, would limit the size and seriousness of any brain tumour risk that may exist. Reducing exposures may also help to reduce the other possible harms that are not considered in this case study.

21.16 Epilogue

The Italian Supreme Court affirmed a previous ruling that the Insurance Body for Work (INAIL) must grant worker's compensation to a businessman who had used wireless phones for 12 years and developed a neurinoma in the brain (http://www.applelettrosmog.it/public/news.php?id_news=44;

<http://microwavenews.com/news-center/italian-supreme-court-affirms-tumor-risk>). He had used both mobile and cordless phones for five to six hours per day preferably on the same side as the tumour developed. The neurinoma was located in the trigeminal Gasser's ganglion in the brain. This 5th cranial nerve controls facial sensations and muscles. It is the same type of tumour as the acoustic neuroma in the 8th cranial nerve located in the similar area of the brain. Although neurinoma is a benign tumour it causes persistent disabling symptoms after treatment with neurological impairment that severely affects the daily life. The Italian case fulfils the criteria for a causal association; more than 10 years use of wireless phones, high cumulative exposure on the same side as the tumour appeared, and a tumour type that would be predicted based on previous research on use of wireless phones and brain tumour risk. No further appeal of the Supreme Court decision is possible.

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Real-world cell phone radiofrequency electromagnetic field exposures

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ABSTRACT

In 2011 the International Agency for Research on Cancer classified radiofrequency electromagnetic fields (RF EMF) from cell phones as possibly carcinogenic to humans. The National Toxicology Program and the Ramazzini Institute have both reported that RF EMF exposures significantly increase gliomas and Schwannomas of the heart in rodent studies. Recent studies indicate that RF EMF exposures from cell phones have negative impacts on animal cells and cognitive and/or behavioral development in children. Case-control epidemiological studies have found evidence for cell phone use and increased risk for glioma and localization of the glioma associated with the consistent exposure site of regular cell phone use. Understanding the exposure level, or power density, from RF EMF emitted by cell phones under real-world usage and signal reception conditions, as distinct from the published measurements of maximum Specific Absorption Rate values, may help cell phone users decide whether to take behavioral steps to reduce RF EMF exposure. Exposure measurements were conducted on phone models from four major mobile network operators (MNOs) in the USA for calls received under strong and weak reception signal conditions, near the phone face and at several distances up to 48 cm. RF EMF exposure from all phones was found to be greater under weak (1–2 display bars) than under strong (4–5 display bars) reception signal conditions by up to four orders of magnitude. Notably, RF EMF exposure levels under weak reception signal conditions at a distance of 48 cm from the phone were similar to or greater than those detected under strong reception signal conditions at a distance of 4 cm. Under weak reception signal conditions, power density reductions of up to 90% occurred at 16 cm typical for speaker phone or texting over the 4 cm near-ear exposure. The results of this investigation of second-generation (2G) technology suggest that reduced and precautionary use of cell phones under weak signal conditions could lower a user's RF EMF exposure by up to several orders of magnitude. Bluetooth headset power density exposures were 10–400 times lower than those of the cell phones to which they were connected and dependent on the headset rather than the connected phone. The results of this study informed the development of public health guidance regarding cell phone use.

1. Introduction

Worldwide cell phone usage has increased sharply in recent years. The number of wireless phone accounts in the United States increased from 33.8 million in 1995 to near 400 million in 2017 (CTIA, 2017). At the end of 2019, the number of cell phone accounts worldwide is expected to exceed five billion (Sawers, 2017). The substantial increase in cell phone usage has raised concerns about potential adverse health effects from long-term radiofrequency electromagnetic fields (RF EMF) exposures. There continues to be evidence that RF EMF exposure from cell phones has negative impacts on animal cells and cognitive and/or behavioral development in children (Zalata et al., 2015; Calvente et al., 2016). In 2011 the International Agency for Research on Cancer (IARC)

classified RF EMF from cell phones as possibly carcinogenic to humans (IARC, 2011). The National Toxicology Program (2018) and the Ramazzini Institute (Falcioni et al., 2018) have reported that both near-field and far-field RF EMF exposures significantly increase gliomas and Schwannomas of the heart in rodent studies. Case-control epidemiological studies have found evidence for cell phone use and increased risk for glioma (Coureau et al., 2014), as well as for glioma localization associated with the consistent exposure site of regular cell phone use (Grell et al., 2016). The IARC classification was based on limited evidence of carcinogenicity from the results of several epidemiological studies associating long-term cell phone use with increased risks of glioma, a malignant brain tumor, and of acoustic neuroma, a benign tumor of the acoustic nerve (IARC, 2011; Baan et al., 2011). Also,

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Table 1

FCC MPE Limits for the general population. Power density limits between 300 and 1500 MHz, dependent on operating frequency.

MPE Limits: General Population/Uncontrolled Exposure		
Frequency Range (MHz)	Power Density (mW/cm ²)	Averaging Time (min)
300–1500	Frequency/1500	30
1500–100,000	1.0	30

Federal Communications Commission, OET Bulletin 65 Supplement C Appendix A, p. 26.

several governmental agencies and public health organizations, in the U.S. and elsewhere, have issued official public health guidance on cell phone use to minimize RF EMF exposure (Health Canada, 2015; President's Cancer Panel, 2010; NHS, 2016; WHO, 2014).

In the U.S. the Federal Communications Commission (FCC) regulates RF intensity of exposure using Maximum Permissible Exposure (MPE) limits, as measured by power density in milliwatts per square centimeter (mW/cm²). General population MPE limits as given in Table 1 are based on measurements and standards developed by the National Council on Radiation Protection and Measurements (NCRP) and the Institute of Electrical and Electronics Engineers (IEEE) (Means and Chan, 2001). Maximum EMF from RF devices used in close proximity to the body (principally cell phones) is regulated using the Specific Absorption Rate (SAR), a measure of the rate of RF energy absorption by the body. The FCC MPE limits, and the NCRP and American National Standards Institute (ANSI)/IEEE limits on which they are based, are derived from exposure criteria quantified in terms of SARs. Measurements of SARs require a complex model laboratory system to simulate peak energy absorption at the highest cell phone exposure power density level. Peak SAR limits in watts per kilogram (W/kg) are determined for cell phones under maximum emission intensity rather than a range of more typical usage conditions (Table 2). In this study, we measured power density (the basis for the FCC's MPE limits) under different cell phone reception signal strength conditions designed to mimic typical real-world exposures. These measurements represent the fundamental RF EMF environmental exposure levels from the cell phone emission source rather than estimates of energy absorption by the body.

Previous studies have investigated cell phone RF power emissions under real-world use conditions during travel, when power control causes the transmitted level to vary in response to changes in signal strength received from the cell tower. European studies considering the Global System Mobile (GSM) transmission technology used in California also found the same power control inverse relationship between cell phone transmission level and the cell tower reception signal strength (Gati et al., 2009; Kuhn and Kuster, 2013; Wiart et al., 2000). This cell phone power control produces a temporary peak in transmission power at call initiation or cell tower handover during travel.

Previous measurements in the San Francisco Bay Area for MNOs using a number of second generation digital phones (2G) with GSM and CDMA cell phone technology reported a similar power control effect, with increasing cell phone transmission power when traveling due to reductions in reception signal strength (Kelsh et al., 2010).

Unlike these previous studies, this investigation was designed to

Table 2

FCC SAR Limits for the general population. Partial-Body SAR is the main limit discussed when considering cell phones.

SAR Limits: General Population/Uncontrolled Exposure (W/kg)		
Whole-Body	Partial-Body	Hands, Wrists, Feet and Ankles
0.08	1.6	4.0

Federal Communications Commission, OET Bulletin 65 Supplement C Appendix A, p. 27.

examine power output of a variety of phones under stationary conditions, providing laboratory-based comparisons of cell phone RF power densities that can be absorbed by the body under different reception signal strength conditions typical of normal use, without the power control changes associated with travel between cell towers. Unlike the SAR, which is a measure of the RF EMF interaction with laboratory surrogates for human tissue, power density represents an environmental measurement of the RF EMF exposure from the cell phone emission source (Usman et al., 2009).

2. Materials and methods

2.1. Cell phones tested

In this study, we tested twenty-two cell phones spanning seventeen models, six manufacturers, supported by four different Mobile Network Operators (MNOs) with different contract service plans, ranging from Go Phones (pay as you go) to data-capable plans. The phones included devices using second generation wireless mobile telecommunications GSM and CDMA technology during the period 2011–2013, representing RF EMF exposure before the widespread deployment of 3G and 4G technology. The MNOs are referred to in this report as MNOs A, B, C, and D. The majority of test phones were from MNOs A (n = 7) and B (n = 10), both of which had nearly equivalent numbers of subscribers, and substantially more than MNOs C (n = 3) and D (n = 2) (Dano, 2013). For comparison, the SAR value, body style, antenna type, and broadcast technology for each cell phone employed in the study is provided in Table 3.

2.2. Measurement instrument and test stand

Cell phone measurements were made using the EMR 300 Radiation Meter (Narda Safety Test Solutions, Hauppauge, NY, USA) with probe type 18 (100 kHz–3 GHz). The three-axis isotropic probe continuously cycles through all three orthogonal axes and displays an electric field value (E) in volts per meter (V/m) by integrating the values from all three axes. The typical measurement range is from 0.2 to 320 V/m, although the specific probe utilized provided reproducible levels as low as 0.1 V/m. The fundamental electric field measurements are then converted to power density (S) in milliwatts per square centimeter (mW/cm²), using Eq. (1) (Ulcek and Cleveland, 1997):

$$S = \frac{E^2}{377 \times 10^4} \quad (1)$$

where the impedance of free space constant (377 Ω) is multiplied by ten to yield mW/cm².

Cell phone EMF measurements were made with a test stand shown in Fig. 1, which utilized a non-conductive rail system made of fiberglass channel (Harrington Plastics: Aickinstrut, Chino, CA, USA), thereby avoiding measurement artifacts due to RF-induced electric fields within metal components. The rail system incorporated a cradle to elevate the EMR 300 in a fixed position so that the probe orientation toward the test cell phone would always be the same. Each phone was mounted in a universal cradle (iGrip, Pforzheim, Germany) designed to hold it in an orientation typical of use during calls. For each measurement the cradle elevation was adjusted to align the EMR fixed probe directly in line with the usual ear listening position on the cell phone face. Measurements at different distances between the cell phone and the EMR probe were made by moving the phone cradle horizontally along the rail system while maintaining the vertical alignment. Accurate measurements of the separation of the probe and cell phone under test provided for a high degree of position reproducibility in the power density measurements as a function of distance from the cell phone face.

Table 3

Phone details including SAR value, body style, antenna type, and technology.

Phone Code	SAR Value (W/kg)	Body Style	Antenna Type	Technology
A 1	1.14	Flip	Internal	CDMA: 850, 1900 MHz
A 2	1.46	Candy Bar	Internal	CDMA: 850, 1900 MHz
A 3	1.27	Flip	Internal	CDMA: 850, 1900 MHz
A 4	1.31	Candy Bar/Flip	Internal	CDMA: 850, 1900 MHz
A 5	0.78	Flip	Internal	CDMA: 850, 1900 MHz
A 6	1.31	Slider	Internal	CDMA: 850, 1900 MHz
A 7	1.14	Flip	Internal	CDMA: 850, 1900 MHz
B 1	1.14	Flip	External	GSM: 850, 1900 MHz
B 2	0.85	Candy Bar	Internal	GSM: 850, 1900 MHz
B 3	0.85	Candy Bar	Internal	GSM: 850, 1900 MHz
B 4	0.85	Candy Bar	Internal	GSM: 850, 1900 MHz
B 5	0.74	Flip	Internal	GSM: 850, 1900 MHz
B 6	1.47	Flip	Internal	GSM: 850, 1900 MHz
B 7	1.26	Slider	Internal	GSM: 850, 1900 MHz
B 8	1.29	Candy Bar	Internal	GSM: 850, 1900 MHz
B 9	1.29	Candy Bar	Internal	GSM: 850, 1900 MHz
B 10	0.95	Candy Bar	Internal	GSM: 850, 1900 MHz
C 1	0.54	Flip	Internal	GSM: 1700, 1900 MHz
C 2	0.49	Candy Bar/Slider	Internal	GSM: 1700, 1900 MHz
C 3	1.55	Candy Bar	Internal	GSM: 1700, 1900 MHz
D 1	1.43	Candy Bar	Internal	CDMA: 800, 1900 MHz
D 2	1.43	Candy Bar	Internal	CDMA: 800, 1900 MHz

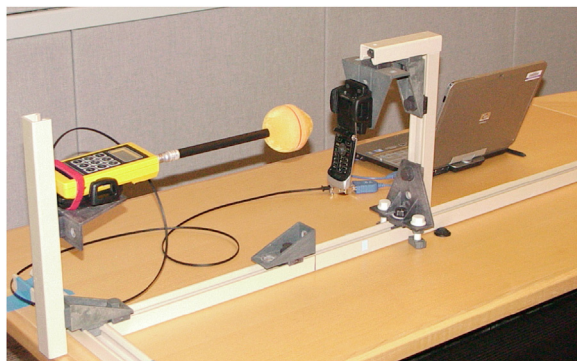


Fig. 1. Rail measurement system for cell phone and Bluetooth headset power density determinations. EMR 300 probe is held stationary while the cradle holding the device to be tested is positioned in height and distance. (As a potential RF EMF source, the laptop computer was moved away during measurements.)

2.3. Frequency analysis and far-field distance

An important consideration in determining cell phone power density is the near-field region around the source, where the RF EMF is nonuniform and is therefore difficult to measure. Conversely, farther from the source (far field), the RF EMF is homogeneous. In the current measurement application, the minimum distance away from the cell phone antenna for far-field measurements was calculated by Eq. (2), where d is the distance to the far field and λ is wavelength of the broadcast e-field. (WHO IPCS, 1993)

$$d = \frac{\lambda}{2\pi} \quad (2)$$

The operating frequencies in both strong and weak reception signal locations for cell phones from each MNO are given in Table 4, as determined using the frequency spectrum capability of the SRM 3006 Selective Radiation Meter (Narda Safety Test Solutions, Hauppauge, NY, USA). The technologies used by all four MNOs have the capability of operating on multiple frequency bands, as indicated in Table 4, with MNOs B and D operating on separate frequency bands under strong and weak signal conditions. Some MNOs utilize a shift to a lower frequency band in weak reception areas, since in general lower frequencies allow carriers to provide coverage over a larger area, while higher frequencies

Table 4

Operating frequencies, resulting wavelengths, and technology for each MNO under both strong and weak signal conditions.

MNO	Operating Frequency (MHz)		Wavelength (λ) (cm)		Technology
	Strong Signal	Weak Signal	Strong Signal	Weak Signal	
A	835	835	35.9	35.9	CDMA
B	1865	835	16.1	35.9	GSM
C	1890	1890	16.1	16.1	GSM
D	1850	835	16.1	35.1	CDMA

allow carriers to provide service to more customers in a smaller area. From Eq. (2), the minimum far-field distances for the measured frequencies of 835 MHz and 1865 MHz were 5.7 cm and 2.6 cm, respectively. Although the far-field distance varies somewhat with frequency, we used a distance of 4 cm from the cell phone surface normally placed against the ear to the probe forward surface for all measurements, to provide uniformity in data interpretation, as well as a basis for comparison of cell phone power density exposure under reproducible conditions. This is also consistent with the distance between the on-ear cell phone emission source and the exposure target organs, which are further away than the 3.5 cm length of the typical adult ear canal. We also used the SRM-3006 to verify the cell phone transmission frequency and the stability of the power density during the call, which permitted us to rely on the simplicity of operation afforded by the EMR 300 broadband instrument for cell phone transmission level measurements. EMR 300 measurements of cell phones under weak signal conditions were within five percent of the more sensitive SRM 3006 spectrometer.

2.4. Cell phone power density with source distance

Power density levels were determined as a function of distance from test cell phones in both strong and weak reception signal conditions, using the non-conductive rail system shown in Fig. 1. Measurements were made at the minimum of 4 cm from the cell phone face to the probe forward surface, and at increasing distances up to a maximum of 48 cm. At every distance, three measurements consisting of 75 data points each (obtained during contiguous 0.4 s intervals, for a total of 30 s) were completed for each cell phone during the incoming call connected mode. To account for other detectable sources of RF EMF,

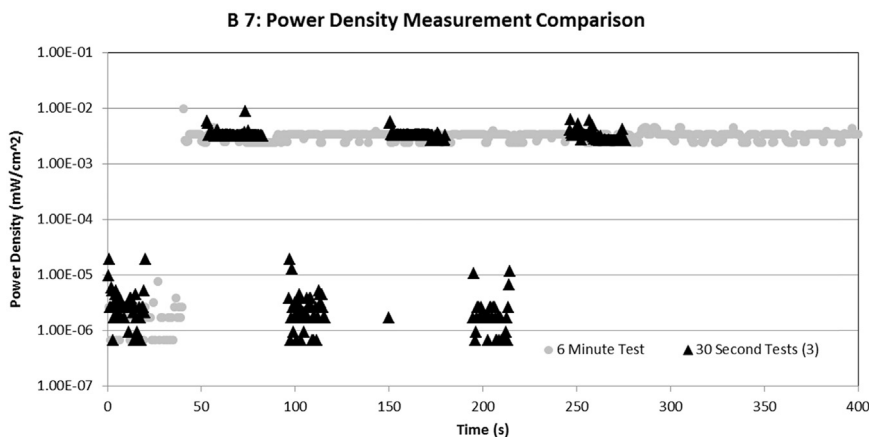


Fig. 2. Comparison of phone B 7 when measured over a six minute period and 30 s periods.

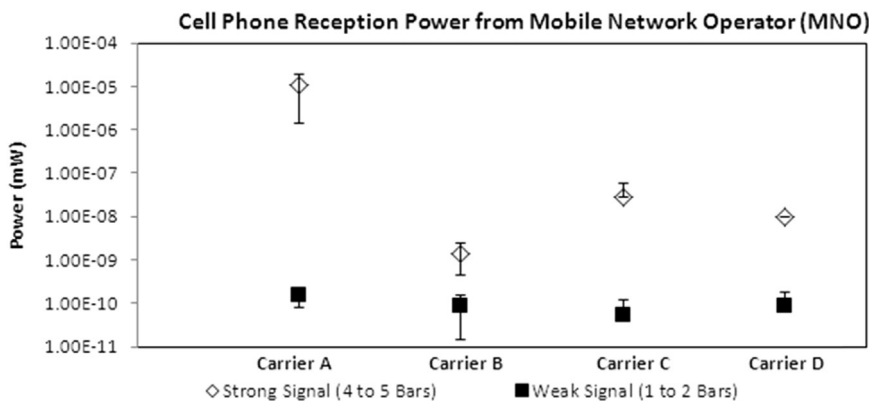


Fig. 3. Comparison of reception signal power associated with cell phone signal strength bar indicator display for different Mobile Network Operators.

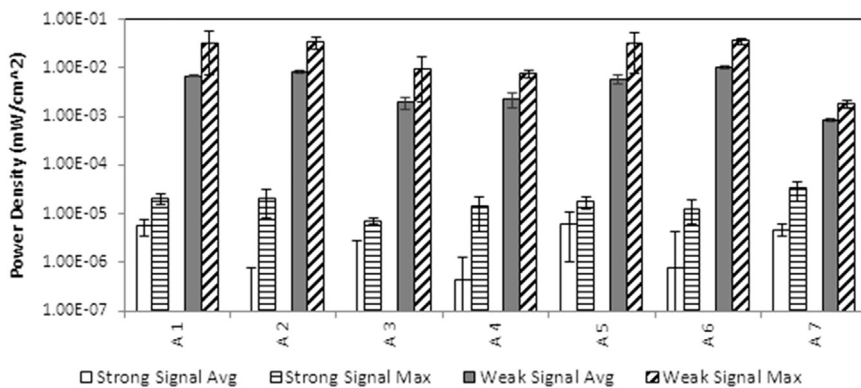


Fig. 4. Mobile Network Operator A cell phones. Comparison of average and maximum power density measured 4 cm from the typical cell phone ear position, under strong (4–5 display bars) and weak (1–2 display bars) signal reception conditions.

baseline power density levels prior to each call consisted of 50 data points obtained over 20 s. For each measurement distance, the consistently low baseline level before the call was subtracted from the measurement during the call to yield adjusted average and adjusted maximum power density levels.

An example of measurement details is provided in Fig. 2, where clock time duration of the entire three measurement sequence (non-call emissions [baseline], call connection spike, and call connected levels used to characterize the phone emission) is shown superimposed on a greater than 6 min measurement conducted on the same MNO phone. This example demonstrates that, after the initial connection spike, the on-call transmission level was constant and the calculated mean level and standard deviation for the 30 s segmented measurements and the

continuous 6 min measurements were nearly identical. Power control is essential when the reception signal varies (e.g., while traveling), requiring adjustments in the cell phone transmission power, but for a static measurement the power control is primarily used to reduce the power density from call initiation levels to a steady state within seconds.

Cell phones were tested under both strong and weak reception signal conditions. A strong reception signal, when a phone has the best communication, was considered to be represented by 4–5 bars in the cell phone signal display, while a weak reception signal, when a phone has poor communication, was represented by 1–2 display bars. Signal display bars were selected as the most accessible indication of the reception signal strength for the general public, with the relationship

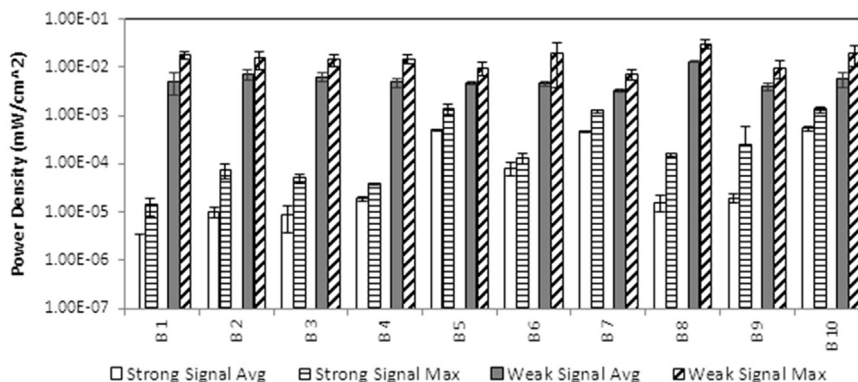


Fig. 5. Mobile Network Operator B cell phones. Comparison of average and maximum power density measured 4 cm from the typical cell phone ear position, under strong (4–5 display bars) and weak (1–2 display bars) signal reception conditions.

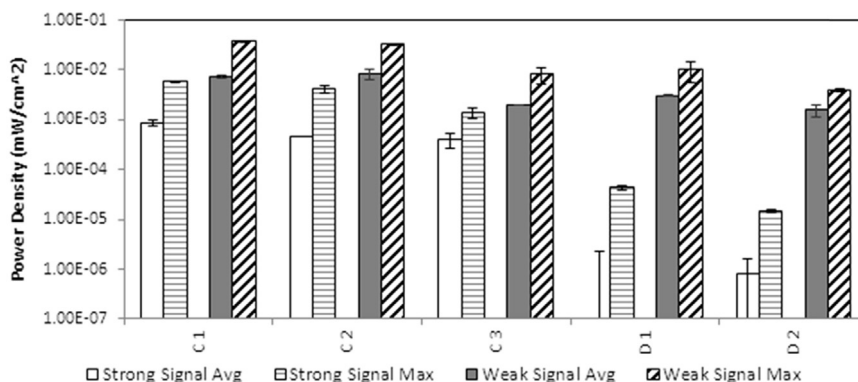


Fig. 6. Mobile Network Operators C and D cell phones. Comparison of average and maximum power density measured 4 cm from the typical cell phone ear position, under strong (4–5 display bars) and weak (1–2 display bars) signal reception conditions.

between display bars and reception signal strength power level discussed in the results section. Different unoccupied conference rooms at the California Department of Public Health (CDPH) campus in Richmond, California, were chosen to provide strong and weak reception signal environments. All strong reception signal condition measurements were performed in the same conference room, which provided a 4–5 bar signal strength environment for all phone models. Weak reception signal condition measurements for MNOs A and D were performed in a different conference room than those for MNOs B and C, to ensure that all phones could operate in a 1–2 signal display bar environment.

2.5. Bluetooth headsets

Use of Bluetooth headsets is one approach to reducing RF EMF exposure from cell phones. To investigate the magnitude of this potential reduction, power density measurements were conducted on nine different Bluetooth headsets, using the same experimental set-up shown in Fig. 1, with the associated cell phone operating under weak reception signal conditions. Each headset was positioned in the cradle and the power density measured. Bluetooth headset measurements were performed using the same experimental protocol, in the same conference rooms utilized for the weak reception signal cell phone measurements.

After establishing equivalence with the results obtained from the EMR 300 instrument, used for all cell phone measurements, the updated model, NBM 550 Broadband Field Meter (Narda Safety Test Solutions, Hauppauge, NY, USA) with probe type EF 0691 (100 kHz–6 GHz, 0.35–650 V/m), was employed for power density measurements on all the Bluetooth headsets tested. Bluetooth headsets operate in the frequency band between 2400 and 2480 MHz (as verified using the SRM-3006 spectrometer), which is the upper frequency range

of the EMR 300 and middle of the NBM 550 range. The equivalency of the measurements from the newer NBM-550 and the older EMR-300 provided a quality assurance validation of the EMR-300 cell phone measurements.

Bluetooth headset power density measurements were conducted while connected to one cell phone model each from MNOs A and B with the cell phones connected to a call under weak signal conditions. To ensure the power density measurement was only attributable to the headsets, the connected cell phones were placed 4–5 m behind and away from the measurement probe. Power density measurements were made at a 6 cm distance from the typical ear location on the headset, to ensure the probe RF EMF sensing region was well within the far-field region. Power density measurements for the two cell phones, used to connect with the Bluetooth headsets, were also conducted separately at 6 cm distance from the typical ear location using the NBM 550 Broadband Field Meter. As with the cell phone measurements, baseline power density was measured before activation of the Bluetooth-connected call, and this typically small correction was applied to all power density measurements.

3. Results

3.1. Cell phone power density and signal strength

In order to compare the reception signal strength represented by the cell phone display bars for the different MNOs, the reception power was determined by using the field test mode function available for most phone models (wpsantennas.com, 2017). In the field test mode, activated by a combination of key strokes, the signal power received was indicated on the cell phone display in dB_m, the standard measurement unit for power based on a one milliwatt (mW) reference signal (dBm =

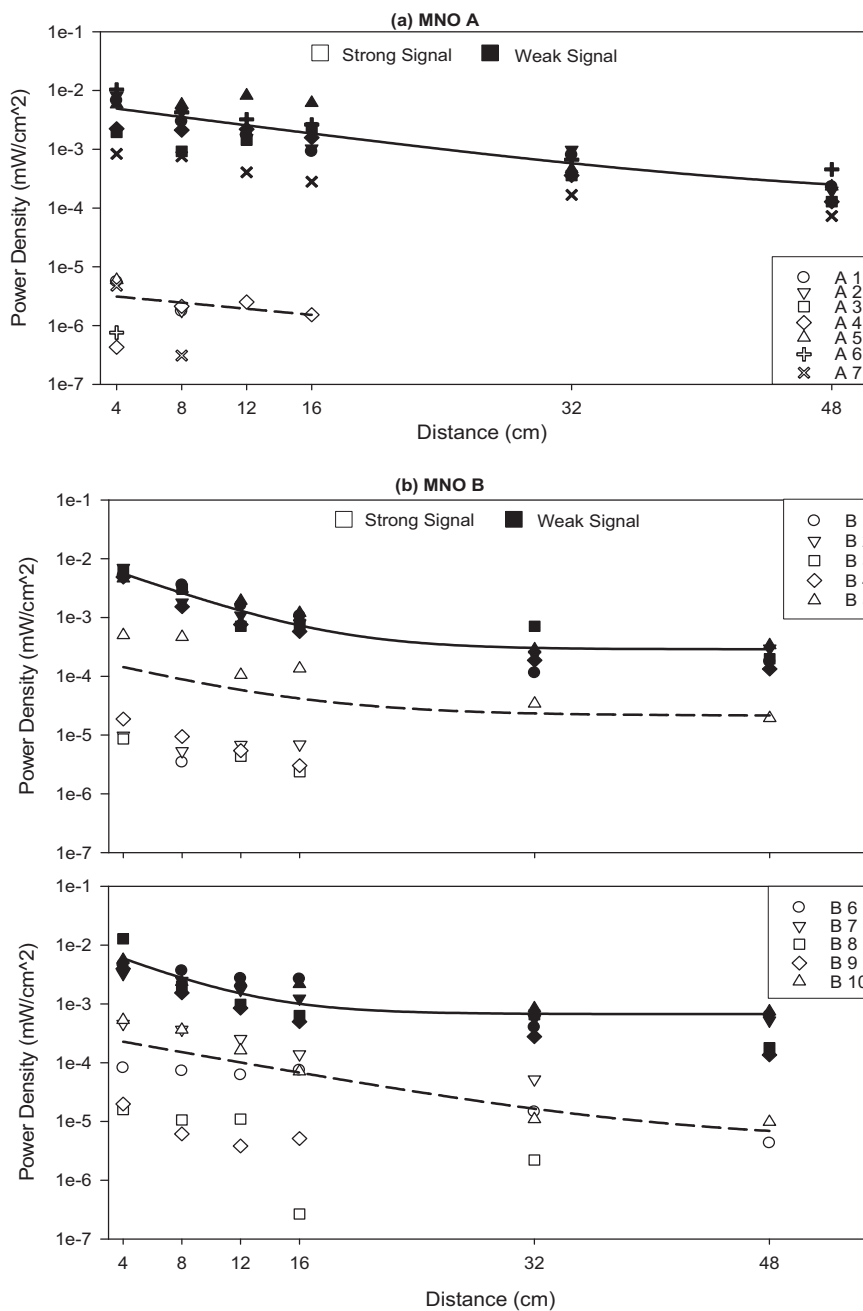


Fig. 7. Comparison of measured power density with distance for cell phone models under strong and weak reception conditions for (a) Mobile Network (MNO) A and (b) Mobile Network (MNO) B.

\log_{10} Signal Power / 0.001 W), which was converted to mW and determined for each of the four MNOs studied under both strong and weak reception conditions.

As shown in Fig. 3, for the strong reception signal environment, the power received by phones from the different MNOs varied by several orders of magnitude. In contrast, all four MNOs were found to have a similar relationship between weak reception signals based on the 1–2 bar display and the actual reception power. Display bars were used as indicators of reception signal strength in this study, since this metric is readily available to all cell phone users.

Comparisons of the power density measurements for cell phone models tested under different reception signal conditions at the closest distance of 4 cm for the two larger MNOs, A and B, are given in Figs. 4 and 5, respectively. All seven MNO A cell phones tested under strong reception signal conditions (4–5 display bars) produced power density

measurements very close to baseline levels. Power density levels from two MNO A phones (A2 and A3) were so low they could not be reliably distinguished from the baseline. The other five MNO A cell phones power density levels were in a range between 4.3×10^{-7} and 6.0×10^{-6} mW/cm² averaged over the measurement duration. A maximum power density level recorded during each measurement interval was well above baseline for all seven MNO A phones and ranged from 7.0×10^{-6} to 3.2×10^{-5} mW/cm², but represented only 1.3% of the measurement time interval.

Under weak reception signal conditions, power density from all MNO A cell phones were well above baseline, and orders of magnitude higher than under strong reception signal conditions. Power density levels ranged over more than an order of magnitude from 8.3×10^{-4} to 1.0×10^{-2} mW/cm² averaged over the measurement duration, while maximum power density levels ranged from 1.81×10^{-3} to

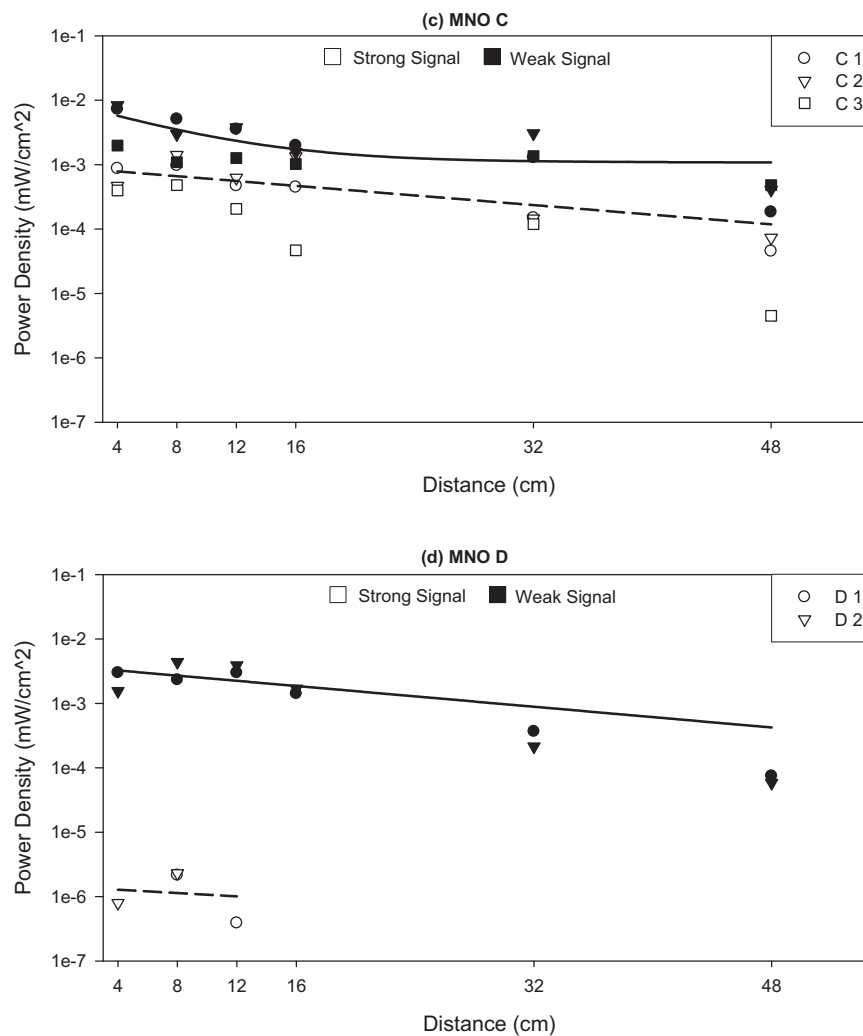


Fig. 8. Comparison of measured power density with distance for cell phone models under strong and weak reception conditions for (a) Mobile Network C and (b) Mobile Network D.

3.48×10^{-2} mW/cm².

From Fig. 5, of the ten MNO B cell phones measured at 4 cm under strong reception signal conditions, nine produced power density levels above baseline, while all ten were well above baseline under weak reception signal conditions. Average and maximum power density levels for strong reception spanned two orders of magnitude, with the average level range from 8.6×10^{-6} to 5.3×10^{-4} mW/cm², while maximum levels were higher in a range from 1.4×10^{-5} to 1.4×10^{-3} mW/cm². Under weak reception conditions much higher levels were measured, with average weak signal levels from 3.3×10^{-3} to 1.3×10^{-2} mW/cm² and maximum levels from 6.9×10^{-3} to 3.0×10^{-2} mW/cm².

The results of power density measurements at 4 cm for MNOC and D cell phones are given in Fig. 6. Under strong reception signal conditions all three MNO C phones and one of two MNO D phones had power density levels above baseline, while all five cell phones for both MNOC and D were well above baseline under weak reception signal conditions. MNO C average and maximum power density levels for strong reception signal conditions spanned less than one order of magnitude, with an average range of 4.0×10^{-4} to 8.7×10^{-4} mW/cm² and maximum range of 1.4×10^{-3} to 4.3×10^{-3} mW/cm², while the one MNO D phone with power density above baseline had average and maximum strong signal emission levels of 8.0×10^{-7} and 1.5×10^{-5} mW/cm², respectively. Power density for weak cell tower reception signal levels spanned one order of magnitude or less for both MNOC and D, with a MNO C average range of 2.0×10^{-3} to 8.3×10^{-3} mW/cm²

and MNO D range from 1.6×10^{-3} to 3.0×10^{-3} mW/cm². MNOC and D had maximum power density ranges of 8.0×10^{-3} to 3.6×10^{-2} and 3.9×10^{-3} to 9.7×10^{-3} mW/cm², respectively.

3.2. Cell phone power density with distance

Power density measurements were also performed at distances greater than 4 cm from the typical cell phone ear position to determine the effect of distance on measured power density. Measurements of power density were made at six distances between 4 and 48 cm under both strong and weak cell phone reception signal conditions. A comparison between measured power density levels under strong and weak reception signal conditions at all distances is given in Fig. 7 for MNOC and B and in Fig. 8 for MNOC and D. At distances greater than 16 cm under strong reception signal conditions, most measured power density levels were not distinguishable from baseline levels.

For cell phones supported by MNOC and D, power density levels under weak reception signal conditions were between two and three orders of magnitude greater than under strong reception signal conditions at every distance investigated. However, cell phones using MNOC and B displayed less of a difference, with power density measurements for weak reception signal conditions exceeding measurements under strong reception signal conditions by one to two orders of magnitude. For almost all MNO cell phones, the measured power density at the furthest distance of 48 cm under weak reception signal conditions

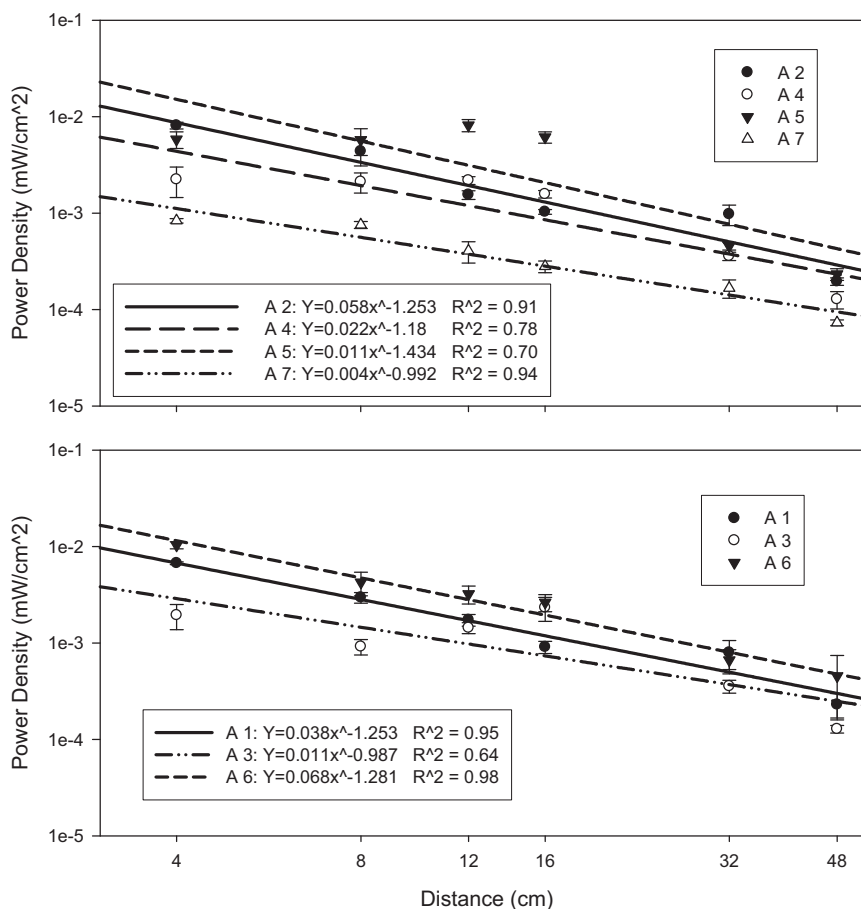


Fig. 9. Mobile Network Operator A power density as a function of distance from cell phone face under weak reception signal conditions. Power curve fit yields well behaved regression line to allow prediction of power density levels at intervening distances.

was equal to or greater than the power density measured at the nearest distance of 4 cm under strong reception signal conditions.

To further investigate cell phone higher power density levels under weak reception signal conditions, the levels for phones using MNOs A and B were fitted with a power curve regression in Figs. 9 and 10, respectively. Regression line fits for the majority of cell phones and associated MNOs were determined to have a coefficient of determination, R^2 , greater than 0.9, indicating that the power curve fit can be used to estimate power density cell phone levels at distances between measurements. There is a variation in the dependence of the power density with distance between cell phone models with different MNOs, yielding a power curve of $1/X^n$ with n between 0.81 and 1.634. This was a much less rapid drop in power density than the expected decrease proportional to the inverse square of the distance, which is consistent with a complex design for cell phone antennas intended to extend the range of the RF EMF transmission. The consistent relationship between power density and distance, down to the closest measurement at 4 cm, confirmed that the instrument readings were performed in the far-field region, where RF EMFs are well formed.

3.3. Bluetooth headset power density

Measurements of power density for all nine Bluetooth headsets, while connected to each of two cell phone models supported by MNOs A and B under weak signal conditions, are given in Fig. 11a and b. Each Bluetooth headset was found to have minimal difference in the measured power density between call connections with the MNO A and B phones. Conversely, there was a wide variation in power density between the different Bluetooth models, regardless of which call-

connected MNO phone was used. For comparison with cell phone exposure level without a Bluetooth headset, power density readings from the headsets were at least an order of magnitude lower for the measurement period average, and nearly two orders lower than the maximum level. When connected to the MNO A cell phone, the different Bluetooth headset average emission ranged from 1.2×10^{-5} to 2.1×10^{-4} mW/cm², compared to the direct cell phone power density measured at the same 6 cm distance of 1.8×10^{-3} mW/cm². For the MNO B cell phone, different Bluetooth headset average emissions ranged from 5.1×10^{-6} to 2.2×10^{-4} mW/cm², compared to the direct cell phone emission measured at the same 6 cm distance of 2.2×10^{-3} mW/cm².

4. Discussion

4.1. Comparison with previous studies

The primary purpose of this study was to determine real-world power density as a measure of exposure for a number of cell phone models registered with different mobile network operators, under both weak and strong reception signal conditions. Unlike many previous investigations, the measurements of power density were made under stationary conditions for both GSM and CDMA technology. At the Richmond study site in the San Francisco Bay Area, some mobile network operators (MNO) were found to utilize different frequency bands depending on the reception signal strength. Measurements reported in other studies under mobile conditions are subject to continuous variations in the cell phone transmission level due to the power control adjustments in response to the reception signal strength. This was

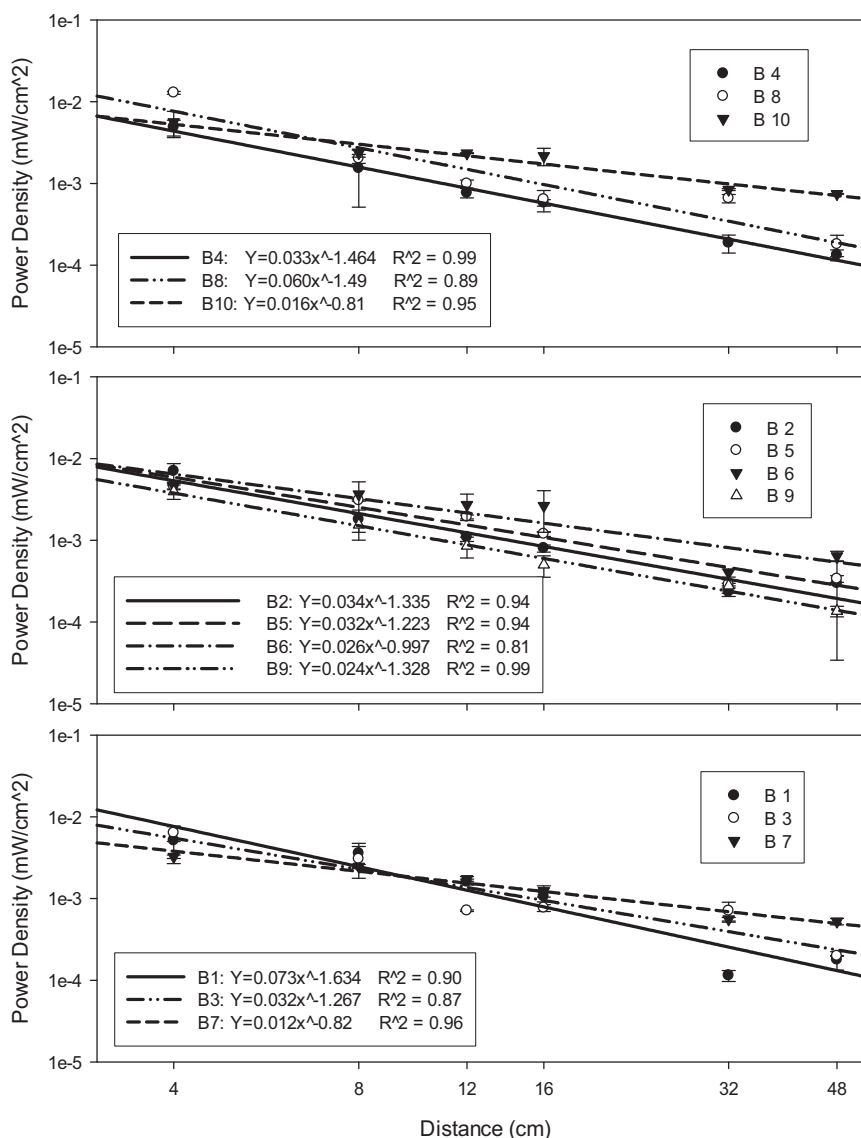


Fig. 10. Mobile Network Operator B power density as a function of distance from cell phone face under weak reception signal conditions. Power curve fit yields well behaved regression line to allow prediction of power density levels at intervening distances.

evident in European studies, which identified increases in cell phone transmission power in response to reduced reception strength, with the principal effect occurring during cell tower handover (Gati et al., 2009; Kuhn and Kuster, 2013; Wiart et al., 2000). Previous measurements in the San Francisco Bay Area for MNOs using GSM and CDMA cell phone technology reported a similar power control effect with increasing cell phone transmission power when moving due to reductions in reception signal strength (Kelsh et al., 2010).

4.2. Signal reception environments

In this study, the finding of significantly higher cell phone RF EMF power density exposure measured in weak signal reception environments, noted for emission power in previous studies, (Gati et al., 2009; Kuhn and Kuster, 2013; Wiart et al., 2000; Kelsh et al., 2010; Hardell et al., 2006; Hillert et al., 2006) was extended to include a large variety of commonly used cell phones employing different MNO services. All 22 cell phones had power density levels between one and four orders of magnitude higher when operating under weak signal conditions. The difference between weak and strong reception signal environments was at least two orders of magnitude higher for 73% of the phones tested. In

contrast, under strong reception signal conditions, the measured power density from some phones was so low as to be indistinguishable from the baseline RF EMF. Based on the 2G technology investigated, reduced and precautionary use of cell phones under weak signal conditions could lower a user's RF EMF exposure by up to several orders of magnitude.

4.3. Effect of exposure distance

Measurement of power density at increasing distances from the cell phone indicated the same trend, with measured power density orders of magnitude higher for weak rather than strong reception signal environments at each distance. Under both weak and strong reception signal conditions, the power density decreased by up to two orders of magnitude as the distance from the phone increased up to 48 cm. The RF EMF power density for some phones at 48 cm under weak reception signal conditions was equal to or greater than the power density at 4 cm under strong reception signal conditions. Under weak reception signal conditions, power density reductions of up to 90% occurred at 16 cm (a typical distance for speaker phone or texting) compared to the 4 cm near-ear exposure. Depending on the Bluetooth headset model,

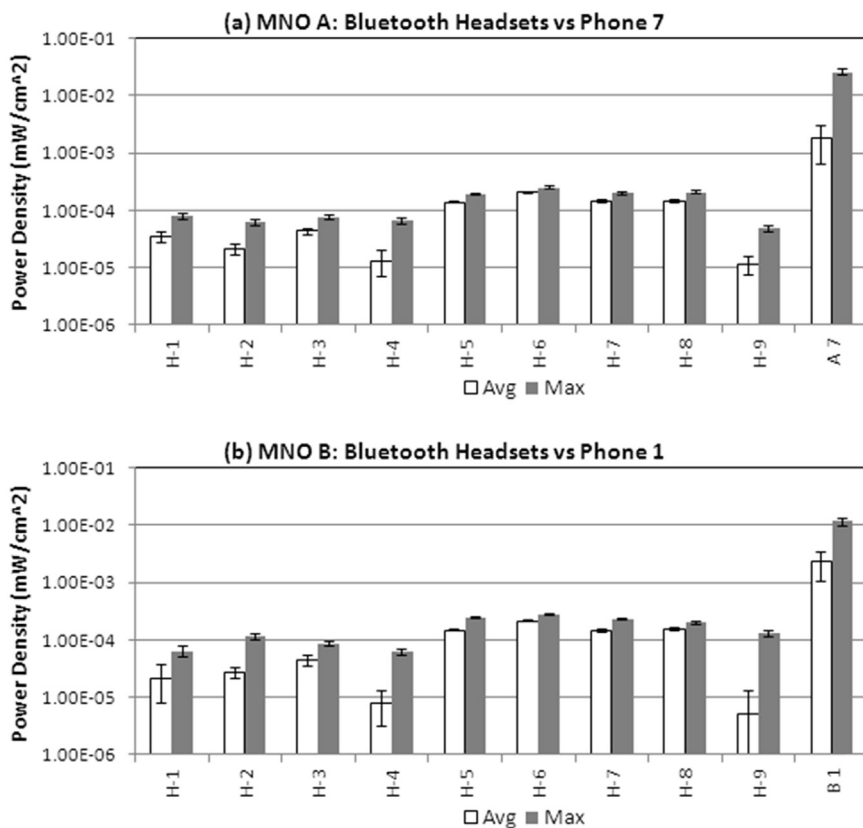


Fig. 11. Comparison of power density levels emitted by a number of Bluetooth headsets (H 1–9) during calls when connected to (a) a cell phone served by Mobile Network Operator (MNO) A (A 7) and (b) a cell phone served by Mobile Network Operator (MNO) B (B 1). Headsets and cell phones were both measured at a distance of 6 cm from the typical ear listening position.

exposures were 10–400 times lower than direct near-ear exposure from the phones to which they were connected.

4.4. Exposure effects

Cell phone RF EMF exposure may cause both thermal and non-thermal tissue effects. The FCC power density MPE limits, and the NCRP and ANSI/IEEE limits on which they are based, are derived from exposure criteria quantified in terms of SARs. The FCC's SAR standard is based on a 1986 U.S. Air Force study that estimated "safe" exposure levels for thermal effects. Evidence for both thermal and nonthermal effects was evaluated, but only the thermal effects were considered scientifically established as a basis for setting exposure limits. Accordingly, the SAR was based on thermal effects for a healthy adult male, with disclaimers that the results would differ for a person of a different size, age, or general health condition (Durney et al., 2013). Recent research indicates that exposure at the level of the current SAR may result in energy deposition in children's heads and bone marrow twice and ten times, respectively, higher than in adults (Gandhi et al., 2012). Significant increases in gliomas and Schwannomas of the heart in rodent studies have been reported for both near-field and far-field RF EMF exposure by the National Toxicology Program (2018) and the Ramazzini Institute (Falcioni et al., 2018). Several epidemiological studies of cell phone use and intracranial malignancy, in which the investigators examined potential impacts of longer latency ipsilateral use (i.e., holding the phone next to the same side of the head where the tumor developed), have reported significantly increased risks of total malignant brain tumors, mainly gliomas (Hardell et al., 2006, 2011; INTERPHONE Study Group, 2010). A population-based case-control study conducted in France (CERENAT) reported significantly increased risks of glioma among heavy phone users compared with non-regular users. These risks showed positive exposure-response relationships with self-reported average calling time per month and cumulative hours of use, and were higher among those with occupational exposures, with

tumors of the temporal vs frontal lobe, and with ipsilateral vs contralateral tumors (Coureau et al., 2014). Also, an analysis of tumor localization data from the INTERPHONE study found an association between intracranial distribution of gliomas and self-reported preferred side of the head for cell phone use (Grell et al., 2016).

Evidence of nonthermal effects associated with RF EMF exposure from cell phones is mixed. Changes in the brain from exposure to cell phone electromagnetic fields below levels associated with thermal changes were reported in a study of 47 healthy people during a 50-min cell phone call (Volkow et al., 2011). Exposure to RF EMF from cell phones has been associated with effects on gene and protein expression (Hardell et al., 2013; Baan et al., 2011; Megha et al., 2015) and oxidation (Friedman et al., 2007; Yakymenko et al., 2016). These studies demonstrate the potential existence of biological changes at nonthermal RF EMF exposure levels, but the relationship of these changes to long-term health effects is unknown.

4.5. Classification of exposure risk

In 2011, the International Agency for Research on Cancer (IARC) classified RF EMF as possibly carcinogenic to humans (Group 2B) (IARC, 2011; IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 2013). This classification was based on limited evidence from epidemiological studies of a possible increased risk of gliomas and acoustic neuromas associated with cell phone RF EMF exposure (Baan et al., 2011; IARC, 2011). Major technological changes in the cell phone RF EMF emission signal characteristics over the past decade may affect the applicability of earlier health effects studies to current exposures. However, the marked increase of cell phone users, the high frequency of typical cell phone use, and the classification of RF EMF as a possible carcinogen have prompted interest in measures to reduce exposure to cell phone RF EMF emission levels under normal use conditions.

Although the levels of cell phone power density measured in this

study were orders of magnitude below the FCC MPE limits for the general population, those limits were derived from exposure criteria quantified in terms of SARs for constant exposures. The FCC has reported that laboratory-derived SAR values do not provide sufficient information to compare RF exposure levels between cell phone models under typical usage conditions (FCC, 2017). Other research indicates that exposures at SAR levels are likely to produce much greater energy deposition in children than adults (IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 2013).

5. Conclusion

The results of this study, based on typical strong (4–5 display bars) and weak (1–2 display bars) cell phone reception signal environments, suggest a number of potential self-protective measures to reduce RF EMF exposure. Due to the higher emission levels for cell phones operating in weak reception signal environments, avoiding or limiting cell phone use under these conditions is the most obvious measure to reduce exposure. Since this may often be impractical, using the cell phone at a moderate distance by employing speaker-phone mode, wired headset, or by texting rather than talking can reduce RF EMF exposure by up to two orders of magnitude in weak reception signal areas. Bluetooth headsets allow a greater separation from the cell phone during conversations and, although these headsets do emit RF EMF, the power densities measured in this study were as much as 400-fold lower than those from the cell phone itself. Using a cell phone for internet browsing, email or streaming audio or video will generally increase the distance between the phone and the body; however, the exposure characteristics of the associated data signals are different from those of telephonic voice signals. The effects of prolonged exposures to such data signals have not been investigated and may potentially affect other organ systems. Further research is also needed to assess exposures resulting from more current cell phone technology, as well as exposures to individuals in close proximity to a cell phone user, which would require measurements of RF EMF power density from the back and sides of the phone. Based in part on the results of this study, the California Department of Public Health published “How to Reduce Exposure to Radiofrequency Energy from Cell Phones” (CDPH, 2017). Cell phones have become an integral part of the fabric of modern life; additional research is needed to delineate how best to use these devices to ensure protection of public health.

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Cancer - Brain Tumors; Meta-analysis of long-term mobile phone use
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Meta-analysis of long-term mobile phone use and the association with brain tumours

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Abstract. We evaluated long-term use of mobile phones and the risk for brain tumours in case-control studies published so far on this issue. We identified ten studies on glioma and meta-analysis yielded OR = 0.9, 95% CI = 0.8-1.1. Latency period of ≥ 10 -years gave OR = 1.2, 95% CI = 0.8-1.9 based on six studies, for ipsilateral use (same side as tumour) OR = 2.0, 95% CI = 1.2-3.4 (four studies), but contralateral use did not increase the risk significantly, OR = 1.1, 95% CI = 0.6-2.0. Meta-analysis of nine studies on acoustic neuroma gave OR = 0.9, 95% CI = 0.7-1.1 increasing to OR = 1.3, 95% CI = 0.6-2.8 using ≥ 10 -years latency period (four studies). Ipsilateral use gave OR = 2.4, 95% CI = 1.1-5.3 and contralateral OR = 1.2, 95% CI = 0.7-2.2 in the ≥ 10 -years latency period group (three studies). Seven studies gave results for meningioma yielding overall OR = 0.8, 95% CI = 0.7-0.99. Using ≥ 10 -years latency period OR = 1.3, 95% CI = 0.9-1.8 was calculated (four studies) increasing to OR = 1.7, 95% CI = 0.99-3.1 for ipsilateral use and OR = 1.0, 95% CI = 0.3-3.1 for contralateral use (two studies). We conclude that this meta-analysis gave a consistent pattern of an association between mobile phone use and ipsilateral glioma and acoustic neuroma using ≥ 10 -years latency period.

Introduction

Worldwide there has been a rapid development of wireless technology and along with that an increased use of wireless telephone communication during the last decade. Everyone is exposed to radiofrequency/microwave (RF) radiation emissions from wireless devices such as cellular phones and cordless phones, cellular antennas and towers, broadcast transmission towers, voice and data transmission for cell phones, pagers and personal digital assistants (PDAs) and other sources of RF radiation. This has raised concern of health risks, primarily an increased risk for brain tumours since the brain is the target organ for microwave exposure during mobile phone calls.

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Key words: mobile phone, brain tumours, meta-analysis, latency period

Since Sweden was one of the first countries in the world to adopt this wireless technology a brief history is given in the following. First, analogue phones (NMT; Nordic Mobile Telephone System) were introduced on the market in the early 1980's using both 450 and 900 Megahertz (MHz) fields. NMT 450 was used in Sweden since 1981 but closed down in December 31, 2007, whereas NMT 900 operated during 1986-2000.

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1,800 MHz, started to operate in 1991 and now dominates the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900 MHz RF fields has been introduced worldwide since a few years, in Sweden in 2003.

Desktop cordless phones (DECT) started in 1988 using first analogue 800-900 MHz RF fields, but since early 1990's the digital 1,900 MHz system. In our studies on tumour risk associated with use of wireless phones we have also assessed use of DECT. However, most other research groups have not published such data or only in a scanty way, so exposure to RF from DECT is not further discussed here. Instead the reader is referred to our publications with the results as published previously (1-3).

The initial studies on brain tumour risk had too short latency periods to give a meaningful interpretation of long-term risk. However, during recent years studies have been published that enable evaluation of ≥ 10 -years latency period risk, although still mostly based on low numbers (4,5). A ≥ 10 -years latency period seems to be a reasonable minimum period to indicate long-term carcinogenic risks from exposure to RF fields during use of cellular or cordless phones.

Long-term exposure to RF fields from mobile phones and brain tumour risk is of importance to evaluate not the least since the use of cellular phones is globally widespread with high prevalence among almost all age groups in the population.

Materials and methods

In addition to our constant gathering of new studies in this area we used the Pub Med database (www.ncbi.nlm.nih.gov) for search of all relevant studies. We used mobile/cellular/cordless telephone and brain tumour/neoplasm/acoustic neuroma/meningioma/glioma as searching terms. If a study had several publications on certain aspects we used the latest publication giving the most relevant data.

Table I. Odds ratios (ORs) and 95% confidence intervals (CIs) from 10 case-control studies on glioma including meta-analysis of the studies.^a

Study Author, year of publication, country, ref. no.	No. of cases	No. of controls	OR	95% CI
Inskip <i>et al</i> 2001, USA (12)	201	358	1.0	0.7-1.4
Auvinen <i>et al</i> 2002, Finland (13)	Not given	Not given	1.5	1.0-2.4
Lönn <i>et al</i> 2005, Sweden (14)	214	399	0.8	0.6-1.0
Christensen <i>et al</i> 2005, low-grade glioma, Denmark (15)	47	90	1.1	0.6-2.0
Christensen <i>et al</i> 2005, high-grade glioma, Denmark (15)	59	155	0.6	0.4-0.9
Hepworth <i>et al</i> 2006, UK (16)	508	898	0.9	0.8-1.1
Schüz <i>et al</i> 2006, Germany (17)	138	283	1.0	0.7-1.3
Hardell <i>et al</i> 2006, Sweden (1), all glioma	346	900	1.4	1.1-1.7
Low-grade glioma	65	900	1.4	0.9-2.3
High-grade glioma	281	900	1.4	1.1-1.8
Lahkola <i>et al</i> 2006, Denmark, Norway, Finland, Sweden, UK (18)	867	1,853	0.8	0.7-0.9
Hours <i>et al</i> 2007, France (19)	59	54	1.2	0.7-2.1
Klaeboe <i>et al</i> 2007, Norway (20)	161	227	0.6	0.4-0.9
Meta-analysis	Not given ^b	Not given ^b	0.9	0.8-1.1

^aNumbers of exposed cases and controls are given. ^bTotal number could not be calculated since numbers were not presented in one publication (13).

Brain tumours include both malignant and benign types. Thus, it is worthwhile to give results for different types and in the following we discuss glioma, acoustic neuroma and meningioma, the major tumour types, separately. Compared with our previous publications (4,5) we have now up-dated the number of included studies and made some further analysis. For details about the studies the reader is referred to our previous reviews and the original studies. We give overall results as well as ≥ 10 -years latency period results and, if presented, ipsilateral use of the cellular phones, i.e. same side of tumour and microwave exposure, and contralateral (opposite side) use. If the study did not have users with a ≥ 10 -year latency period only the overall results are presented.

Statistical methods. For statistical analysis Stata 8.2 was used (Stata/SE 8.2 for Windows; StataCorp., College Station TX). Random effects model was used for all meta-analysis, to allow for between-study statistical heterogeneity. The analyses were based on the adjusted ORs in the different studies. In our studies (1,2) the unexposed group consisted of cases and controls with no reported use of either mobile or cordless phones. On the contrary almost all other studies did not assess use of cordless phones, and cases and controls with such use were included in the 'unexposed' group when mobile phone use was analyzed.

Results

We identified two publications from a cohort study of mobile phone users (6,7) and 19 case-control studies on this topic (1,2,8-25; note refs. 8 and 9 are the same study). Two publications (18,23) overlapped partly already published studies,

but were included since also new results were presented in these publications. No mortality studies were included.

The Danish cohort study with two publications (6,7) had several limitations, such as exclusion of the heaviest mobile phone users, no truly unexposed comparison group, skewed sex distribution and no data were given on laterality of phone use in relation to tumour localisation in the brain. This study was uninformative regarding long-term health effects from mobile phone use, as has been discussed elsewhere (4). Furthermore, this was a cohort study that gave standardised incidence rates and not odds ratios (OR) and 95% confidence intervals (CI) as in the case-control studies. For these reasons this cohort study was excluded from this review.

Two case-control studies were excluded since results were not presented separately for glioma, acoustic neuroma and meningioma (8-10). Our first study on this topic was the first one to indicate an association between use of mobile phones and ipsilateral brain tumours, although based on low numbers (8,9). In one case-control study on acoustic neuroma overall results were not presented, only for some time periods without data for ≥ 10 -years latency period, and it was thus excluded from this review (11). The following presentation was based on results from 16 case-control studies.

Glioma. Ten case-control studies gave results for glioma risk associated with the use of mobile phones (1,12-20). Seven of these studies (14-20) were part of the Interphone study on this issue, and one of these (18) overlapped partly three of other Interphone studies (14-16) but included also results for Finland (Table I). Later also results from Norway have been published separately (20). It should be noted that in one study the group of glioma cases was heterogenic including also ependymoma, i.e., a benign tumour, but probably few subjects

Table II. Odds ratios (ORs) and 95% confidence intervals (CIs) from 6 case-control studies on glioma including meta-analysis of the studies using ≥ 10 years latency period.^a

Study Author, year of publication, country, latency, refs. no.	Total			Ipsilateral			Contralateral		
	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI
Lönn <i>et al</i> 2005, Sweden, ≥ 10 years (14)	25/38	0.9	0.5-1.5	15/18	1.6	0.8-3.4	11/25	0.7	0.3-1.5
Christensen <i>et al</i> 2005, Denmark, low-grade glioma, ≥ 10 years (15)	6/9	1.6	0.4-6.1	-	-	-	-	-	-
Christensen <i>et al</i> 2005, Denmark, high-grade glioma, ≥ 10 years (15)	8/22	0.5	0.2-1.3	-	-	-	-	-	-
Hepworth <i>et al</i> 2006, UK, >10 years (16)	66/112	0.9	0.6-1.3	Not given ^b	1.6	0.9-2.8	Not given ^b	0.8	0.4-1.4
Schüz <i>et al</i> 2006, Germany, ≥ 10 years (17)	12/11	2.2	0.9-5.1	-	-	-	-	-	-
Hardell <i>et al</i> 2006, Sweden, >10 years (1), all glioma	78/99	2.7	1.8-3.9	41/28	4.4	2.5-7.6	26/29	2.8	1.5-5.1
Low-grade glioma	7/99	1.5	0.6-3.8	2/28	1.2	0.3-5.8	4/29	2.1	0.6-7.6
High-grade glioma	71/99	3.1	2.0-4.6	39/28	5.4	3.0-9.6	22/29	3.1	1.6-5.9
Lahkola <i>et al</i> 2006, Denmark, Norway, Finland, Sweden, UK, ≥ 10 years (18)	143/220	0.95	0.7-1.2	77/117	1.4	1.01-1.9	67/121	1.0	0.7-1.4
Meta-analysis	338/511	1.2	0.8-1.9	Not given ^b	2.0	1.2-3.4	Not given ^b	1.1	0.6-2.0

^aNumbers of exposed cases and controls are given. ^bTotal number could not be calculated since numbers were not presented in one publication (16).

(13). The risk was significantly decreased in the Danish part (15) for high-grade glioma with OR = 0.6, 95% CI = 0.4-0.9, for all glioma in the study in Norway (20) with OR = 0.6, 95% CI = 0.4-0.9, and the Finnish publication (18) with OR = 0.8, 95% CI = 0.7-0.9. In the Swedish part of Interphone studies decreased OR of borderline significance was presented (14). In a register based case-control study from Finland (13), that was not part of the Interphone study, an increased OR = 1.5 of borderline significance was reported (95% CI = 1.0-2.4). In our Swedish study (1), independent from Interphone, OR = 1.4, 95% CI = 1.1-1.7 was reported for all glioma. Meta-analysis of the 10 case-control studies yielded OR = 0.9, 95% CI = 0.8-1.1.

In Table II results are presented for the six studies (1,14-18) that gave results for a latency period of at least 10 years. Most of the results in the various studies were based on low numbers. Meta-analysis gave OR = 1.2, 95% CI = 0.8-1.9. In four case-control studies results for ipsilateral use of a mobile phone were presented (1,14,16,18). All showed increased OR and meta-analysis yielded OR = 2.0, 95% CI = 1.2-3.4. However, contralateral use did not increase the risk significantly, OR = 1.1, 95% CI = 0.6-2.0.

Acoustic neuroma. Regarding acoustic neuroma nine case-control studies have been published, Table III (2,12,19-25). Seven of these were part of the Interphone studies (19-25). One of these (23) overlapped partly two other Interphone studies (21,22) and one published later (20). One of the largest studies came from Sweden and was not part of the Interphone studies (2). It gave significantly increased OR = 1.7, 95% CI = 1.2-2.3. Six of the seven Interphone studies reported somewhat decreased ORs, although not significantly so. Meta-analysis gave OR = 0.9, 95% CI = 0.7-1.1.

Results for a latency period of 10 years or more were reported in four (2,21-23) of these nine studies (Table IV). Again, using this latency period most of the results were based on low numbers. In total, meta-analysis gave OR = 1.3, 95% CI = 0.6-2.8, whereas for ipsilateral use of the mobile phone OR increased to 2.4, 95% CI = 1.1-5.3, based on three studies. Contralateral use yielded OR = 1.2, 95% CI = 0.7-2.2.

Meningioma. For meningioma results have been published from seven case-control studies, Table V (2,12,14,15,17,19,20). Of these, five (14,15,17,19,20) were part of the Interphone study and all gave decreased OR for meningioma, significantly

Table III. Odds ratios (ORs) and 95% confidence intervals (CIs) from 9 case-control studies on acoustic neuroma including meta-analysis of the studies.^a

Study Author, year of publication, country, ref. no.	No. of cases	No. of controls	OR	95% CI
Inskip <i>et al</i> 2001, USA (12)	40	358	0.8	0.5-1.4
Lönn <i>et al</i> 2004, Sweden (21)	89	356	1.0	0.6-1.5
Christensen <i>et al</i> 2004, Denmark (22)	45	97	0.9	0.5-1.6
Schoemaker <i>et al</i> 2005, Denmark, Finland, Sweden, Norway, Scotland, UK (23)	360	1,934	0.9	0.7-1.1
Hardell <i>et al</i> 2006, Sweden (2)	130	900	1.7	1.2-2.3
Takebayashi <i>et al</i> 2006, Japan (24)	51	192	0.7	0.4-1.2
Klaeboe <i>et al</i> 2007, Norway (20)	22	227	0.5	0.2-1.0
Schlehofer <i>et al</i> 2007, Germany (25)	29	74	0.7	0.4-1.2
Hours <i>et al</i> 2007, France (19)	58	123	0.9	0.5-1.6
Meta-analysis	824	4,261	0.9	0.7-1.1

^aNumbers of exposed cases and controls are given.

Table IV. Odds ratios (ORs) and 95% confidence intervals (CIs) from 4 case-control studies on acoustic neuroma including meta-analysis of the studies using ≥ 10 years latency period.^a

Study Author, year of publication, country, latency, refs. no.	Total			Ipsilateral			Contralateral		
	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI
Lönn <i>et al</i> 2004, Sweden, ≥ 10 years (21)	14/29	1.8	0.8-4.3	12/15	3.9	1.6-9.5	4/17	0.8	0.2-2.9
Christensen <i>et al</i> 2004, Denmark, ≥ 10 years (22)	2/15	0.2	0.04-1.1	-	-	-	-	-	-
Schoemaker <i>et al</i> 2005, Denmark, Finland, Sweden, Norway, Scotland, UK, ≥ 10 years (23)	47/212	1.0	0.7-1.5	31/124	1.3	0.8-2.0	20/105	1.0	0.6-1.7
Hardell <i>et al</i> 2006, Sweden, >10 years (2)	20/99	2.9	1.6-5.5	10/28	3.5	1.5-7.8	6/29	2.4	0.9-6.3
Meta-analysis	83/355	1.3	0.6-2.8	53/167	2.4	1.1-5.3	30/151	1.2	0.7-2.2

^aNumbers of exposed cases and controls are given.

so in the Swedish part with OR = 0.7, 95% CI = 0.5-0.9 (14). The largest study was a Swedish investigation independent from Interphone based on 347 exposed cases. It gave OR = 1.1, 95% CI = 0.9-1.3. Meta-analysis gave significantly decreased risk with OR = 0.8, 95% CI = 0.7-0.99.

Four case-control studies remained for the analysis of a 10-years latency period, Table VI (2,14,15,17). In total no study showed significantly increased OR and meta-analysis gave OR = 1.3, 95% CI = 0.9-1.8. The analysis of ipsilateral microwave exposure was based on two studies and the meta-analysis gave OR = 1.7, 95% CI = 0.99-3.1. Regarding

contralateral exposure no increased risk was found, OR = 1.0, 95% CI = 0.3-3.1.

Discussion

Different biological effects have been reported from exposure to radiofrequency/microwave fields, for an overview see two recent reports (5,26). Of special concern is the risk for brain tumours due to the high near field exposure to the brain during mobile phone calls compared with other sources of RF fields. In total 19 case-control studies have been performed

Table V. Odds ratios (ORs) and 95% confidence intervals (CIs) from 7 case-control studies on meningioma including meta-analysis of the studies.^a

Study Author, year of publication, country, ref. no.	No. of cases	No. of controls	OR	95% CI
Inskip <i>et al</i> 2001 (USA) (12)	67	358	0.8	0.5-1.2
Lönn <i>et al</i> 2005 (Sweden) (14)	118	399	0.7	0.5-0.9
Christensen <i>et al</i> 2005 (Denmark) (15)	67	133	0.8	0.5-1.3
Schüz <i>et al</i> 2006 (Germany) (17)	104	234	0.8	0.6-1.1
Hardell <i>et al</i> 2006 (Sweden) (2)	347	900	1.1	0.9-1.3
Klaeboe <i>et al</i> 2007 (Norway) (20)	96	227	0.8	0.5-1.1
Hours <i>et al</i> 2007 (France) (19)	71	80	0.7	0.4-1.3
Meta-analysis	870	2,331	0.8	0.7-0.99

^aNumbers of exposed cases and controls are given.

Table VI. Odds ratios (ORs) and 95% confidence intervals (CIs) from 4 case-control studies on meningioma including meta-analysis of the studies using ≥ 10 years latency period.^a

Study Author, year of publication, country, latency, refs. no.	Total			Ipsilateral			Contralateral		
	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI
Lönn <i>et al</i> 2005, Sweden, ≥ 10 years (14)	12/36	0.9	0.4-1.9	5/18	1.3	0.5-3.9	3/23	0.5	0.1-1.7
Christensen <i>et al</i> 2005, Denmark, ≥ 10 years (15)	6/8	1.0	0.3-3.2	-	-	-	-	-	-
Schüz <i>et al</i> 2006, Germany, ≥ 10 years (17)	5/9	1.1	0.4-3.4	-	-	-	-	-	-
Hardell <i>et al</i> 2006, Sweden, ≥ 10 years (2)	38/99	1.5	0.98-2.4	15/28	2.0	0.98-3.9	12/29	1.6	0.7-3.3
Meta-analysis	61/152	1.3	0.9-1.8	20/46	1.7	0.99-3.1	15/52	1.0	0.3-3.1

^aNumbers of exposed cases and controls are given.

on that topic, but since few subjects have used the mobile phone for at least 10 years conclusions on long-term effects have been hampered. By now a number of studies exist with such data, so presentation of the results in the various studies is meaningful as well as meta-analysis of the data.

As to carcinogenesis usually latency period of at least 10 years is needed for more firm conclusions. For several carcinogens such as smoking and asbestos exposure and the risk for lung cancer, dioxins and certain cancer types even longer latency periods may be required (27,28). Thus, it is premature to draw conclusions on the association between mobile phones and brain tumours based on short latency period, as has been the situation in some commentaries (29).

This review included 19 case-control studies. Two publications from a Danish cohort study on mobile phone users (6,7) were excluded due to limitations in the study design, as discussed above. Our first study on this topic was excluded, since analysis was not performed for different histology types (8,9). This was one of the first studies in this area and the

first to indicate an association between mobile phone use and ipsilateral brain tumours. Two studies from USA were excluded for the same reason as our first one or because overall data were not presented (10,11). However, in that study mobile phone use during 3-6 years, that was the longest observation time, gave OR = 1.7, 95% CI = 0.5-5.1 based on 11 cases and 6 controls (11).

It should be noted that several of the overall ORs in the Interphone studies were < 1.0 , some even significantly so. As an example, in the Danish Interphone study on glioma (15) all 17 ORs for high-grade glioma were < 1.0 , four significantly decreased. In the Swedish Interphone study on glioma 46 ORs were presented with overall results (14). Of these ORs 45 were < 1.0 , six even significantly so. On the contrary, regarding glioma using a latency period of ≥ 10 years increased ORs for ipsilateral exposure were found in all Interphone studies that present such data, see Table II. The overall decreased risks would thus bias the 10-years latency period calculations towards unity. These results in the Interphone

studies give concern about the methods used, such as assessment and interpretation of exposure and statistical analysis.

For biological reasons it is not believed that microwave exposure from mobile phones do prevent brain tumours, as indicated in some results in the Interphone studies. Thus, the design and performance of these studies, using the same core protocol, seem to be biased in certain respects. This has been discussed by others and us elsewhere (4,5,30,31). In a Danish Interphone study it was concluded that the cognitive function in brain tumour cases was affected leading to e.g. deficient memory (15). Patients scored significantly lower than controls with problems to recall words (aphasia), writing and drawing due to paralysis.

Also the interviewing of cases in such short time after diagnosis in the Interphone studies, even bedside (e.g. 17), might have biased assessment of exposure due to a stressful situation for the patient with memory and other defects of the cognitive functions. It should further be noted that some of the Interphone studies had very low response rates with the possibility of selection bias. In the publication on mobile phone use and risk of glioma in five North European countries 37-81% (total 60%) of the cases and 42-69% (total 50%) of the controls participated (18). This is to be compared with the response rates in our studies (1,2). Of cases with malignant brain tumours 905 (90%) answered the questionnaire. The corresponding results were for cases with benign brain tumours 1,254 (88%) and controls 2,162 (89%).

In addition to selection bias of cases and controls in the Interphone studies, recall bias due to e.g. cognitive defects in the patients might have been introduced. Computer guided face-to-face interviews of cases at the hospitals shortly after operation may have been a contributing factor. We used postal questionnaires both for cases and controls. The cases could answer the questionnaire some time after the operation, usually about two months later. If necessary, the answers were supplemented over the phone. All assessment of exposure and coding of data in our studies were blinded as to case or control status. On the contrary, face-to-face interviews of both cases and controls in the Interphone studies might have introduced observational bias since it was known if it was a patient or a referent that was interviewed.

Some articles have discussed methodological issues in the Interphone studies (30,31). The actual use of mobile phones was underestimated in light users and overestimated in heavy users. Random recall bias could lead to large underestimation in the risk of brain tumours associated with mobile phone use. It was further suggested that selection bias in the Interphone study resulted in under selection of unexposed controls with decreasing risk at low to moderate exposure levels.

Furthermore, it should be added that in our studies we also assessed use of cordless phones (1,2). The unexposed group consisted of cases and controls with no use of mobile or cordless phones. In contrast, e.g. the Interphone studies did not assess use of cordless phones or did not report any details (14,17). Such use seems to have been included in the unexposed group in the statistical analysis of an association between mobile phone use and brain tumours. We found increased OR for glioma and acoustic neuroma associated with use of both mobile and cordless phones, whereas overall

OR was not significantly increased for meningioma (1,2). It has been shown that the GSM phones have a median power in the same order of magnitude as cordless phones (32). Moreover, cordless phones are usually used for longer calls than mobile phones (1,2). Including subjects using cordless phones in the 'unexposed' group in studies on this issue, as for example in the Interphone investigations, would thus underestimate the risk.

We report here results from ten case-control studies on glioma. No association was found with mobile phone use in the overall meta-analysis. However, using a ≥ 10 -years latency period showed increased OR in the four studies with data on ipsilateral use of the mobile phone, significantly so in the meta-analysis. Contralateral use yielded OR close to unity. These findings are most likely of biological relevance taking into account both a reasonable latency period and tumour localisation in relation to microwave exposure and should therefore be considered in relation to carcinogenesis (33,34).

Since one publication on glioma (18) partly overlapped three other Interphone studies (14-16) we excluded them in one analysis. Later also results from Norway have been published but without any 10-years latency period data (20). Using ≥ 10 -years latency period yielded OR = 1.7, 95% CI = 0.8-3.9, ipsilateral exposure OR = 2.4, 95% CI = 0.8-7.4 and contralateral exposure OR = 1.6, 95% CI = 0.6-4.4.

Also regarding acoustic neuroma ipsilateral exposure to microwaves yielded increased OR in the three studies with such data, significantly so in the meta-analysis. Contralateral exposure did not give significantly increased OR. These findings are similar as for glioma. Since one of the Interphone publications (23) partly overlapped two other (21,22) with 10-years latency data we excluded these two studies in one analysis. Using ≥ 10 -years latency period yielded OR = 1.7, 95% CI = 0.6-4.7, ipsilateral exposure OR = 2.0, 95% CI = 0.8-5.3 and contralateral exposure OR = 1.4, 95% CI = 0.6-3.2.

Results on meningioma for ≥ 10 years latency period were presented in four studies and ipsilateral exposure in two investigations. Thus, these results were based on lower numbers than for glioma or acoustic neuroma. No significant association was found although ipsilateral exposure gave OR = 1.7 with 95% CI 0.99-3.1.

It might be discussed if the results would be changed if our studies (1,2) were excluded from the meta-analysis. Regarding glioma this yielded for ≥ 10 -years latency period overall OR = 1.0, 95% CI = 0.8-1.2, ipsilateral exposure OR = 1.5, 95% CI = 1.1-1.9 and contralateral exposure OR = 0.9, 95% CI = 0.7-1.2. For acoustic neuroma the corresponding results gave overall OR = 0.9, 95% CI = 0.4-2.0, ipsilateral exposure OR = 2.1, 95% CI = 0.7-6.1 and contralateral exposure OR = 1.0, 95% CI = 0.6-1.6. Regarding meningioma overall OR was 1.0, 95% CI = 0.6-1.6. Only one study (14) remained for calculations of ipsilateral and contralateral exposure (Table VI).

As shown above an association was still found between mobile phone use and ipsilateral glioma and acoustic neuroma, significantly so for glioma, even if our studies (1,2) were excluded. Another meta-analysis that did not include our studies found a significant association between mobile phone use and all brain tumours using ≥ 10 years latency

period with OR = 1.25, 95% CI = 1.01-1.54 (35). One more meta-analysis was performed on mobile phone use yielding for contralateral brain tumours OR = 1.0, 95% CI = 0.8-1.4 and for ipsilateral brain tumours OR = 1.3, 95% CI = 0.99-1.9. No analysis was performed for ≥ 10 year latency time (36).

In conclusion this meta-analysis gave a consistent pattern of an association between mobile phone use and ipsilateral glioma and acoustic neuroma using ≥ 10 -years latency period. No association was found for contralateral tumours. These results are most likely of biological relevance and further strengthen the hypothesis of a carcinogenic effect from microwave emissions from mobile phones.

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Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use

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Abstract. Previous studies have shown a consistent association between long-term use of mobile and cordless phones and glioma and acoustic neuroma, but not for meningioma. When used these phones emit radiofrequency electromagnetic fields (RF-EMFs) and the brain is the main target organ for the hand-held phone. The International Agency for Research on Cancer (IARC) classified in May, 2011 RF-EMF as a group 2B, i.e. a 'possible' human carcinogen. The aim of this study was to further explore the relationship between especially long-term (>10 years) use of wireless phones and the development of malignant brain tumours. We conducted a new case-control study of brain tumour cases of both genders aged 18-75 years and diagnosed during 2007-2009. One population-based control matched on gender and age (within 5 years) was used to each case. Here, we report on malignant cases including all available controls. Exposures on e.g. use of mobile phones and cordless phones were assessed by a self-administered questionnaire. Unconditional logistic regression analysis was performed, adjusting for age, gender, year of diagnosis and socio-economic index using the whole control sample. Of the cases with a malignant brain tumour, 87% (n=593) participated, and 85% (n=1,368) of controls in the whole study answered the questionnaire. The odds ratio (OR) for mobile phone use of the analogue type was 1.8, 95% confidence interval (CI)=1.04-3.3, increasing with >25 years of latency (time since first exposure) to an OR=3.3, 95% CI=1.6-6.9. Digital 2G mobile phone use

rendered an OR=1.6, 95% CI=0.996-2.7, increasing with latency >15-20 years to an OR=2.1, 95% CI=1.2-3.6. The results for cordless phone use were OR=1.7, 95% CI=1.1-2.9, and, for latency of 15-20 years, the OR=2.1, 95% CI=1.2-3.8. Few participants had used a cordless phone for >20-25 years. Digital type of wireless phones (2G and 3G mobile phones, cordless phones) gave increased risk with latency >1-5 years, then a lower risk in the following latency groups, but again increasing risk with latency >15-20 years. Ipsilateral use resulted in a higher risk than contralateral mobile and cordless phone use. Higher ORs were calculated for tumours in the temporal and overlapping lobes. Using the meningioma cases in the same study as reference entity gave somewhat higher ORs indicating that the results were unlikely to be explained by recall or observational bias. This study confirmed previous results of an association between mobile and cordless phone use and malignant brain tumours. These findings provide support for the hypothesis that RF-EMFs play a role both in the initiation and promotion stages of carcinogenesis.

Introduction

In May, 2011, the International Agency for Research on Cancer (IARC) at WHO evaluated the carcinogenic effect to humans from radiofrequency electromagnetic fields (RF-EMF). It included radiation from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields. It was concluded that RF-EMF is a group 2B, i.e. a 'possible' human carcinogen (1,2).

The IARC evaluation of mobile phones was based mainly on case-control studies from the Hardell group in Sweden and the IARC Interphone study. Both sets of studies provided corroborative results, demonstrating an association between two types of brain tumours, glioma and acoustic neuroma, with exposure to RF-EMF from wireless phones. There was no consistent pattern of an association within the studied latency period (time since first exposure) with the most common benign brain tumour, meningioma, suggesting specificity for these other tumour types. However, it should be noted that in Interphone a reduced risk was found for glioma among regular users of mobile phones but an increased risk was found in the highest cumulative exposure group, >1,640 h (3). Clearly an increased risk was found

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using 1-1.9 years as reference entity (data not shown). The pros and cons in the Interphone study have been discussed in several articles, e.g. Hardell *et al* (4,5), Cardis and Sadetzki (6).

We first provide some background to the development of the wireless technology because of its relevance to understanding the nature of exposures and exposure assessments.

The Nordic countries were among the first countries in the world to widely adopt wireless telecommunications technology. Analogue phones (NMT, Nordic Mobile Telephone System) were introduced in the early 1980s using both 450 and 900 Megahertz (MHz) frequencies. NMT 450 was used in Sweden from 1981, but closed down on 31 December, 2007; NMT 900 operated during 1986-2000.

The digital system (GSM, Global System for Mobile Communication) using dual band, 900 and 1,800 MHz, started to operate in 1991, and it now dominates the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900/2,100 MHz RF fields has been introduced worldwide in recent years, and in Sweden in 2003. Currently, the fourth generation, 4G (Terrestrial 3G), operating at 800/2,600 MHz, and Trunked Radio Communication (TETRA 380-400 MHz) are being established in Sweden and elsewhere in Europe. Nowadays mobile phones are used more than landline phones in Sweden (<http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf>). Worldwide, an estimate of 5.9 billion mobile phone subscriptions was reported at the end of 2011 by the International Telecommunication Union (<http://www.itu.int/ITU-D/ict/facts/2011/material/ICTFactsFigures2011.pdf>).

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800-900 MHz RF fields, but since the early 1990s using a digital 1,900 MHz system. They are very common, overtaking phones connected to landlines. Also, these devices emit RF-EMF radiation when used and should be equally considered as mobile phones when human health risks are evaluated.

The old analogue phones in Sweden, the so called NMT, had an output power of 1 W and were very seldom down-regulated giving lower RF-EMF emissions when used since the distance between the base stations was several kilometers. The GSM phones are transmitting in a pulsed mode, active 1/8 of the time, and with a maximum output power of 2 W. This could be downregulated depending on the distance to the base stations. A typical mean value for the average output power is around 50-60 mW. The phone always starts the call with the maximum power before going down in power. The digital cordless phones operate in pulsed mode with a duty cycle of 1/24, the peak power is 250 mW. It is only the newer models that have regulation of the output power. The old ones always stayed with peak 250 mW, giving a time average of about 10 mW.

The absorption pattern, i.e. SAR values, associated with the phones is very different between different phones; some can give the peak value above the ear, some on the ear, and some even below the ear, see for instance Wilén *et al* (7). There are no known measurements of SAR for the cordless phones.

The first indication of an increased risk for brain tumours associated with the use of mobile phones was published more than 10 years ago (8). For tumours located in the temporal, occipital or temporoparietal lobe areas of the brain, an increased risk was found for ipsilateral mobile phone use.

Exposure to radiation from wireless phones (mobile and cordless) is generally highest in the part of the brain that is near to the ear, the temporal lobe, on the same side of the head as the phone is generally held, ipsilateral exposure (9).

However, because these early results were based on low numbers of exposed people and different histopathological types of brain tumours, no firm conclusions could be drawn. Furthermore, this first study did not include the use of cordless phones (8,10). The next study from the Hardell group included cases diagnosed in the period 1997-2003, and was larger than the first study. This time, the use of cordless phones was also assessed. Further details may be found in the various publications that are based on the results from these studies (11-16).

The Interphone study was conducted at 16 research centres in 13 countries during varying time periods between 2000 and 2004. It was an international collaboration on brain tumour risk and mobile phone use, conducted under the aegis of IARC. Cases were diagnosed during 2000-2004, with slight variations in the different study regions (3,17). In contrast to the Hardell group studies, Interphone did not assess or present results for cordless phone use. These are the only studies to date that provide results for latency periods exceeding 10 years.

Exponential increases in access to and ownership of wireless phones in most countries has occurred since the end of the 1990s. Because the technology is relatively recent, results on health risks for long-term use, exceeding decades, are still lacking. Moreover, in Sweden the major increase in use (duration in minutes of calls) and exposure to radiation fields from these phones (not merely access to or ownership of) in the general population is most evident after 2003 (18).

To obtain results for longer exposure periods of wireless phone use, we conducted an entirely new study on brain tumours. In this article, we present the most recent results for malignant brain tumours. Updated results and discussions of this research area can be found elsewhere (5,19). The study was approved by the ethics committee: Regional Ethics Committee, Uppsala University; Uppsala, Sweden. DNR 2005:367.

Materials and methods

Case ascertainment. Sweden comprises six administrative medical regions each having a cancer registry; annually, these registries are linked to the national Swedish cancer register. The reporting to us of newly diagnosed brain tumour cases varied between these six regions, from once a month to once a year from one region (Umeå). In our previous studies covering the time period 1997-2003, we received reports on new cases as these arose, or one to two times per month. For logistical reasons, this was not possible in the present study for the different cancer registries.

Inclusion criteria. The inclusion criteria specified both men and women aged 18-75 years at the time of brain tumour diagnosis (ICD-7 code 193.0) during the period 2007 to 2009. Furthermore, the diagnosis had to be verified histopathology for all cases and only living cases were included in the study. The cases were reported to us from population-based cancer registries from across all regions of Sweden. For administrative reasons, the Gothenburg region could be included for only the years 2008 and 2009. All patients, both with a malignant

or a benign brain tumour, were included in the whole study. Once the inclusion criteria were satisfied, the attending physician was contacted for permission to include the case in the study. The present publication presents results for cases with a malignant brain tumour.

The Swedish Population Registry was used for identification of controls. One control matched on gender and in 5-year age groups was used for each case, both malignant and benign brain tumour cases. All controls were recruited from the same source population (residential) as the cases. Controls were only selected to the finally included living cases. They were assigned the same year as the diagnosis of the respective case as the cut-off in assessing exposure. Thus, the same methods were used as in our previous studies (12,13).

Exposure assessment. Use of wireless phones, both mobile and cordless, was assessed by a self-administered questionnaire supplemented over the phone. Both cases and controls received an introduction letter and were asked if they were willing to participate and answer the included questionnaire. To get as high response rate as possible two reminders were sent. All mobile phones in Sweden have had either prefix 010 (analogue type) or prefix 07 (digital type). Thus by asking for the prefix it was possible both to verify use of a mobile phone and the type. The questionnaire also contained a number of other questions on, for example, occupational history, exposure to different agents, smoking habits, medical history including hereditary risk factors, and exposure to ionizing radiation. All questions were supplemented over the phone by the interviewer at the same time. A structured protocol was used for all questions as a prompt. The written questionnaire was evaluated and further interviews were made according to the protocol. Most subjects were also phone interviewed to clarify different aspects in the questionnaire. There was no difference regarding supplementary interviews according to being a case (75% supplemented) or a control (70% supplemented). Adjusting for whether or not a supplementary interview was performed did not change the results of the logistic regression analysis.

The ear that had mostly been used during calls with mobile and/or cordless phones was assessed by separate questions; >50% of the time for one side, or equally much for both sides. After informed consent from the patients, medical records including computer tomography (CT) and/or magnetic resonance imaging (MRI) were used to define tumour localization. The matched control was assigned the same side as the tumour of the respective case using the same method as in previous studies (3,12,13,17). The whole procedure was blind to exposure status. Use of the wireless phone was defined as ipsilateral ($\geq 50\%$ of the time), or contralateral ($< 50\%$ of the time) in relation to tumour side.

All questionnaires received a unique identity number that did not indicate case or control status. Thus, the interviewer was blind to case or control status throughout data processing. The interviewers used a structured protocol that avoided questions that could reveal if the interviewee was a case or a control. All information was coded and entered into a database. A random sample of the questionnaires was coded twice by two independent persons with similar results. Being a case or control was revealed only during the statistical analyses.

Statistical methods. All analyses were done using StataSE 12.1. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis including the whole control sample (i.e. matched to both malignant and benign cases) to increase the power in the study. This was possible since adjustment/stratification was made for the two matching variables (gender, and age within 5 years).

The unexposed category consisted of people who reported no use of mobile or cordless phones, or a latency period ≤ 1 year (amount of time between first use of the phone and year of diagnosis). As noted earlier, the same year as for each case diagnosis was used for the corresponding control as the cut-off for exposure accumulation. Furthermore, because of the low number of unexposed cases, a further criterion was used, i.e. regardless of latency being ≤ 1 year, cumulative use ≤ 39 h (3rd percentile) of wireless phones in total among the controls was also used as cut-off for the referent group of 'no exposure' among cases and controls. The 3rd percentile was chosen to approximately correspond to one working week.

A latency period ≤ 1 year was used, as in our previous studies, to make it possible to analyse a late effect (promotion) in brain tumour genesis (12,13). Note that latency (time since first use until date of diagnosis) was calculated separately for the respective phone type or combination of phones that were analysed.

Latency was analysed using six time periods, >1-5 years, >5-10 years, >10-15 years, >15-20 years, >20-25 years and >25 years. Cumulative use of the phone types was analysed in quartiles based on use of wireless phones in total among the controls (first quartile >39-405 h, second quartile 406-1,091 h, third quartile 1,092-2,376 h, fourth quartile >2,376 h). Wald's test was performed to analyze the trend of the ORs across the quartiles of the phone types. Latency and cumulative use were also analysed as continuous variables (per year of latency, per 100 h cumulative use) to further explore the dose-response relations.

Adjustment was made for the matching variables gender, age (as a continuous variable) and year of diagnosis. In addition, adjustment was made for socio-economic index (SEI) divided into four categories (blue-collar worker, white-collar worker, self-employed, no work). Note that laterality of the tumour was not available for all cases, e.g., for midline tumours, or for tumours in both hemispheres (n=38). These were dropped from the laterality analysis together with controls (n=306) matched to cases without laterality data in the whole material. Laterality analysis was not made for the whole group of wireless phone users since the side differed for mobile phone and cordless phone for some of the included persons using both phone types (8.3% of the cases, 8.9% of the controls).

Restricted cubic splines were used to visualize the relationship between cumulative use and latency of wireless phones and malignant brain tumours. Adjustment was made for the same variables as in the logistic regression. Four knots were used at the 5th, 35th, 65th and 95th percentiles as suggested by Harrell (20). A p-value for non-linearity was estimated by testing if the coefficient of the second and third spline was equal to zero (20).

Most of the participating cases with a benign brain tumour (n=814) had meningioma (n=709). These results will be presented in another publication. As a further step to evaluate potential recall or observational bias the meningioma cases in the same study were used as the reference entity to the cases with malignant brain tumour, c.f. Hardell (21).

Table I. Descriptive data on the study sample of malignant brain tumour cases diagnosed between 2007 and 2009.

	Malignant
Reported from cancer registries	1,334
Deceased	520
Wrong diagnosis	18
Diagnosed other years	2
No address available	6
Language problems	2
Not capable to participate	47
No permission from physician	56
Total included	683
Refused to participate	90
Answered the questionnaire	593

Results

In Table I, the number of reported malignant cases from the regional cancer registries is shown. The largest numbers of cases excluded from the study were those who were ‘deceased’ (n=520), mostly with an astrocytoma WHO grade IV (glioblastoma multiforme). The implications of this exclusion are addressed below in the discussion section. The second largest group excluded was that with ‘no permission from the treating physician’ (n=56). Thus, of the 1,334 cases with a malignant tumour, 683 (51%) remained eligible for inclusion. Regarding cases with a benign brain tumour (n=920) these results are presented in separate articles; one on meningioma (22) one on acoustic neuroma (23).

Medical records and reports to the cancer registries were used to classify tumour histopathology. Of the 683 cases of malignancy, 593 (87%) answered the questionnaire; 350 were men and 243 women. In Table II, the various diagnoses of malignant brain tumours are shown. Most of the cases were diagnosed with a glioma (astrocytoma, oligodendroglioma, other/mixed glioma; n=546; 92%) with astrocytoma being the most common subtype (n=415; 76% of glioma).

For the total sample of 1,601 cases, an equal number of matched controls received a questionnaire. Note that one case had two tumours, astrocytoma grade IV and meningioma and another case had ependymoma and acoustic neuroma. Of the included controls, 1,368 (85%) answered the questionnaire, 564 were men and 804 women. The mean age was 52 years for cases with malignant brain tumour (median 55, range 18-75) and 55 years for all controls (median 58, range 19-75). Of the cases with meningioma 200 were men and 509 were women. The mean age was 57 years (median 59, range 23-75 years).

In Table III, the results are shown for all malignant brain tumours and use of wireless phones. Analogue phones yielded OR=1.8, 95% CI=1.04-3.3 increasing to OR=3.3, 95% CI=1.6-6.9 in the latency group of >25 years. Note that the latency time was counted from the first use of the specific telephone type; for instance, a 2G user may have used an analogue phone before.

Use of digital 2G phones gave an overall OR=1.6, 95% CI=0.996-2.7. In the latency group >1-5 years, an OR=1.8, 95% CI=1.01-3.4 was calculated. Lower ORs were obtained in the latency groups >5-10 years and >10-15 years increasing to

Table II. Histopathology of all malignant brain tumours.

Histopathology	Men		Women		Total	
	n	%	n	%	n	%
Astrocytoma grade I-II	53	15.1	44	18.1	97	16.4
Grade I	6	1.7	5	2.1	11	1.9
Grade II	47	13.4	39	16.0	86	14.5
Astrocytoma grade III-IV	205	58.6	113	46.5	318	53.6
Grade III	30	8.6	15	6.2	45	7.6
Grade IV	175	50.0	98	40.3	273	46.0
Medulloblastoma	3	0.9	2	0.8	5	0.8
Oligodendroglioma	32	9.1	37	15.2	69	11.6
Ependymoma	10	2.9	9	3.7	19	3.2
Other/mixed glioma	39	11.1	23	9.5	62	10.5
Other malignant	8	2.3	15	6.2	23	3.9
All malignant	350		243		593	

an OR=2.1, 95% CI=1.2-3.6 with latency >15-20 years, which was the longest latency interval.

The results for digital 3G phones showed highest risk in the >5-10 years latency group, OR=1.6, 95% CI=0.5-4.9. This result was based on low numbers and no long-term users existed since this technology is new. One case and no control reported use of only a 3G phone.

A similar pattern as for digital 2G phones was found for use of cordless phones with increased risk in the shortest latency period, then dropping off and again increasing in the latency group >15-20 years to an OR=2.1, 95% CI=1.2-3.8. Only 6 cases and 13 controls reported use of cordless phone with latency >20-25 years, so these results are less reliable.

In Table III we also display results for all uses of digital phones (2G, 3G and/or cordless phone; ‘digital type’). The pattern of an association was similar to 2G and cordless phones, with a statistically significant increased risk in the shortest latency period, then dropping off and again statistically significant increased risk in the latency group >15-20 years giving an OR=2.2, 95% CI=1.3-3.6.

We further show results for all wireless phone use combined. An increased risk was found overall with an OR=1.7, 95% CI=1.04-2.8, increasing in the shortest latency period >1-5 years to an OR=2.6, 95% CI=1.4-5.0, then decreasing somewhat with increasing latency; but with the highest risk is in the longest latency period >25 years with an OR=3.0, 95% CI=1.5-6.0.

In Table IV results are displayed when patients with meningioma in the same study are used as controls. The results were similar as in Table III using the population based controls. Most ORs were somewhat higher using meningioma cases as controls.

Overall, in Table V, ipsilateral use of analogue phones was associated with a higher risk, OR=2.3, 95% CI=1.2-4.5, than contralateral use, yielding OR=1.4, 95% CI=0.7-2.9. Ipsilateral use of digital 2G phones yielded a higher OR than contralateral use. Mobile phones overall for ipsilateral use, resulted in an OR=1.7, 95% CI=1.01-2.9; and for contralateral use, an OR=1.4, 95% CI=0.8-2.5. Ipsilateral use of cordless phones yielded an OR=1.9, 95% CI=1.1-3.2 compared with an OR=1.6, 95% CI=0.9-2.8 for contralateral use.

Table III. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours (n=593).

Latency	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone			Digital type			Wireless phone					
	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co			
Total, >1 year	1.8	1.04-3.3	144/260	1.6	0.996-2.7	546/1,208	1.2	0.6-2.4	67/140	1.6	0.99-2.7	548/1,217	1.7	1.1-2.9	461/1,015	1.7	1.04-2.8	571/1,261	1.7	1.04-2.8	571/1,261	1.7	1.04-2.8	571/1,261
>1-5 years	-	-	0/0	1.8	1.01-3.4	42/109	1.2	0.6-2.4	55/126	1.8	1.002-3.4	41/108	2.0	1.1-3.4	102/209	2.6	1.4-4.9	33/63	2.6	1.4-5.0	32/61	2.6	1.4-5.0	32/61
>5-10 years	0.6	0.1-3.1	2/10	1.6	0.97-2.7	213/477	1.6	0.5-4.9	12/14	1.7	0.98-2.8	190/423	1.6	0.95-2.7	188/436	1.6	0.9-2.7	177/421	1.6	0.98-2.8	163/378	1.6	0.98-2.8	163/378
>10-15 years	1.4	0.7-3.0	25/51	1.3	0.8-2.2	187/453	-	-	0/0	1.3	0.8-2.2	163/399	1.6	0.9-2.8	108/248	1.4	0.8-2.3	212/523	1.3	0.8-2.2	184/466	1.3	0.8-2.2	184/466
>15-20 years	1.4	0.7-2.7	39/86	2.1	1.2-3.6	104/169	-	-	0/0	1.5	0.8-2.6	76/174	2.1	1.2-3.8	57/109	2.2	1.3-3.6	143/241	1.7	1.02-3.0	110/231	1.7	1.02-3.0	110/231
>20-25 years	2.1	1.1-4.0	48/80	-	-	0/0	-	-	0/0	1.9	1.1-3.5	48/80	1.5	0.5-4.6	6/13	1.5	0.5-4.6	6/13	1.9	1.04-3.4	52/92	1.9	1.04-3.4	52/92
>25 years	3.3	1.6-6.9	30/33	-	-	0/0	-	-	0/0	2.9	1.4-5.8	30/33	-	-	0/0	-	-	0/0	3.0	1.5-6.0	30/33	3.0	1.5-6.0	30/33

Unexposed latency ≤1 year; wireless phone use ≤39 h (3rd percentile). Number of exposed cases (Ca) and population based controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

Table IV. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours (n=593) and meningioma cases (n=708) as reference entity.

Latency	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone			Digital type			Wireless phone					
	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co			
Total, >1 year	2.2	1.1-4.1	144/108	1.8	1.1-3.2	545/592	2.3	0.9-5.7	67/47	1.8	1.1-3.2	547/593	1.8	1.03-3.1	460/521	1.8	1.1-3.1	570/640	1.8	1.1-3.1	570/640	1.8	1.1-3.1	570/640
>1-5 years	-	-	0/0	1.7	0.9-3.4	42/70	2.4	0.96-6.1	55/40	1.7	0.9-3.4	41/69	2.0	1.1-3.7	102/109	2.1	1.05-4.3	33/43	2.1	1.04-4.3	32/42	2.1	1.04-4.3	32/42
>5-10 years	1.1	0.1-8.3	2/3	2.0	1.1-3.5	212/235	1.4	0.3-6.0	12/7	1.9	1.1-3.4	189/216	1.7	0.96-3.0	187/216	1.8	1.05-3.2	176/221	1.9	1.05-3.3	162/205	1.9	1.05-3.3	162/205
>10-15 years	2.0	0.8-4.9	25/21	1.5	0.9-2.7	187/212	-	-	0/0	1.5	0.8-2.7	163/185	1.6	0.9-2.8	108/128	1.5	0.9-2.7	212/248	1.4	0.8-2.5	184/226	1.4	0.8-2.5	184/226
>15-20 years	1.8	0.8-3.7	39/39	2.3	1.2-4.3	104/75	-	-	0/0	1.8	0.9-3.3	76/78	2.1	1.1-4.1	57/61	2.2	1.2-3.9	143/121	1.9	1.1-3.4	110/115	1.9	1.1-3.4	110/115
>20-25 years	2.4	1.1-5.2	48/29	-	-	0/0	-	-	0/0	2.5	1.2-5.2	48/29	1.0	0.3-3.6	6/7	1.1	0.3-3.8	6/7	2.1	1.05-4.2	52/36	2.1	1.05-4.2	52/36
>25 years	3.0	1.3-7.4	30/16	-	-	0/0	-	-	0/0	3.1	1.3-7.1	30/16	-	-	0/0	-	-	0/0	3.1	1.3-7.0	30/16	3.1	1.3-7.0	30/16

Unexposed latency ≤1 year; wireless phone use ≤39 h (3rd percentile). Number of exposed cases (Ca) and controls (Co) are given. One subject with both a malignant brain tumor and a meningioma was excluded from the analysis. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

Table V. Odds ratio (OR) and 95 % confidence interval (CI) for malignant brain tumours, total, ipsilateral and contralateral exposure.

	All			Ipsilateral			Contralateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Analogue	144/260	1.8	1.04-3.3	84/118	2.3	1.2-4.5	46/84	1.4	0.7-2.9
Digital (2G)	546/1,208	1.6	0.996-2.7	322/530	1.7	1.02-2.9	190/404	1.4	0.8-2.5
Digital (UMTS, 3G)	67/140	1.2	0.6-2.4	38/69	1.2	0.5-2.8	24/45	1.1	0.4-3.1
Mobile phone, total	548/1,217	1.6	0.99-2.7	324/534	1.7	1.01-2.9	190/407	1.4	0.8-2.5
Cordless phone	461/1,015	1.7	1.1-2.9	272/454	1.9	1.1-3.2	156/327	1.6	0.9-2.8

Ipsilateral, $\geq 50\%$ use of the phone on the same side as the tumour was located. Contralateral, $< 50\%$ use of the phone on the same side as the tumour was located. Tumor laterality not available for 38 cases and 306 controls. Number of exposed cases (Ca) and population based controls (Co) for ever use of the phone type according to exposure criteria are displayed. Note that the subjects could have used more than one phone type. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

Cumulative use of wireless phones was analysed in quartiles based on use of wireless phones in total among the controls, see Table VI. Note that for the various phone types, the cumulative time was counted for use of the specific phone, but for the category 'mobile phones' all types of mobile phones were included, and for 'wireless phones' also use of cordless phones was included. For all phone types and combinations thereof, the highest ORs were found in the fourth quartile, see Table VI. Thus, for analogue phones, an OR=7.7, 95% CI=2.5-24 (p-trend=0.01) was calculated, although based on low numbers. The digital (2G) phone yielded an OR=3.2, 95% CI=1.8-5.6 (p-trend <0.0001) in the same category. Also, UMTS (3G) resulted in an increased risk with an OR=5.1, 95% CI=0.8-32 (p-trend=0.28); but based on low numbers. The fourth quartile of cumulative cordless phone use yielded an OR=3.1, 95% CI=1.8-5.5 (p-trend <0.0001). Wireless phone use overall resulted in an OR=2.5, 95% CI=1.5-4.2 (p-trend=0.0001) in the fourth quartile with >2,376 h of cumulative use.

The ORs increased to statistically significant per 100 h of cumulative use for all types of phones except for UMTS (3G) with borderline significance, see Table VII. In a multivariate analysis including all phone types (i.e. analogue, 2G, 3G and cordless phone) similar results were found although not statistically significant for analogue phones (OR=1.015, 95% CI=0.996-1.034; data not shown). Wireless phone use increased the risk with an OR=1.009, 95% CI=1.006-1.012 per 100 h of cumulative use, Table VII. The risk increased also per additional year of latency, mostly for analogue phones, OR=1.044, 95% CI=1.019-1.070. These results did not change if years of use of any mobile or cordless phone prior to the respective type was included as a covariate in each analysis of the individual phone types (data not shown). Wireless phones overall yielded OR=1.018, 95% CI=1.001-1.036.

In Table VIII, results are presented for malignant brain tumours localized in the temporal lobe or overlapping temporal and adjacent lobe. Higher risk estimates were obtained than for the overall results. Thus, mobile phone use in the latency group >25 years resulted in an OR=4.8, 95% CI=1.7-14 compared with an OR=2.9, 95% CI=1.4-5.8 overall (see Table III for comparison). Cordless phone use in the group with the longest latency, >20-25 years, resulted in an OR=3.3, 95% CI=0.8-14 in the temporal lobe versus an OR=1.5, 95% CI=0.5-4.6 overall, although based on low numbers. Also, for overall wireless phone use, the highest OR was found among those with the

longest latency, >25 years, with an OR=5.1, 95% CI=1.8-15 for tumours in the temporal lobe.

In Table IX, results are displayed for use of only one type of wireless phone. Regarding analogue phones, all cases and controls had also used other phone types. Use of only digital 2G types resulted in the highest risk in the shortest latency period >1-5 years with an OR=3.4, 95% CI=1.2-9.5. The risk decreased somewhat with longer latency, but increased again in the longest latency group >15-20 years to an OR=1.8, 95% CI=0.6-4.9. A similar risk pattern was found for use of cordless phones only, with even higher risk estimates, although based on low numbers in the longest latency groups. Use of wireless phones of only the digital type (2G, 3G, cordless phone) yielded an OR=1.7, 95% CI=1.01-2.7 overall, increasing to an OR=2.7, 95% CI=1.4-5.3 in the latency group >1-5 years. A decreased risk was seen with the longer latency period, but, again, it increased with latency >15-20 years to an OR=1.9, 95% CI=1.1-3.4.

Most types of malignant brain tumours were glioma (n=546). Separate analysis of that group of tumours gave similar results as for the whole group of malignant brain tumours. Mobile phone use with latency >25 years resulted in an OR=2.8, 95% CI=1.4-5.7 (data not shown). Also, for cordless phone use, the results were similar as in the overall analysis. Thus, with a latency >15-20 years, an OR=1.9, 95% CI=1.05-3.5 was found.

Fig. 1 illustrates the results for cumulative use of wireless phones using the restricted cubic splines method. There was a linear increasing trend of the risk up to 10,000 h (p, non-linearity=0.52). Fig. 2 demonstrates a borderline statistically significant non-linear relationship for the risk and latency using data up to 28 years from first use of a wireless phone before tumour diagnosis (p, non-linearity=0.05). Highest risk was found with longest latency. This finding gives support for RF-EMFs to play a role in the initiation and promotion stages of carcinogenesis.

Discussion

Main results and latency (time since first exposure) effects. The main result of this study was a statistically significant increased risk for malignant brain tumours associated with use of wireless phones, OR=1.7, 95% CI=1.04-2.8. The risk increased further in the latency group >1-5 years, but lower ORs were found in the latency groups >5-10 years and >10-15 years. With longer latency periods, the OR increased

Table VI. Malignant brain tumours (n=593).

Quartile	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone			Digital type			Wireless phone		
	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co
First	1.7	0.9-3.0	90/184	1.4	0.8-2.3	202/620	1.1	0.5-2.4	35/87	1.4	0.8-2.3	190/587	1.3	0.8-2.2	164/434	1.5	0.9-2.5	113/327	1.5	0.9-2.5	108/317
Second	1.6	0.8-3.4	22/47	1.9	1.1-3.3	138/260	1.0	0.4-2.6	16/34	1.7	1.02-3.0	126/261	1.7	1.01-3.0	120/278	1.4	0.8-2.4	113/320	1.4	0.8-2.4	110/314
Third	2.6	1.2-6.0	18/23	1.4	0.8-2.5	84/199	1.7	0.6-4.8	11/17	1.5	0.9-2.7	95/210	2.1	1.2-3.7	98/194	1.7	1.01-2.9	139/317	1.7	1.003-2.9	137/315
Fourth	7.7	2.5-24	14/6	3.2	1.8-5.6	122/129	5.1	0.8-32	5/2	2.8	1.6-4.8	137/159	3.1	1.8-5.5	79/109	2.6	1.5-4.3	206/297	2.5	1.5-4.2	216/315

Odds ratio (OR) and 95% confidence interval (CI) for cumulative use of wireless phones in quartiles based on use of wireless phones among controls in total. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used. First quartile >39-405 h; second quartile 406-1,091 h; third quartile 1,092-2,376 h; fourth quartile >2,376 h. p-trend (Wald's test): analogue, p=0.001; digital (2G), p<0.0001; digital (UMTS, 3G), p=0.28; mobile phone, total, p=0.0001; cordless phone, p<0.0001; digital type, p<0.0001; wireless phone, p=0.0001.

Table VII. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours per 100 h cumulative use and per year of latency.

	Per 100 h cumulative use		Per year of latency	
	OR	95% CI	OR	95% CI
Analogue	1.037	1.014-1.060	1.044	1.019-1.070
Digital (2G)	1.012	1.007-1.017	1.013	0.989-1.037
Digital (UMTS, 3G)	1.031	0.988-1.076	1.043	0.894-1.216
Mobile phone, total	1.011	1.006-1.015	1.016	0.999-1.034
Cordless phone	1.013	1.007-1.020	1.014	0.992-1.036
Digital type	1.010	1.006-1.013	1.016	0.994-1.039
Wireless phone	1.009	1.006-1.012	1.018	1.001-1.036

Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used.

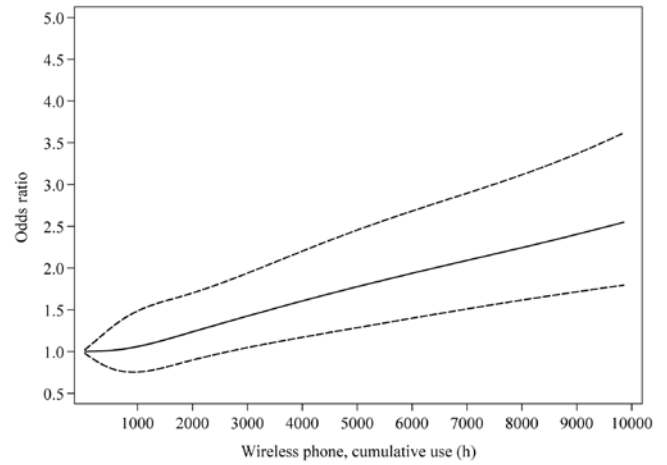


Figure 1. Restricted cubic spline plot of the relationship between cumulative use of wireless phones and malignant brain tumours. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used.

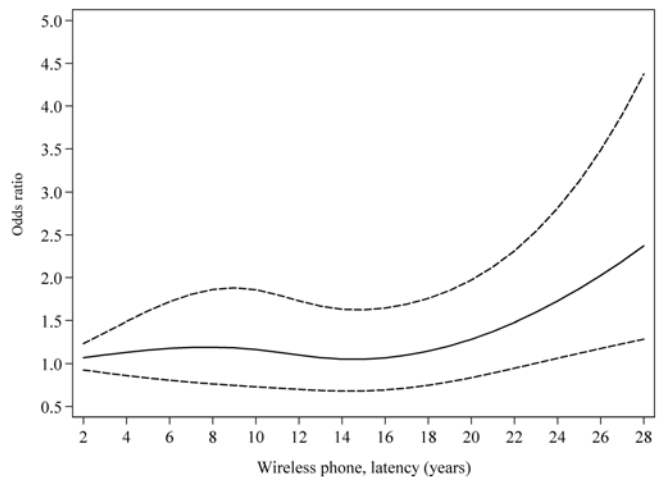


Figure 2. Restricted cubic spline plot of the relationship between latency of wireless phones and malignant brain tumours. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used.

Table VIII. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours located in temporal (n=161) and overlapping lobes [temporofrontal (n=31), temporoparietal (n=22), temporooccipital (n=13)]; in total n=227.

Latency	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone			Digital type			Wireless phone					
	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co			
Total, >1 year	2.4	0.9-6.1	67/260	2.4	0.99-5.6	211/1,208	1.7	0.5-5.9	17/140	2.3	0.99-5.6	212/1,217	2.5	1.04-6.0	175/1,015	2.5	1.05-5.9	221/1,261	2.5	1.05-5.9	221/1,261	2.5	1.05-5.9	221/1,261
>1-5 years	-	-	0/0	3.3	1.2-8.7	19/109	1.6	0.5-5.9	14/126	3.1	1.2-8.4	18/108	3.0	1.2-7.6	41/209	4.4	1.6-12	15/64	4.5	1.6-13	14/61	4.5	1.6-13	14/61
>5-10 years	0.9	0.1-9.1	1/10	2.4	0.96-5.7	79/477	2.1	0.3-14	3/14	2.4	0.97-5.8	69/423	2.2	0.9-5.4	68/436	2.4	0.99-5.9	68/420	2.4	0.98-5.9	60/378	2.4	0.98-5.9	60/378
>10-15 years	1.6	0.5-5.3	11/51	1.8	0.7-4.3	69/453	-	-	0/0	1.6	0.7-4.1	57/399	2.3	0.9-5.7	41/248	1.8	0.8-4.5	77/523	1.8	0.7-4.4	66/466	1.8	0.7-4.4	66/466
>15-20 years	1.7	0.6-5.0	18/86	3.0	1.2-7.4	44/169	-	-	0/0	2.0	0.8-5.2	31/174	2.8	1.05-7.4	21/109	3.0	1.2-7.4	57/241	2.3	0.9-5.8	42/231	2.3	0.9-5.8	42/231
>20-25 years	2.6	0.9-7.2	21/80	-	-	0/0	-	-	0/0	2.7	1.02-7.3	21/80	3.3	0.8-14	4/13	3.4	0.8-14	4/13	3.4	0.8-14	4/13	2.7	1.04-7.2	23/92
>25 years	5.1	1.7-16	16/33	-	-	0/0	-	-	0/0	4.8	1.7-14	16/33	-	-	0/0	-	-	0/0	5.1	1.8-15	16/33	5.1	1.8-15	16/33

Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used.

further with highest risk in the latency group >25 years, OR=3.0, 95% CI=1.5-6.0. From Table III, analogue mobile phones produced a risk increasing with latency, with the highest risk in the latency group >25 years. The OR increased statistically significantly per year of latency, see Table VII. A different pattern was seen for digital wireless phones, both the mobile and cordless types. The risk was higher in the short latency group >1-5 years, then dropped off and increased again with >15 years of latency. Regarding digital 3G mobile phones no conclusions could be drawn. The technique is new and no subject had latency >10 years.

No case or control had used a digital mobile phone with latency >25 years. Only 6 cases and 13 controls had used a cordless phone with latency >20-25 years, so the results for cordless phones with longest latency time were less reliable. Only one case had used only a 3G phone, so firm conclusions about the risk with 3G mobile phone use are not possible from this study. Regarding the use of digital 2G mobile and cordless phones, the OR increased per year of latency with statistically borderline significance. This was explained by the fact that the risk increase was U-shaped in relation to latency period. A further illustration is given in the restricted cubic spline plot showing a borderline statistically significant non-linear relationship, see Fig. 2.

Regarding long-term use of wireless phones and the association with brain tumours, it has not been possible to study longer latency periods than >10 years previously since the technology is too recent. This is the first study to examine effects with a latency time >25 years. This was for analogue phones. Regarding digital 2G mobile phones, the longest duration of latency was >15-20 years. The longest latency for use of cordless phones was >20-25 years with few subjects in that category. The results in this study indicate an early effect in brain tumour genesis seen both for analogue and digital phones, an initiator. Regarding digital phones, we found also a late effect in tumour development, a promoter.

Of interest is that we found that the risk was elevated among those who reported using only digital 2G mobile phones and only cordless phone, see Table IX. The risk was even higher for the use of only cordless phones, a fact that is of importance since all studies other than those from the Hardell group have not paid attention to such use. Including the use of cordless phones in the 'unexposed group' would have biased risk estimates towards unity, as discussed elsewhere (4,5).

Cumulative use. Cumulative use of wireless phones in our present study was divided into quartiles based on cumulative use of wireless phones overall among controls. For all phone types, the highest risk was found in the fourth quartile >2,376 h of cumulative use. This corresponds to about 40 min of wireless phone use per day for 10 years. There was a statistically significant trend for the different phone types, mobile phone use overall, and wireless phones overall. An especially elevated OR was calculated for analogue phone use, OR=7.7, 95% CI=2.5-24, in the fourth quartile. Also, 3G mobile phone use resulted in increasing risk, highest in the fourth quartile, but based on low numbers and no statistically significant trend (p=0.28). These results are also reflected in Table VII, with statistically significant increasing risk per 100 h of cumulative use for all phone types, except for 3G with borderline statistical significance. A

Table IX. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours (n=593).

Latency	Analogue only			Digital (2G) only			Digital (UMTS, 3G) only			Cordless phone only			Digital type only		
	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co
Total, >1 year	-		0/0	1.6	0.9-2.9	78/176	-		1/0	3.5	1.6-7.8	23/44	1.7	1.01-2.7	427/1,001
>1-5 years	-		0/0	3.4	1.2-9.5	9/13	-		1/0	5.8	2.0-17	10/14	2.7	1.4-5.3	32/61
>5-10 years	-		0/0	1.6	0.8-3.2	33/79	-		0/0	3.7	1.3-11	9/19	1.7	1.03-3.0	162/370
>10-15 years	-		0/0	1.3	0.6-2.6	28/68	-		0/0	2.0	0.4-9.4	3/8	1.3	0.8-2.2	163/418
>15-20 years	-		0/0	1.8	0.6-4.9	8/16	-		0/0	2.9	0.2-39	1/2	1.9	1.1-3.4	68/140
>20-25 years	-		0/0	-		0/0	-		0/0	-		0/1	0.6	0.1-2.7	2/12
>25 years	-		0/0	-		0/0	-		0/0	-		0/0	-		0/0

Number of exposed cases (Ca) and population based controls (Co) are given. Results are given for use of only a specific phone type or use of both mobile and cordless phones. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

linear relationship between cumulative use of wireless phones and the risk for malignant brain tumours is given in Fig. 1.

Consistency with our previous research. Clearly, digital mobile and cordless phones increase the risk of malignant brain tumours in our present study, as well as in our previous studies. For use of digital type wireless phones only, we found an OR=1.7, 95% CI=1.01-2.7. This finding is consistent with our previous result for the study period 1997-2003. Use of digital mobile and cordless phones yielded an OR=1.4, 95% CI=1.1-1.8 in that study (13). Further analysis in our previous study on use of only mobile phones yielded for glioma increased risk in the >10 year latency group, OR=2.6, 95% CI=1.7-4.1. For use of only cordless phones, an increased risk was found in the >5-10 years latency group, OR=1.9, 95% CI=1.3-2.9, whereas the result for >10 year latency was based on rather small numbers (5,15).

Furthermore, it should be noted that for the study period 1997-2003, we found an increased risk of malignant brain tumours in the latency period >5-10 years for users of wireless phones of the digital type. Thus, digital 2G phones yielded an OR=1.7, 95% CI=1.2-2.2, and for cordless phones, an OR=1.5, 95% CI=1.1-2.0 in that latency group (13). These risks increased further in the latency group >10 years, which was the longest time of wireless phone use in that study. This pattern was different for use of analogue phones, with statistically significant risk only in the group with a latency >10 years, giving an OR=2.4, 95% CI=1.6-3.4, a similar finding to that in the present study.

In summary, our results are consistent with an early effect in carcinogenesis (initiator) by analogue mobile phones, and both an early (initiator) and late (promoter) effect by wireless phones of the digital type.

Comparison with other studies, e.g. Interphone. In Interphone (data not shown), a statistically significant increased risk for glioma was seen in the group 2-4 years for regular use, with 1-1.9 years use as reference category, OR=1.68, 95% CI=1.16-2.41 (3). The highest OR was found in the 10+ years category for regular use, OR=2.18, 95% CI=1.43-3.31. Results were not presented according to type of mobile phone used. Overall, cumulative use >1,640 h in the shortest latency group of 1-4 years before reference date resulted in an increased risk, OR=3.77, 95% CI=1.25-11.4.

The highest absorption of RF-EMF emissions from a handheld phone is on the same side of the brain (ipsilateral) as the phone is used (9). Highest dose is absorbed in the temporal lobe of the brain. In previous studies, we have found risk being highest for ipsilateral wireless phone use (5,13). In Interphone, cumulative call time of mobile phones >1,640 h, resulted in glioma in the temporal lobe with an OR=1.87, 95% CI=1.09-3.22, and for ipsilateral mobile phone use, an OR=1.96, 95% CI=1.22-3.16 (3). Likewise, in our present study, the OR was higher for ipsilateral use of mobile or cordless phones, see Table V, and for malignant brain tumours in the temporal and overlapping lobes, see Table VIII.

A mean duration of mobile phone use of 2.8 years was reported in a study from USA (24). Overall, no increased risk was found for malignant brain tumours, except for a rare type, neuroepithelioma with OR=2.1, 95% CI=0.9-4.7. The type of mobile phone was not reported. No increased risk for glioma overall or in different groups of duration of regular use, at most >5 years, was reported in another study from USA (25). The type of mobile phone used was not published. An increased risk for glioma with short duration of analogue mobile phone use (1-2 years) was seen in a Finnish study, whereas no increased risk was found for digital phones (26). These results were based on low numbers. Cordless phone use was included in the 'unexposed' category in these studies, which is of interest to note since we have found an association with such phone use as reported above.

In a record linkage study from Denmark mobile phone subscribers from January 1, 1982, until December 31, 1995, were identified from the computerized files of the two Danish operating companies, TeleDenmark Mobil and Sonofon, which partly also funded the study. It has produced four articles that we have made a thorough review of (27). We concluded that its many limitations - embedded in the study design from the very beginning and mainly related to poor exposure assessment - cloud the findings of the four reports to such an extent that render them uninformative, at best. The Danish cohort study was included in the IARC evaluation of RF-EMF but the conclusion was that 'phone provider, as a surrogate for mobile phone use, could have resulted in considerable misclassification in exposure assessment' (1). Thus, the Danish cohort study is uninformative as to cancer risks from mobile phone use.

Strengths and limitations. The present study included cases of malignant brain tumours diagnosed during 2007-2009 from across Sweden. For the cases diagnosed during 1997-2003 in our previous study (5), the prevalence of use of mobile phones was highest in the age group 30-54 years for men, and 35-54 years for women. Thus, we included the age group 18-75 years in this study to allow for the longest possible latency time (28). This is in contrast to the Interphone study, which included cases aged 30-59 years. Glioma is the most common malignant brain tumour, and the most common glioma subtype is astrocytoma. Glioblastoma multiforme (WHO grade IV) accounts for 60-75% of all astrocytoma, in this study 66% of the cases with astrocytoma. The peak incidence is between 45-75 years, with a mean age of 61 years and with 80% older than 50 years (29). Thus, limiting the upper age to 59 years for cases as in Interphone (3) would diminish the possibility of finding an increased risk for the long-term use of mobile phones.

Recall and observational bias might be an issue in case-control studies. We investigated in more detail the possibility of that in one of our previous studies (11). Reporting a previous cancer or if a relative helped to fill in the questionnaire did not change the results. Potential observational bias during phone interviews was analysed by comparing the results based on exposure assessment before and after additional phone interviews. The results were similar with no statistically significant differences, showing that our results were unlikely to be explained by observational bias (11).

To further validate exposure in the present study we used meningioma cases as the referents, see Table IV. Thereby the results were similar to those obtained using the population based controls with consistency of the main findings for the main phone types, see Table III. It should be mentioned that a similar method was used previously on the controversy of cancer risks from certain chemicals. Based on clinical observations an increased risk for soft-tissue sarcoma (30) and malignant lymphoma (31) was postulated for exposure to phenoxyacetic acids, chlorophenols and contaminating dioxins. These bed-side observations were followed by case-control studies confirming an association, e.g. Hardell and Sandström (32), Hardell *et al* (33). Using colon cancer cases as referents yielded similar results as when population based controls were used, that is the increased risks were unlikely to be explained by recall or observational bias (21). Thus, similar conclusions can be made in the present study.

In our previous studies, we included only living cases so as to be able to solicit as good an assessment of exposure as possible (10,13). Especially side of head mostly used during phone calls would be difficult to assess using proxy interviews. Excluding deceased cases might, theoretically, bias the results, notably if there is no association between use of wireless phones and brain tumour in that patient group or even a protective effect. We, therefore, did a separate case-control study on deceased cases diagnosed during 1997-2003 with a malignant brain tumour in our previous studies (13) using deceased controls. Relatives of both groups were interviewed and we were able to confirm an increased risk for use of mobile phones (15,34). Thus, inclusion of only living cases and controls in this study would not likely bias the results away from unity.

In total, 1,334 cases were reported from the cancer registries covering all of Sweden. From the Gothenburg region,

it was possible to get reports only of cases diagnosed during 2008 and 2009 for administrative reasons. However, exclusion of cases diagnosed during 2007 could not conceivably have biased the results. It has been published that the reporting of new brain tumour cases to the Swedish cancer registry is insufficient (35,36). It is, however, not likely that such omission from our study of not reported cases would be related to the status of being a user or not of wireless phones.

The majority of the cases with a histopathological brain tumour diagnosis that were excluded from this study were deceased (n=520; 39%). As mentioned above we have found an association with use of wireless phones also among the deceased cases (34). Furthermore, for glioma we have found an increased hazard ratio (HR) for survival (37). This was based on all glioma cases, both alive and deceased at the time of the studies as presented in Hardell *et al* (15). An increased hazard ratio was found for >10 years latency for both mobile phone use, HR=1.3, 95% CI=1.0005-1.6, and cordless phone use, HR=1.3, 95% CI=0.9-1.9. HR increased also with the cumulative number of hours of mobile and cordless phone use, with statistically significant trend for tertiles (p=0.01) of use of both phone types. For glioblastoma multiforme (WHO grade IV) use with >10 years latency for mobile phones increased the ratio, HR=1.3, 95% CI=0.9-1.7, and cordless phone, HR=1.8, 95% CI=1.2-2.8, indicating decreased survival for long-term and high cumulative use of wireless phones.

Most of the deceased cases in the present study had a diagnosis of glioblastoma multiforme, WHO grade IV. The median survival in that patient group is less than one year (38). We have reported a higher risk for mobile phone use for high grade glioma (WHO grades III-IV) than for low grade glioma (WHO-grades I-II) (5). Hence, the exclusion of deceased cases with glioblastoma multiforme with poor prognosis in this study might actually have biased the risk estimates towards unity.

We included only cases with a histopathological diagnosis of a brain tumour. We asked the six regional cancer registries not to report cases with only a clinical diagnosis. The reason was that we wanted to insure a confirmed diagnosis of the brain tumour for separate analyses for each tumour type. If necessary, we supplemented the histopathological reports with records from pathology departments around the country after informed consent from the respective case. Thus, we were able to classify all brain tumours based on WHO codes, see Table II. It is not probable that exclusion of cases with only a clinical diagnosis would have biased the results. We checked the Swedish Cancer Registry for the total number of patients with a brain tumour during the study period in the relevant age group. In total, 2,553 patients aged 20-74 years with a brain tumour were reported to the Swedish Cancer Registry versus 2,310 aged 20-74 years with a diagnosis based on histopathological diagnosis in our present study. This is in good agreement with expected numbers since, during 2007-2009, roughly 90% of brain tumour diagnoses in the Swedish Cancer Register were based on histology (<http://www.socialstyrelsen.se/statistik/statistikdatabas>).

An advantage of this study was the fairly high response rate among both cases and controls. The response rate was 87% (n=593) among the eligible cases. Of the controls, 85% (n=1,368) participated. These response rates were similar to those in our previous studies on malignant brain tumours, 85%

(n=1,251) among cases and 84% (n=2,438) among controls (5). Lower response rates were obtained in the Interphone study, namely 64%, range by centre 36-92%, (n=2,765) for glioma cases, and 53%, range 42-74%, (n=7,658) for controls (3). To obtain the most valid results possible, it is always necessary to have the highest possible response rate. In fact, not responding controls in Interphone tended to be less frequent users of mobile phones than participating controls, leading to an underestimation of the risk (4,39,40).

Our study was not designed to include a mini-interview on the use of wireless phones among non-responding cases and controls as done in parts of the Interphone study; we had no ethics clearance for that. Certainly, it would have been of value to verify the use of mobile phones by operator data on the phone traffic. We had no possibility to do this since we did not obtain valid information on the operator used over the years in spite of asking. Furthermore, use of cordless phones, an important source of RF-EMF exposure, is not possible to validate by operator data.

Statistical considerations. In view of the fact that practically everybody is using a wireless phone of some type today, it is not possible to obtain a large enough 'unexposed' group for meaningful statistical calculations. We, therefore, in addition to a latency ≤ 1 year, used the 3rd percentile (39 h) of cumulative time as a cut-off. Another option to obtain more 'unexposed' individuals would have been to change the cut-off for latency. However, doing this would limit the possibility of studying a late effect (promotion) in brain tumour genesis. Furthermore, it is difficult to find users that have been using only one single technology, i.e. NMT, GSM, UMTS, etc. Most users have used several technologies, and those with 3G phones who reported such use may have been unaware that the phone might have been operating on a 2G net for voice, if that was available. The analysis must be viewed with these facts in mind.

In the unconditional logistic regression analysis, all controls, both to cases with malignant and benign brain tumours, were used so as to maximise the statistical power. Analysis using conditional logistic regression yielded overall for wireless phones OR=2.1, 95% CI=1.1-3.7 versus OR=1.7, 95% CI=1.04-2.8 using unconditional logistic regression, see Table III. Using unconditional logistic regression only with controls matched to the malignant cases yielded overall for wireless phones OR=2.0, 95% CI=1.1-3.5. Similar differences were seen for the different phone types i.e. slightly higher risk estimates using conditional logistic regression or unconditional logistic regression with matched controls, although with wider confidence intervals. The latter was due to the fact that only controls matched to malignant cases could be included and also because only discordant matched pairs are considered in a conditional logistic regression analysis. The considerably smaller material would limit the possibility of performing several of the subgroup analyses in this article using this method. Using unconditional logistic regression analysis was possible since adjustment was made for the matching variables of age, gender and year of diagnosis. In addition, adjustment was made for socio-economic index since an association between white-collar work and brain tumours has been reported (41). Not adjusting for any of these variables yielded for wireless phone overall crude OR=2.2, 95% CI=1.4-3.5. No

statistically significant interactions were found between the adjustment factors and wireless phone use. In our previous study, we found that heredity and previous X-ray investigations of the head increased the risk for glioma. However, these were independent risk factors with no interaction with use of wireless phones (16). Thus, it was not necessary to adjust for these risk factors in the present study.

More women than men were included as controls. This was because all controls in the study were included in the analysis. Among the cases with benign brain tumour, meningioma was about 2.5 times more common among women than men, an expected number. Thus, adjustment for gender was necessary.

Biological mechanisms. There is no generally accepted mechanism by which RF-EMF exposure produces changes in DNA. The energy level associated with exposure is too low to cause direct DNA strand breaks and DNA crosslinks. However, DNA damage can be caused by cellular biochemical activities such as free radicals. Several studies indicate that RF-EMFs increase free radical activity in cells (42,43). This process is probably mediated via the Fenton reaction. Hydrogen peroxide is converted into hydroxyl free radicals that are potent cytotoxic molecules. This reaction is catalyzed by iron. High levels of iron are found in metabolic active cells such as cancer cells as well as in cells undergoing abnormal proliferation, but also in brain cells. Glia cells might turn cancerous from DNA damage.

In a recently published study, it was demonstrated that RF-EMF exposure induced the formation of oxidative base damage in a mouse spermatocyte-derived cell line (44). This was mediated by reactive oxygen species (ROS) production. To further elucidate the central role of ROS in RF-EMF exposure-induced DNA base damage, the authors used α -tocopherol pretreatment to antagonize the oxidation of ROS; α -tocopherol is an important lipophilic chain-breaking antioxidant that can inactivate harmful ROS. The protective role of α -tocopherol pretreatment confirmed that ROS are involved in RF-EMF exposure-induced DNA base damage (44). These findings support the idea that low energy RF-EMF that is insufficient to directly induce DNA strand breaks may nonetheless produce genotoxic effects in the form of DNA base damage.

We know little about the earliest events in the genesis of glioma in humans for obvious reasons. However, progression of glioma has been studied in a large series of tumours of different malignancy grades. Patients with low-grade glioma have been followed with later progression to high-grade glioma (45). Thus, since the natural history of most glioma cases, from earliest events to clinical manifestation, is unknown but, most likely requires several decades, the exposure duration has in most studies been incompatible with a tumour initiating effect. This is the first study with long-term use of wireless phones. Interestingly, the most elevated OR was found in the latency group >25 years use. We also found results indicating a late effect on tumour development (promotion).

Initiation and promotion have different effects on the incidence of brain tumours. An initiating effect would have the most direct effect on the incidence. Our results indicate that such an effect would be apparent after more than a 20-year use of mobile phones, and thus be too early to be found in cancer registries. On the other hand, if the exposure acts as a promoter, this would decrease latency time for already existing tumours, giving a

temporary, but not a continuous, increase in incidence. In addition, it must be noted that any such effect on tumour development is limited by the magnitude of the shift of the age-incidence function and its slope for the respective tumour type (28).

In conclusion, this study confirmed previous results of an association between use of mobile and cordless phones and malignant brain tumours. The risk was highest for ipsilateral use and tumours in the temporal lobe. The results are consistent with initiation carcinogenesis for analogue phones, and both initiation and promotion carcinogenesis for digital wireless phones.

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Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma

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Abstract

The International Agency for Research on Cancer (IARC) at WHO evaluation of the carcinogenic effect of RF-EMF on humans took place during a 24–31 May 2011 meeting at Lyon in France. The Working Group consisted of 30 scientists and categorised the radiofrequency electromagnetic fields from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields (RF-EMF), as Group 2B, i.e., a ‘possible’, human carcinogen. The decision on mobile phones was based mainly on the Hardell group of studies from Sweden and the IARC Interphone study. We give an overview of current epidemiological evidence for an increased risk for brain tumours including a meta-analysis of the Hardell group and Interphone results for mobile phone use. Results for cordless phones are lacking in Interphone. The meta-analysis gave for glioma in the most exposed part of the brain, the temporal lobe, odds ratio (OR) = 1.71, 95% confidence interval (CI) = 1.04–2.81 in the ≥ 10 years (>10 years in the Hardell group) latency group. Ipsilateral mobile phone use ≥ 1640 h in total gave OR = 2.29, 95% CI = 1.56–3.37. The results for meningioma were OR = 1.25, 95% CI = 0.31–4.98 and OR = 1.35, 95% CI = 0.81–2.23, respectively. Regarding acoustic neuroma ipsilateral mobile phone use in the latency group ≥ 10 years gave OR = 1.81, 95% CI = 0.73–4.45. For ipsilateral cumulative use ≥ 1640 h OR = 2.55, 95% CI = 1.50–4.40 was obtained. Also use of cordless phones increased the risk for glioma and acoustic neuroma in the Hardell group studies. Survival of patients with glioma was analysed in the Hardell group studies yielding in the >10 years latency period hazard ratio (HR) = 1.2, 95% CI = 1.002–1.5 for use of wireless phones. This increased HR was based on results for astrocytoma WHO grade IV (glioblastoma multiforme). Decreased HR was found for low-grade astrocytoma, WHO grades I–II, which might be caused by RF-EMF exposure leading to tumour-associated symptoms and earlier detection and surgery with better prognosis. Some studies show increasing incidence of brain tumours whereas other studies do not. It is concluded that one should be careful using incidence data to dismiss results in analytical epidemiology. The IARC carcinogenic classification does not seem to have had any significant impact on governments’ perceptions of their responsibilities to protect public health from this widespread source of radiation.

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Keywords: Brain tumour; Glioma; Meningioma; Acoustic neuroma; Wireless phones; Incidence; Adolescent risk; CEFALO; Danish cohort

1. Introduction

On 31 May 2011 the International Agency for Research on Cancer (IARC) at WHO categorised the radiofrequency electromagnetic fields (RF-EMF) from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields, as a Group 2B, i.e., a ‘possible’, human carcinogen [1,2]. Nine years earlier IARC had also classified extremely

low frequency (ELF) magnetic field as Group 2B carcinogen [3].

The IARC evaluation of the carcinogenic effect of RF-EMF on humans took place during a 24–31 May 2011 meeting at Lyon in France. The Working Group consisted of 30 scientists representing four areas: ‘animal cancer studies’, ‘epidemiology’, ‘exposure’ and ‘mechanistic and other relevant data’. The expert groups initially prepared a written draft prior to the IARC meeting. Further work was done in the expert groups and a final agreement, sentence by sentence, was obtained during plenary sessions with all experts participating.

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The IARC decision on mobile phones was based mainly on two sets of case-control human studies; the Hardell group of studies from Sweden and the IARC Interphone study. Both provided complementary and supportive results on positive associations between two types of brain tumours; glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones.

The final IARC decision was confirmed by voting of 29 scientists (one not present). A large majority of participants voted to classify RF-EMF radiation as 'possibly carcinogenic' to humans, Group 2B. The decision was also based on occupational studies.

In this paper an up-to-date review of the evidence of an association between use of wireless phones and brain tumours is presented. The Nordic countries were among the first countries in the world to widely adopt wireless telecommunications technology. Analogue phones (NMT; Nordic Mobile Telephone System) were introduced in the early 1980s using both 450 and 900 Megahertz (MHz) frequencies. NMT 450 was used in Sweden from 1981 but closed down on 31 December 2007, NMT 900 operated during 1986–2000.

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1800 MHz, started to operate in 1991 and dominates now the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1900/2100 MHz RF fields has been introduced worldwide in recent years, in Sweden in 2003. Currently the fourth generation, 4G (Terrestrial 3G), operating at 800/2600 MHz and Trunked Radio Communication (TETRA 380–400 MHz) are being established in Sweden and elsewhere. Nowadays mobile phones are used more than landline phones in Sweden (<http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf>). Worldwide, an estimate of 5.9 billion mobile phone subscriptions was reported at the end of 2011 by the International Telecommunication Union (ITU; <http://www.itu.int/ITU-D/ict/facts/2011/material/ICTFactsFigures2011.pdf>). Many users are children and adolescents, which is of special concern regarding potential health effects.

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800–900 MHz RF fields, but since early 1990s using a digital 1900 MHz system. The cordless phones are becoming more common than traditional landlines. Also these phones emit RF-EMF radiation similar to that of mobile phones. Thus, it is also necessary to consider the usage of cordless phones along with mobile phones, when human health risks are evaluated. It should be noted that the usual cordless base stations emit RF-EMF continuously. They are often installed in offices close to the person using a cordless phone handset or in homes even in bedrooms next to the head of a sleeping person.

The real increase in use and exposure to electromagnetic fields from wireless phones (mobile phones and cordless phones) in most countries has occurred since the end of the

1990s. When used they emit RF-EMFs. The GSM phones and to a lesser extent the cordless phones emit also ELF-EMF from the battery when used [4,5]. The brain is the main target organ during use of the handheld phone [6]. Thus, fear of an increased risk for brain tumours has dominated the debate during the last one or two decades. While RF-EMFs do not have sufficient energy to break chemical bonds like ionising radiation, at least not directly, they can nevertheless have harmful effects on biological tissues. Plausible biological mechanisms for these effects include impairment of DNA repair mechanisms and epigenetic changes to DNA.

Primary brain tumours (central nervous system; CNS) constitute of a heterogeneous group of neoplasms divided into two major groups; malignant and benign. They are of different histological types depending on tissue of origin with different growth patterns, molecular markers, anatomical localisations, and age and gender distributions. The clinical appearance, treatment and prognosis are quite different depending on tumour type.

Ionising radiation is an established risk factor for primary brain tumours [7], but there are no well-established environmental causes. Higher socio-economic status tends to be related to higher incidence and some rare inherited cancer syndromes account for a small fraction of tumours [7]. Familial aggregation of glioma has been reported. In a large study 77% more glioma cases than expected were reported among family members [8].

The purpose of this article is to give a comprehensive review of the association between use of mobile and cordless phones and brain tumours, primarily based on the results of the major publications in this field. We include the Hardell group papers and the WHO Interphone study [9–11]. Also some additional analyses of the risk for brain tumours based on these results are given. Some early studies not part of these two major study groups are also included. More discussion of the results and responses, agreements and disagreements of the findings of the Hardell group and Interphone studies can be found elsewhere [12]. In addition, this review includes studies published after the IARC evaluation in May 2011.

2. Materials and methods

The PubMed database (www.ncbi.nlm.nih.gov) was used for an up-dated search of published studies in this area using mobile/cellular/cordless telephone and brain tumour/neoplasm/acoustic neuroma/meningioma/glioma as searching terms. Personal knowledge of published studies was also used in order to get as comprehensive a review as possible. All of the authors have long experience in this research area and have published the pioneer studies indicating an association between use of wireless phones and certain types of brain tumours. They represent different supportive areas of competence such as oncology, cancer epidemiology, statistics and physics.

Table 1
Summary of studies on the use of mobile phones and brain tumour risk.

Study	Years; study type	Age	Tumour type	No. of exposed cases	Odds ratio, 95% confidence interval	Comments
Hardell et al. [15,16] Sweden	1994–1996; Case-control	20–80 years	Brain tumours (<i>n</i> = 209)	78	OR 0.98 (0.69–1.41)	Analogue and digital mobile phone use
				34	OR 1.07 (0.64–1.80)	<i>Ipsilateral</i> mobile phone use
				16	OR 1.20 (0.56–2.59)	>10 year latency, analogue mobile phone use
Muscat et al. [17] USA	1994–1998; Case-control	18–80 years	Brain tumours (<i>n</i> = 469)	66	OR 0.8 (0.6–1.2)	Mean duration of mobile phone use 2.8 years
			Neuroepithelioma (<i>n</i> = 35)	14	OR 2.1 (0.9–4.7)	

2.1. Statistical methods

All analyses in the Hardell group studies were done using StataSE 10.1 (Stata/SE 10.1 for Windows; StataCorp., College Station TX). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis. Further details can be found in the publications.

Meta-analyses were performed on use of mobile phones in the Hardell group [13,14] and Interphone group [9,10] studies. No duplicate data from different articles published by the same group of authors were included. Model was chosen based on test for heterogeneity in the overall (≥ 10 years and ≥ 1640 h) groups. In the analysis of survival of patients with glioma, Cox proportional hazards model was used to calculate hazard ratios (HR) and corresponding 95% confidence intervals. Follow-up time was counted from the date of diagnosis to the date of death or until May 30, 2012 for living cases.

3. Results

3.1. Brain tumours overall

The first study by Hardell et al. [15,16] included cases and controls during 1994–1996 in parts of Sweden and was the first published study on this issue. Only living cases diagnosed during 1994–1996 were included. Two controls were selected to each case from the Population Registry. In total 209 (90%) of the cases and 425 (91%) of the controls that met the inclusion criteria answered the mailed questionnaire. Overall no association between mobile phone use and brain tumours was found. A slightly increased, but not statistically significant, risk was found for analogue phone (NMT) use and for a latency period greater than 10 years, OR = 1.20, 95% CI = 0.56–2.59, Table 1.

Exposure to the radiation from the phones is generally higher in the temporal lobe, the part of the brain that is near to the ear [6]. For tumours located in the temporal, occipital or temporoparietal lobe areas of the brain an increased risk was found for ipsilateral exposure, that is the telephone

was mostly used on the same side of the head as the tumour appeared, yielding OR = 2.42, 95% CI = 0.97–6.05 [16]. This was the first study in the world that indicated an association between use of mobile phones and an increased risk for brain tumours. However, all results were based on low numbers of exposed subjects and different histopathological types of brain tumours so no firm conclusions could be drawn. Furthermore, this first study did not include use of cordless phones.

Muscat et al. [17] studied patients with malignant brain tumours from five different hospitals in USA, Table 1. Controls were hospital patients. Data from 469 (82%) cases and 422 (90%) controls were available. Overall no association was found, OR for handheld cellular phones was 0.8, 95% CI = 0.6–1.2, but the mean duration of use was short, only 2.8 years for cases and 2.7 years for controls. For neuroepithelioma OR = 2.1, 95% CI = 0.9–4.7, was reported. The study was inconclusive since no data were available on long-term users (≥ 10 years latency period). Some support of an association was obtained since of 41 evaluable tumours, 26 occurred at the side of the head mostly used during calls and 15 on the contralateral side.

3.2. Glioma

Glioma is the most common malignant brain tumour and represents about 60% of all central nervous system tumours. The most common glioma subtype is astrocytoma. Astrocytic tumours are divided in two groups depending on the malignant potential; low-grade (WHO grades I–II) and high-grade (WHO grades III–IV). Low-grade astrocytoma has a relatively favourable prognosis, whereas survival is shorter for patients with high-grade glioma. Glioblastoma multiforme (WHO grade IV) accounts for 60–75% of all astrocytoma. The peak incidence is between 45 and 75 years of age with median survival less than one year [18].

In the study by Hardell et al. [15] analysis of the cases with astrocytoma produced OR = 1.09, 95% CI = 0.64–1.84 (*n* = 36 cases), Table 2. OR increased further for ipsilateral exposure for right sided tumours, OR = 1.30, 95% CI = 0.54–3.13 (*n* = 13 cases), whereas no association was

Table 2
Summary of studies on the use of wireless phones and glioma risk.

Study	Years; study type	Age	Tumour type	No. of exposed cases	Odds ratio, 95% confidence interval	Comments	
Hardell et al. [15] Sweden	1994–1996; Case-control	20–80 years	Astrocytoma WHO grade I–IV (n = 94)	36	OR 1.09 (0.64–1.84)	Analogue and digital mobile phone use	
				13	OR 1.30 (0.54–3.13)	<i>Ipsilateral</i> mobile phone use, <i>right</i> sided tumours	
				3	OR 0.35 (0.07–1.81)	<i>Ipsilateral</i> mobile phone use, <i>left</i> sided tumours	
Inskip et al. [19] USA	1994–1998; Case-control	≥ 18 years	Glioma (n = 489)	11	OR 0.6 (0.3–1.4)	≥ 5 years of mobile phone use	
Auvinen et al. [20] Finland	1996; Case-control, register based	20–69 years	Glioma (n = 198)	Not given	OR 1.5 (1.0–2.4)	Analogue and digital mobile phone “ever” use	
				25	OR 2.1 (1.3–3.4)	Analogue mobile phone “ever” used	
				11	OR 2.4 (1.2–5.1)	Analogue mobile phone use, 1–2 years	
				11	OR 2.0 (1.0–4.1)	Analogue mobile phone use, >2 years	
Hardell et al. [26–28] Carlberg, Hardell [29] Sweden	1997–2003; Case-control	20–80 years	Glioma (n = 1148)	123	OR 2.5 (1.8–3.3)	>10 year latency, mobile phone	
				57	OR 2.9 (1.8–4.7)	>10 year latency, mobile phone, <i>ipsilateral</i> , only living	
				50	OR 2.6 (1.7–4.1)	>10 year latency, <i>mobile phone only</i>	
				45	OR 1.7 (1.1–2.6)	>10 year latency, cordless phone	
				20	OR 3.8 (1.8–8.1)	>10 year latency, cordless phone, <i>ipsilateral</i> , only living	
				9	OR 1.2 (0.5–2.9)	>10 year latency, <i>cordless phone only</i> ; >5–10 year latency OR 1.9 (1.3–2.9; n = 55)	
				150	OR 2.1 (1.6–2.8)	>10 year latency, wireless phone (mobile and cordless phone)	
				Astrocytoma, high grade (n = 820)	102	OR 3.0 (2.1–4.2)	>10 year latency, mobile phone
				47	OR 3.9 (2.3–6.6)	>10 year latency, mobile phone, <i>ipsilateral</i> , only living	
				37	OR 2.8 (1.7–4.6)	>10 year latency, <i>mobile phone only</i>	
				36	OR 2.0 (1.2–3.2)	>10 year latency, cordless phone	
15	OR 5.5 (2.3–13)	>10 year latency, cordless phone, <i>ipsilateral</i> , only living					
6	OR 0.9 (0.3–2.6)	>10 year latency, <i>cordless phone only</i> ; >5–10 year latency OR 2.4 (1.6–3.7; n = 44)					
121	OR 2.5 (1.8–3.4)	>10 year latency, wireless phone (mobile and cordless phone)					
Interphone Study Group [9] 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000–2004, 2–4 years depending on study region. Case-control	30–59 years	Glioma (n = 2708)	1666	OR 0.81 (0.70–0.94)	Regular use of mobile phone in the past ≥ 1 year	

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Table 2 (Continued)

Study	Years; study type	Age	Tumour type	No. of exposed cases	Odds ratio, 95% confidence interval	Comments
Interphone Study Group [9] Appendix 2	2000–2004, 2–4 years depending on study region. Case-control	30–59 years	Glioma (n = 1211)	210	OR 1.40 (1.03–1.89)	Cumulative hours mobile phone ≥ 1640 h
				78	OR 1.87 (1.09–3.22)	Cumulative hours mobile phone ≥ 1640 h, tumours in temporal lobe
				100	OR 1.96 (1.22–3.16)	Cumulative hours mobile phone ≥ 1640 h, ipsilateral mobile phone use
				460	OR 1.68 (1.16–2.41)	Restricted to ever regular use time since start 2–4 years; 1–1.9 years as reference entity
				468	OR 1.54 (1.06–2.22)	Restricted to ever regular use time since start 5–9 years; 1–1.9 years as reference entity
				190	OR 2.18 (1.43–3.31)	Restricted to ever regular use time since start 10+ years; 1–1.9 years as reference entity
				160	OR 1.82 (1.15–2.89)	Restricted to ever regular use ≥ 1640 h, <5 h as reference entity

seen for astrocytoma in the left hemisphere and ipsilateral exposure, OR = 0.35, 95% CI = 0.07–1.81 (n = 3 cases).

The study by Inskip et al. [19] from USA had few long-term users of mobile phones. Only 11 cases with glioma, 6 with meningioma and 5 with acoustic neuroma had ≥ 5 years regular use. No subject had ≥ 10 years use. Of the hospital-based cases 92% participated. The study comprised 489 cases with glioma, 197 with meningioma and 96 with acoustic neuroma, and 799 (86%) hospital-based controls. Proxy interviews were necessary for 16% of the patients with glioma, 8% of the patients with meningioma, 3% of the patients with acoustic neuroma, and 3% of the controls. Overall no statistically significant associations were found, Table 2. Regarding different types of glioma OR = 1.8, 95% CI = 0.7–5.1 was found for anaplastic astrocytoma (WHO grade III). Regarding hospital-based interviews and use of proxy interviews, see discussion below in relation to the Interphone study.

A register based case-control study on brain and salivary gland tumours was performed in Finland [20]. All cases aged 20–69 years diagnosed in 1996 were included; 398 brain tumour cases and 34 salivary gland tumour cases. The duration of mobile phone use was short, for analogue users 2–3 years and for digital users less than one year. No association was found for salivary gland tumours. For glioma OR = 2.1, 95% CI = 1.3–3.4 was calculated for use of analogue phones, but no association was found for digital mobile phones, Table 2. When duration of use of analogue phones was used as a continuous variable an increased risk was found for glioma with OR = 1.2, 95% CI = 1.1–1.5 per year of use.

The Hardell group in Sweden studied the association between use of mobile and cordless phones and brain tumours diagnosed during 1997–2003. First, cases diagnosed during 1 January 1997 to 30 June 2000 were included. These results were published separately [21,22]. This was followed by the next study period, 1 July 2000 to 31 December 2003 [23,24]. The methods were the same including the same inclusion criteria and an identical questionnaire in both studies; see the publications for further details.

Both men and women aged 20–80 years at the time of diagnosis were included and all were alive at the time of inclusion in the study. They were reported from cancer registries with a brain tumour verified by histopathology. The Swedish Population Registry was used for identification of matched controls. The study included use of wireless phones (mobile and cordless phones), as well as asking questions on e.g., occupational exposures. Use of wireless phones was carefully assessed by a self-administered questionnaire supplemented over the phone. The ear that had mostly been used during calls with mobile phone and/or cordless phone was assessed by separate questions; >50% of the time for one side, or equally for both sides. This information was checked during the supplementary phone calls and finally also by a separate letter with good agreement between these three methods.

Tumour localisation for the cases was defined by using medical records including computer tomography (CT) and/or magnetic resonance imaging (MRI). The matched control was assigned the same side as the tumour of the respective case. Use of the wireless phone was defined as ipsilateral ($\geq 50\%$ of the time), or contralateral ($< 50\%$ of the time) in relation to tumour side. Further details can be found in the publications.

In a review commissioned by the former Swedish Radiation Protection Agency (now called the Swedish Radiation Safety Authority) it was suggested that the exclusion of deceased cases was a source of bias in our studies [25]. As a response to that critique we performed a study on the cases with a malignant brain tumour that had died before inclusion in the case-control studies 1997–2003. These cases represented patients with a poor prognosis, mostly with astrocytoma WHO grade IV (glioblastoma multiforme). Controls were selected from the Death Registry in Sweden.

The study encompassed 464 cases and 464 controls that had died from a malignant disease and 463 controls with other causes of death. Exposure was assessed by a questionnaire sent to the next of kin to each deceased case and control. The questionnaire was similar as in previous studies.

This investigation confirmed the previous results of an association between mobile phones and malignant brain tumours [26].

The Hardell group has previously published pooled analysis of malignant brain tumours diagnosed during the period 1997–2003 [27]. These results were updated including also results for deceased cases with malignant brain tumours [28,29]. The results on use of wireless phones were based on 1251 cases with malignant brain tumour (response rate 85%) and 2438 controls (response rate 84%).

Most cases had glioma ($n = 1148$) so we present in the following results for that type of tumour. Latency was divided in three categories, $> 1-5$ years, $> 5-10$ years, and > 10 years from first use of a wireless phone until diagnosis of glioma. Both use of mobile and cordless phone gave an increased risk overall, highest in the latency group > 10 years, increasing further for ipsilateral use yielding for mobile phone OR = 2.9, 95% CI = 1.8–4.7 and for cordless phone OR = 3.8, 95% CI = 1.8–8.1, Table 2. Highest ORs were found in the > 10 year latency group for total wireless phone use as well, OR = 2.1, 95% CI = 1.6–2.8 or a doubling of glioma risk.

OR increased statistically significant for glioma for cumulative use of wireless phones per 100 h; OR = 1.014, 95% CI = 1.008–1.019, and per year of latency; OR = 1.056, 95% CI = 1.037–1.075 [29]. Separate calculations of mobile phone and cordless phone use yielded similar results with statistically significant increasing risks.

It is common for a person to use both a mobile and a cordless phone. For only use of mobile phone OR increased for glioma with time since first use yielding for > 10 years latency OR = 2.6, 95% CI = 1.7–4.1. For only cordless phone use highest risk was obtained in the $> 5-10$ years latency time; OR = 1.9, 95% CI = 1.3–2.9. However, the calculations in the

longest latency period were based on few subjects regarding cordless phone.

In Table 2 results are presented for high-grade astrocytoma ($n = 820$). The results are similar as for the whole glioma group. Low-grade glioma is less common and the results in this study were based on 132 cases. Ipsilateral use of mobile phone yielded in total OR = 1.8, 95% CI = 1.02–3.1 ($n = 39$ cases) and cordless phone OR = 1.7, 95% CI = 0.98–3.1 ($n = 34$ cases, data not in Table). Further results and discussion may be found elsewhere [29].

The Interphone study was conducted at 16 research centres in 13 countries during varying time periods between 2000 and 2004. It was an international collaboration on brain tumour risk and mobile phone use conducted under the guidance of IARC. The investigation was initiated by recommendations from several expert groups including one of the authors, Kjell Hansson Mild as a member of the EU group, to study possible health effects of exposure to RF-EMF [30,31]. It should be noted that there was no overlap of cases or controls between the Hardell group studies and the Swedish part of Interphone performed by another research group.

Some of the separate country analyses of the Interphone study produced contradictory results, as we have discussed elsewhere [13,32]. An increased risk for brain tumour was found in some studies and decreased risk in other studies. After several years of delay the overall Interphone results were finally published in May 2010 [9].

The study included 4301 glioma cases and the results were based on 2708 participating cases (response rate 64%, range by centre 36–92%). In total 14,354 potential controls were identified and interviews were completed with 7658 (53%, range 42–74%). The low participation rates in some centres may have created selection bias, see Hardell et al. [32].

Regular use of mobile phone in the past ≥ 1 year gave for glioma OR = 0.81, 95% CI = 0.70–0.94, Table 2. Subgroup analyses showed statistically significant increased risk in the highest exposure group, i.e., those with cumulative mobile phone use ≥ 1640 h, which corresponds to about half an hour of use per day for ten years, OR = 1.40, 95% CI = 1.03–1.89. The risk increased further for glioma in the temporal lobe yielding OR = 1.87, 95% CI = 1.09–3.22. In the same exposure category, cumulative use ≥ 1640 h and ipsilateral exposure produced OR = 1.96, 95% CI = 1.22–3.16 in total (no data given for temporal lobe).

In Appendix 2, available on the web [9] analysis was restricted to ever-regular users of mobile phones in the Interphone study. Cumulative call time ≥ 1640 h gave OR = 1.82, 95% CI = 1.15–2.89 compared with use < 5 h. Time since start of regular use (latency) ≥ 10 years produced OR = 2.18, 95% CI = 1.43–3.31; reference entity 1–1.9 years.

The Interphone study group concluded: “*However, biases and errors limit the strength of the conclusions we can draw from these analyses and prevent a causal interpretation.*” In an editorial accompanying the Interphone results the main conclusion of the Interphone results was described as “*both elegant and oracular. . . (which) tolerates diametrically*

opposite readings” [33]. They also pointed out several methodological reasons why the Interphone results were likely to have underestimated the risks, such as the short latency period since first exposures became widespread; less than 10% of the Interphone cases had more than 10 years exposure. “None of the today’s established carcinogens, including tobacco, could have been firmly identified as increasing risk in the first 10 years or so since first exposure”.

As has pointed out elsewhere [32] there were differences between the Hardell group studies and Interphone. Regarding age group the Hardell group studies included subjects aged 20–80 years, versus 30–59 years in Interphone. Furthermore use of cordless phones was not properly assessed, analysed or reported in Interphone. These differences have been discussed in detail by Hardell et al. [14]. Thus, it could be shown that restricting the age group to 30–59 years and considering subjects that used a cordless phone as unexposed in the Hardell group studies reduced the OR and produced results quite similar to Interphone, Table 3; see also Table 11 as discussed below. Latency time >10 years for glioma in the temporal lobe yielded OR = 1.40, 95% CI = 0.70–2.81 in the Hardell group studies and OR = 1.36, 95% CI = 0.88–2.11 in Interphone (latency \geq 10 years). Unfortunately the Interphone study did not give results for glioma in the temporal lobe in the analyses in Appendix 2. Thus, excluding exposure to RF-EMFs from cordless phones as in the Interphone study, as well as excluding the younger and older subjects biased the ORs towards unity, which likely dilutes the ability to see health risks.

Most mobile phone users have not been using one single telephone. It is likely that they have changed their handset several times if they have been using a mobile phone for more than a few years. Many users have also been using different phone systems, such as analogue and digital, and many of them have also been using a cordless phone at home or at work. It is not clear how to combine the use of different phones with different power outputs, systems, frequencies and anatomical specific absorption rate (SAR) distributions into one exposure and dose measure. The difficulties lie in the fact that there is no generally accepted mechanism(s) between the electromagnetic fields emitted from the phone and the biological organism. This includes a mechanism by which RF-EMF exposure produces changes in DNA. The energy level associated with exposure is too low to cause direct DNA strand breaks and DNA cross links. However, DNA damages can be caused by cellular biochemical activities such as free radicals. Several studies indicate that RF-EMFs increase free radical activity in cells, as reviewed by Phillips et al. [34]. This process is probably mediated via the Fenton reaction. It should also be noted that possible biological effects might not have linear dose–response as indicated in some studies [35] and that the effects are depending on the carrier frequencies [36].

The different types of phones have different output power. We applied different weighting factors according to

the mean output power of the phones using for analogue phones (NMT) = 1, GSM = 0.1 and cordless phones = 0.01. The cumulative time for use of the different phone types was multiplied with the respective weighting factor added into one score. The median score among the controls was used as the cut-off in the dose–response calculations. We applied this method for the study period 1 January 1997 to 30 June 2000 [21,22]. Somewhat higher ORs were obtained using the weighting factor, especially with a >10-year latency period, compared with calculations based on cumulative use only, but overall the results were similar [37]. This was explained by the fact that most subjects had used an analogue mobile phone with the weighting factor = 1, thus the weighting factor had little impact on the results.

A further issue is that there is a difference in the output power level from mobile phones between urban and rural areas. This is caused by adaptive power control (APC) in the cellular telephone and is regulated by the distance between base stations. Thus, in areas with a long distance between base stations, usually rural areas, the output power level is higher than in more densely populated areas; that is, urban areas, with a shorter distance between base stations. To further explore these circumstances we used the Swedish population register that contains information on present municipality for all residents. The municipalities are classified by Statistics Sweden into so called homogeneity regions, six categories depending on the population density, and the number of inhabitants in the nearest vicinity of the main city in that municipality. Thus, we used these official statistics for grouping of the subjects in urban or rural areas for the study period 1 January 1997 to 30 June 2000. For use of digital mobile phones (GSM) we found a clear effect of urban versus rural areas [38]. Living in rural areas yielded OR = 1.4, 95% CI = 0.98–2.0, increasing to 3.2, 95% CI = 1.2–8.4 with >5 year latency time for digital phones. The corresponding ORs for living in urban areas were 0.9, 95% CI = 0.8–1.2 and 0.9, 95% CI = 0.6–1.4, respectively. This effect was most obvious for malignant brain tumours.

Estimated RF-EMF dose from mobile phone use in the tumour area was associated with an increased risk of glioma in parts of the Interphone study [11]. OR increased with increasing total cumulative dose of specific energy (J/kg) absorbed at the estimated tumour centre for more than 7 years before diagnosis giving OR = 1.91, 95% CI = 1.05–3.47 (p trend = 0.01) in the highest quintile of exposure. A similar study based on less sound methods was later published by another part of the Interphone study group [39]. The results seemed to contradict the findings of Cardis et al. [11]. However, a different, less clear method was used. Only 42 cases had used mobile phone for more than 10 years and no analysis was made of the most exposed group with longest duration of use. Thus, this study is much less informative and less sophisticated than the one by Cardis et al. [11]. It should have been of great value to apply the method by Cardis et al. for the whole Interphone study.

Table 3
Comparison between Hardell group and Interphone using the same age group 30–59 years and excluding use of cordless phones.

Study	Years; study type	Age	Tumour type	No. of exposed cases	Odds ratio, 95% confidence interval	Comments
Hardell et al. [14]	1997–2003; Case-control	30–59 years	Glioma (<i>n</i> = 490)	56	OR 1.79 (1.19–2.70)	>10 year latency, cordless phone among unexposed, age 30–59 years
				29	OR 1.75 (1.02–3.00)	Cumulative use ≥ 1640 h, cordless phone among unexposed, age 30–59 years
				20	OR 2.18 (1.09–4.35)	Cumulative use ≥ 1640 h, cordless phone among unexposed, age 30–59 years, <i>ipsilateral</i>
				8	OR 1.48 (0.57–3.87)	Cumulative use ≥ 1640 h, cordless phone among unexposed, age 30–59 years, <i>contralateral</i>
Interphone Study Group [9] 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000–2004, 2–4 years depending on study region. Case-control	30–59 years	Glioma (<i>n</i> = 2708)	252	OR 0.98 (0.76–1.26)	Regular use of mobile phone in the past ≥ 1 year, latency ≥ 10 years
				210	OR 1.40 (1.03–1.89)	Cumulative hours mobile phone ≥ 1640 h
				100	OR 1.96 (1.22–3.16)	Cumulative hours mobile phone ≥ 1640 h, <i>ipsilateral</i>
				39	OR 1.25 (0.64–2.42)	Cumulative hours mobile phone ≥ 1640 h, <i>contralateral</i>
				160	OR 1.82 (1.15–2.89)	Restricted to <i>ever regular use</i> ≥ 1640 h, <5 h as reference entity, Appendix 2. Results for ipsilateral and contralateral use not reported.

Table 4

Use of mobile phones and glioma risk, meta-analysis of Hardell et al. [14] and Interphone [9]. Numbers of exposed cases (Ca) and controls (Co) are given.

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
<i>Latency ≥10 years</i>						
-all	88/99	2.26 (1.60–3.19)	252/232	0.98 (0.76–1.26)	340/331	1.48 (0.65–3.35)
-ipsilateral	57/45	2.84 (1.82–4.44)	108/82	1.21 (0.82–1.80)	165/127	1.84 (0.80–4.25)
-contralateral	29/29	2.18 (1.24–3.85)	49/56	0.70 (0.42–1.15)	78/85	1.23 (0.40–3.73)
-temporal lobe	28/99	2.26 (1.32–3.86)	94/69	1.36 (0.88–2.11)	122/168	1.71 (1.04–2.81)
<i>Cumulative use ≥1640 h</i>						
-all	42/43	2.31 (1.44–3.70)	210/154	1.40 (1.03–1.89)	252/197	1.74 (1.07–2.83)
-ipsilateral	29/21	2.94 (1.60–5.41)	100/62	1.96 (1.22–3.16)	129/83	2.29 (1.56–3.37)
-contralateral	12/12	2.10 (0.90–4.90)	39/31	1.25 (0.64–2.42)	51/43	1.52 (0.90–2.57)
-temporal lobe	14/43	2.44 (1.21–4.95)	78/47	1.87 (1.09–3.22)	92/90	2.06 (1.34–3.17)

Random-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥ 10 years and ≥ 1640 h) groups.

3.3. Meta-analysis glioma

We performed a meta-analysis of glioma on use of mobile phones based on Hardell et al. [14] and Interphone Study Group [9]. Random-effects model was used based on test for heterogeneity in the overall (≥ 10 years and ≥ 1640 h) groups. The analysis was based on published results in Interphone since we do not have access to their database. Our results were recalculated to these groups of exposure. Thus, results can be found in Table 4 for latency ≥ 10 years, (>10 years in Hardell et al.), and cumulative use of mobile phone ≥ 1640 h. The meta-analysis yielded for mobile phone use OR = 1.71, 95% CI = 1.04–2.81 for glioma in the temporal lobe in the ≥ 10 years latency group. Ipsilateral mobile phone use ≥ 1640 h in total gave the highest risk, OR = 2.29, 95% CI = 1.56–3.37. Certainly the meta-analysis strengthens a causal association between use of mobile phones and glioma.

3.4. Meningioma

Meningioma is the most common benign brain tumour. It develops from the pia and arachnoid that covers the central nervous system. Meningioma is an encapsulated and well-demarcated tumour. It is rarely malignant. More women than men develop meningioma.

In the first study by Hardell et al. [15] only 46 cases had meningioma. No increased risk was found overall; OR = 1.05, 95% CI = 0.49–2.27, Table 5. Only 16 cases had used a mobile phone. There was no pattern of increased risk for ipsilateral use, although the results were based on low numbers.

The US study by Inskip et al. [19] included 197 cases with meningioma. Regular mobile phone use produced OR = 0.8, 95% CI = 0.4–1.3, Table 5. The risk did not increase with average daily use, cumulative use, or duration of regular use. However, results for duration of regular use ≥ 5 years was based on only 6 exposed cases.

The Finnish register based case-control study on brain tumours by Auvinen et al. [20] included 129 cases with

meningioma. Ever use of mobile phone gave OR = 1.1, 95% CI = 0.5–2.4, analogue phone use OR = 1.5, 95% CI = 0.6–3.5, Table 5. As discussed above the study was limited by short latency and exposure based on subscription information.

The Hardell group made a pooled analysis of benign brain tumours from the two case-control studies 1997–2003 as discussed above [40,41]. Regarding meningioma use of mobile phone gave OR = 1.1, 95% CI = 0.9–1.3, and cordless phone OR = 1.1, 95% CI = 0.9–1.4, Table 5. Using >10 year latency period OR increased; for mobile phone to OR = 1.5, 95% CI = 0.98–2.4, and for cordless phone to OR = 1.8, 95% CI = 1.01–3.2. Ipsilateral mobile phone use in the >10 years latency group yielded OR = 1.6, 95% CI = 0.9–2.9, and cordless phone OR = 3.0, 95% CI = 1.3–7.2. These results were based on rather low numbers of exposed cases, however.

In the Interphone study [9] a statistically significant decreased risk was found for meningioma for regular use of mobile phone, OR = 0.79, 95% CI = 0.68–0.91, Table 5. The risk increased somewhat with cumulative use ≥ 1640 h and ipsilateral mobile phone use to OR = 1.45, 95% CI = 0.80–2.61. The overall pattern of no association did not change if analysis was restricted to tumours in the temporal lobe or only to the group of ever-regular use.

3.5. Meta-analysis meningioma

Similarly as for glioma we performed meta-analysis of meningioma for use of mobile phone on the Hardell group and Interphone results, Table 6. Random-effects model was used in the ≥ 10 years group based on test for heterogeneity in the overall group. For analyses of ≥ 1640 h no heterogeneity was found in the heterogeneity test; random- and fixed effects models produced identical results. In summary no statistically significant decreased or increased risks were found. These results support the conclusion that up to latency ≥ 10 years or cumulative use ≥ 1640 h there is not a consistent pattern of an association between use of mobile phones and meningioma.

Table 5
 Summary of studies on the use of wireless phones and meningioma risk.

Study	Years; study type	Age	Tumour type	No. of exposed cases	Odds ratio, 95% confidence interval	Comments
Hardell et al. [15] Sweden	1994–1996; Case-control	20–80 years	Meningioma (n = 46)	16	OR 1.05 (0.49–2.27)	Analogue and digital mobile phone use
Inskip et al. [19] USA	1994–1998; Case-control	≥18 years	Meningioma (n = 197)	32	OR 0.8 (0.4–1.3)	Regular use
				6	OR 0.9 (0.3–2.7)	≥5 years of mobile phone use
Auvinen et al. [20] Finland	1996; Case-control, register based	20–69 years	Meningioma (n = 129)	Not given	OR 1.1 (0.5–2.4)	Analogue and digital mobile phone “ever” use
				8	OR 1.5 (0.6–3.5)	Analogue mobile phone “ever” used
				3	OR 1.6 (0.4–6.1)	Analogue mobile phone use, 1–2 years
				2	OR 1.0 (0.2–4.4)	Analogue mobile phone use, >2 years
Hardell et al. [40], Hardell, Carlberg [41] Sweden	1997–2003; Case-control	20–80 years	Meningioma (n = 916)	347	OR 1.1 (0.9–1.3)	>1 year latency, mobile phone use
				38	OR 1.5 (0.98–2.4)	>10 years latency of mobile phone use
				18	OR 1.6 (0.9–2.9)	>10 years latency of ipsilateral mobile phone use
				294	OR 1.1 (0.9–1.4)	>1 year latency, cordless phone use
				23	OR 1.8 (1.01–3.2)	>10 years latency of cordless phone use
				11	OR 3.0 (1.3–7.2)	>10 years latency of ipsilateral cordless phone use
Interphone Study Group [9] 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000–2004, 2–4 years depending on study region. Case-control	30–59 years	Meningioma (n = 2409)	1262	OR 0.79 (0.68–0.91)	Regular use of mobile phone in the past ≥1 year
				130	OR 1.15 (0.81–1.62)	Cumulative hours mobile phone ≥1640 h
				21	OR 0.94 (0.31–2.86)	Cumulative hours mobile phone ≥1640 h, tumours in temporal lobe
				46	OR 1.45 (0.80–2.61)	Cumulative hours mobile phone ≥1640 h, ipsilateral mobile phone use
Interphone [9] Appendix 2			Meningioma (n = 842)	362	OR 0.90 (0.62–1.31)	Restricted to ever regular use time since start 2–4 years; 1–1.9 years as reference entity
				288	OR 0.75 (0.51–1.10)	Restricted to ever regular use time since start 5–9 years; 1–1.9 years as reference entity
				76	OR 0.86 (0.51–1.43)	Restricted to ever regular use time since start 10+ years; 1–1.9 years as reference entity
				96	OR 1.10 (0.65–1.85)	Restricted to ever regular use ≥1640 h, <5 h as reference entity

Table 6

Use of mobile phones and meningioma risk, meta-analysis of Hardell, Carlberg [41] and Interphone [9]. Numbers of exposed cases (Ca) and controls (Co) are given.

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
<i>Latency ≥10 years</i>						
-all	38/99	1.52 (0.98–2.37)	110/112	0.83 (0.61–1.14)	148/211	1.10 (0.61–1.99)
-ipsilateral	18/45	1.59 (0.86–2.95)	40/42	0.88 (0.52–1.47)	58/87	1.16 (0.65–2.06)
-contralateral	12/29	1.57 (0.75–3.31)	20/25	0.58 (0.29–1.16)	32/54	0.95 (0.36–2.51)
-temporal lobe	10/99	2.46 (1.08–5.60)	12/12	0.60 (0.22–1.62)	22/111	1.25 (0.31–4.98)
<i>Cumulative use ≥1640 h</i>						
-all	10/43	0.85 (0.41–1.75)	130/107	1.15 (0.81–1.62)	140/150	1.09 (0.80–1.49)
-ipsilateral	6/21	1.11 (0.42–2.88)	46/35	1.45 (0.80–2.61)	52/56	1.35 (0.81–2.23)
-contralateral	3/12	0.98 (0.26–3.61)	28/28	0.62 (0.31–1.25)	31/40	0.69 (0.37–1.27)
-temporal lobe	1/43	0.52 (0.07–3.95)	21/14	0.94 (0.31–2.86)	22/57	0.82 (0.31–2.17)

Random-effects model used for meta-analyses of ≥ 10 years, based on test for heterogeneity in the overall group. For meta-analyses of ≥ 1640 h no heterogeneity was found; random- and fixed effects models produced identical results.

3.6. Acoustic neuroma

Acoustic neuroma or Vestibular Schwannoma is a benign tumour that is located in the eighth cranial nerve that leads from the inner ear to the brain. This tumour type does not undergo malignant transformation. It tends to be encapsulated and grows in relation to the auditory and vestibular portions of the nerve. It is a slow growing tumour in the auditory canal but grows gradually out into the cerebellopontine angle with potential compression of vital brain stem centres. Tinnitus and hearing problems are usual first symptoms of acoustic neuroma. Although neuroma is a benign tumour it causes persistent disabling symptoms after treatment such as loss of hearing and tinnitus that severely affect the daily life. The eighth cranial nerve is located close to the handheld wireless phone when used, so there is particular concern of an increased risk for neuroma development due to exposure to RF-EMF emissions during use of these devices.

In the first study by Hardell et al. [15] in Sweden only 13 cases had acoustic neuroma. Five cases reported use of mobile phone, only one with ipsilateral use. The numbers were too low to make meaningful interpretation of an association, Table 7.

Inskip et al. [19] included 96 cases with acoustic neuroma in their US case-control study. No increased risk was found for regular use of mobile phone, Table 7. Duration of regular use ≥ 5 years gave OR = 1.9, 95% CI = 0.6–5.9. This result was based on only 5 exposed cases and there were no results on long-term use. Furthermore only 1 case had cumulative use >500 h.

Muscat et al. [42] presented results from a hospital based case-control study on acoustic neuroma on 90 (100% response rate) patients and 86 (100%) controls. Mobile phone use 1–2 years gave OR = 0.5, 95% CI = 0.2–1.3 ($n = 7$ cases), increasing to OR = 1.7, 95% CI = 0.5–5.1 ($n = 11$ cases), in the group with 3–6 years use, Table 7. Average use among cases was 4.1 years and among controls 2.2 years.

The pooled analysis of the Hardell group studies yielded in total OR = 2.9, 95% CI = 2.0–4.3 for use of analogue mobile

phone and OR = 1.5, 95% CI 1.1–2.1 for use of digital mobile phone [40]. Use of mobile phones gave for acoustic neuroma OR = 1.7, 95% CI = 1.2–2.3 increasing to OR = 2.9, 95% CI = 1.6–5.5 with >10 years latency period, Table 7. Ipsilateral use increased the risk further; in the >10 years latency group to OR = 3.0, 95% CI = 1.4–4.2 [41]. Cordless phone use gave OR = 1.5, 95% CI = 1.04–2.0 increasing to OR = 1.7, 95% CI = 1.2–2.5 for ipsilateral use.

A case-case study on acoustic neuroma was conducted in Japan [43]. The cases were identified during 2000–2006 at 22 participating neurosurgery departments. The diagnosis was based on histopathology or CT/MRI imaging. Of 1589 cases 816 (51%) agreed to participate and answered a mailed questionnaire. A total of 787 cases were included in the final analysis. Two datasets were analysed, one consisted of 362 cases without any tumour related symptoms 1 year before diagnosis, and another consisted of 593 cases without any symptoms 5 years before diagnosis. Cases with ipsilateral use were regarded as exposed and those with contralateral use were assumed to be unexposed and were used as the reference category. Overall no increased risk was found. However, for average daily call duration >20 min with reference date 1 year Risk Ratio (RR) = 2.74, 95% CI = 1.18–7.85 was found increasing to RR = 3.08, 95% CI = 1.47–7.41 with reference date 5 years before diagnosis, Table 7. Unfortunately no results were given for cumulative number of hours for use over the years. For cordless phones no increased risk was found but the analysis was not very informative.

In the Interphone study [10] 1121 (82%) acoustic neuroma cases participated, range 70–100% by centre. Of the controls 7658 (53%) completed the interviews, range 35–74% by centre. The final matched analysis (1:1 or 1:2) consisted of 1105 cases and 2145 controls. Overall no increased risk was found censoring exposure at one year or at 5 years before reference date, OR = 0.85, 95% CI = 0.69–1.04 and OR = 0.95, 95% CI = 0.77–1.17, respectively, Table 7.

Cumulative number of hours of ipsilateral mobile phone use ≥ 1640 h up to 1 year before reference date gave OR = 2.33, 95% CI = 1.23–4.40 and contralateral use

Table 7
 Summary of studies on the use of wireless phones and acoustic neuroma risk.

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95% confidence interval	Comments
Hardell et al. [15] Sweden	1994–1996; Case-control	20–80 years	Acoustic neuroma (n = 13)	5	OR 0.78 (0.14–4.20)	>1 year latency of mobile phone use
Inskip et al. [19] USA	1994–1998; Case-control	≥18 years	Acoustic neuroma (n = 96)	22	OR 1.0 (0.5–1.9)	Regular mobile phone use
Muscat et al. [42] USA	1997–1999; Case-control	≥18 years	Acoustic neuroma (n = 90)	5	OR 1.9 (0.6–5.9)	≥5 years of mobile phone use
				11	OR 1.7 (0.5–5.1)	3–6 years of mobile phone use
Hardell et al. [40], Hardell, Carlberg [41] Sweden	1997–2003; Case-control	20–80 years	Acoustic neuroma (n = 243)	130	OR 1.7 (1.2–2.3)	>1 year latency of mobile phone use
				20	OR 2.9 (1.6–5.5)	>10 years latency of mobile phone use
				13	OR 3.0 (1.4–6.2)	>10 years of <i>ipsilateral</i> mobile phone use
				4	OR 1.3 (0.4–3.8)	>10 years latency of cordless phone use
				3	OR 2.3 (0.6–8.8)	>10 years latency of <i>ipsilateral</i> cordless phone use
Sato et al. [43] Japan	2000–2006; Case-case	All ages	Acoustic neuroma (n = 787)	97	RR 1.08 (0.93–1.28)	Mobile phone, reference date 1 year before diagnosis, <i>ipsilateral</i>
				86	RR 1.14 (0.96–1.40)	Mobile phone, reference date 5 years before diagnosis, <i>ipsilateral</i>
				18	RR 2.74 (1.18–7.85)	Mobile phone, reference date 1 year before diagnosis, average daily call duration >20 min, <i>ipsilateral</i>
				28	RR 3.08 (1.47–7.41)	Mobile phone, reference date 5 years before diagnosis, average daily call duration >20 min, <i>ipsilateral</i>
				45	RR 0.93 (0.79–1.14)	Cordless phone, reference date 1 year before diagnosis, <i>ipsilateral</i> ; mobile phone non-users
Interphone Study Group [10] 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000–2004, 2–4 years depending on study region. Case-control	30–59 years	Acoustic neuroma (n = 1105)	643	OR 0.85 (0.69–1.04)	Mobile phone regular use up to 1 year before reference date

Table 7 (Continued)

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95% confidence interval	Comments
Interphone [10] 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000–2004, 2–4 years depending on study region. Case-control	30–59 years	Acoustic neuroma (n = 1105)	304	OR 0.95 (0.77–1.17)	Mobile phone regular use up to 5 years before reference date
				77	OR 1.32 (0.88–1.97)	Cumulative hours mobile phone ≥1640 h up to 1 year before reference date
				36	OR 2.79 (1.51–5.16)	Cumulative hours mobile phone ≥1640 h up to 5 years before reference date
				47	OR 2.33 (1.23–4.40)	Cumulative hours mobile phone ≥1640 h up to 1 year before reference date; <i>ipsilateral</i> use
				27	OR 3.53 (1.59–7.82)	Cumulative hours mobile phone ≥1640 h up to 5 years before reference date; <i>ipsilateral</i> use
				37	OR 1.93 (1.10–3.38)	Cumulative hours mobile phone ≥1640 h in the past start ≥10 years before reference date
				28	OR 3.74 (1.58–8.83)	Cumulative hours mobile phone ≥1640 h in the past start ≥10 years before reference date, <i>ipsilateral</i>
				225	OR 1.41 (0.82–2.40)	Restricted to <i>ever regular use</i> time since start 2–4 years; 1–1.9 years as reference entity
				209	OR 1.38 (0.80–2.39)	Restricted to <i>ever regular use</i> time since start 5–9 years; 1–1.9 years as reference entity
				64	OR 1.08 (0.58–2.04)	Restricted to <i>ever regular use</i> time since start 10+ years; 1–1.9 years as reference entity
72	OR 1.74 (0.90–3.36)	Restricted to <i>ever regular use</i> ≥1640 h, <5 h as reference entity				

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OR = 0.72, 95% CI = 0.34–1.53 for acoustic neuroma, Table 7 [10]. For cumulative number of hours of ipsilateral mobile phone use ≥ 1640 h up to 5 years before reference date OR = 3.53, 95% CI = 1.59–7.82, and for contralateral use OR = 1.69, 95% CI = 0.43–6.69 were obtained. The risk increased further for cumulative ipsilateral use ≥ 1640 h with start ≥ 10 years before reference date to OR = 3.74, 95% CI = 1.58–8.83. Contralateral use in that group yielded OR = 0.48, 95% CI = 0.12–1.94, however based on only 4 exposed cases and 9 exposed controls. Overall OR = 1.93, 95% CI = 1.10–3.38 was obtained for long-term use with start ≥ 10 years before reference date and cumulative call time ≥ 1640 h.

Similar analyses of the data as in Appendix 2 for glioma [9], yielded highest OR for acoustic neuroma in the shortest latency group, 2–4 years before reference date, OR = 1.41, 95% CI = 0.82–2.40 [10]. Lower OR was calculated in the ≥ 10 years group, OR = 1.08, 95% CI = 0.58–2.04. Somewhat higher risk than in total, OR = 1.32, 95% CI = 0.88–1.97, was found for cumulative mobile phone use ≥ 1640 h; OR = 1.74, 95% CI = 0.90–3.36, in this analysis restricted to only regular users. No results were given for ipsilateral use.

3.7. Meta-analysis acoustic neuroma

Table 8 shows results for use of mobile phone and the association with acoustic neuroma based on results by the Hardell group and Interphone study. Random-effects model was used based on test for heterogeneity in the overall (≥ 10 years and ≥ 1640 h) groups. The same exposure groups as in the meta-analyses of glioma and meningioma were used. For the latency group ≥ 10 years highest risk was obtained for ipsilateral use, OR = 1.81, 95% CI = 0.73–4.45. The risk increased further for cumulative use ≥ 1640 h yielding OR = 2.55, 95% CI = 1.50–4.40 for ipsilateral use. The meta-analysis strengthens a causal association between use of mobile phones and acoustic neuroma.

3.8. Other types of brain tumours

Results for other types of brain tumours from the Hardell group diagnosed during 1997–2003 included medulloblastoma ($n = 6$), ependymoma ($n = 19$) and other malignant types ($n = 46$). In total using >1 year latency time no statistically significant increased risk was found for mobile phone use, OR = 1.2, 95% CI = 0.7–2.1 for these tumour types grouped together [41]. However, with >10 years latency the risk increased to OR = 3.2, 95% CI = 1.2–8.8 in total; for ipsilateral use OR = 4.1, 95% CI = 1.03–16. For cordless phone use no statistically significant decreased or increased risk was found (data not in Table). For pituitary adenoma ($n = 34$) and other types of benign brain tumours ($n = 62$) no statistically significant associations were found overall. In the >10 year latency group ipsilateral mobile phone use gave OR = 4.7, 95% CI = 1.1–21 for benign tumours other than pituitary adenoma (central location in the brain and not included in these

calculations) but based on only 4 exposed cases. Thus, several of the calculations were based on low numbers.

Takebayashi et al. [44] included 102 cases with pituitary adenoma in the Japanese part of Interphone from December 2000 to November 2004. The response rate was 76%; 102 out of 135 cases. Of the individually matched controls 208 (49%) of 421 participated. In the statistical analysis 161 controls were used to 101 cases; one case was excluded since not diagnosed within study period. Regular mobile phone use yielded OR = 0.90, 95% CI = 0.50–1.61. Cumulative length of use in years or cumulative call time in hours produced no pattern of an association and there was no statistically significant trend. The cut off for highest quartile of cumulative use was 560 h producing OR = 1.33, 95% CI = 0.58–3.09 ($n = 21$ cases, 27 controls exposed). Since pituitary adenoma is a centrally located tumour in the pituitary gland in sella turcica there was no laterality analysis.

In parallel with the Interphone study, pituitary tumours were studied in Southeast England using the same protocol [45]. The inclusion period was from December 2000 until February 2005. In total 506 eligible cases were identified. Of them 317 (63%) were interviewed and 291 (58%) included in the final analysis. Eligible controls from patient lists at general practitioners in the study region were 1464 subjects, and 630 (43%) were interviewed. Regular use of mobile phone gave OR = 0.9, 95% CI = 0.7–1.3. No statistically significant trend for the risk was found for lifetime use in years or cumulative use in hours. For ≥ 10 years since first use and ≥ 51 h of cumulative use (median number in that category) OR = 1.6, 95% CI = 0.8–3.6 ($n = 16$ cases, 23 controls exposed) was found.

3.9. Risks to children and adolescents

Children have smaller head and thinner skull bone than adults. Their brain tissue has also higher conductivity and these circumstances give higher absorption from RF-EMF than for adults [6,46,47]. The developing brain is more sensitive to toxins [48] and it is still developing until about 20 years of age [49]. Use of wireless phones is widespread among children and adolescents [50,51]. The greater absorption of RF energy per unit of time, the greater sensitivity of their brains, and their longer lifetimes with the risk to develop a brain tumour leaves children at a higher risk than adults from mobile phone radiation.

The Hardell group has published results for different age groups at the time of diagnosis [52] or age at first use of wireless phones [12,13,28]. Three age groups for first use of a wireless phone were used: <20 years, 20–49 years and 50–80 years. Highest risk for glioma was found for first use of mobile phone or cordless phone before the age of 20 years, Table 9. Thus, mobile phone yielded for glioma OR = 3.1, 95% CI = 1.4–6.7 and cordless phone OR 2.6, 95% CI = 1.2–5.5. The risk increased further for ipsilateral mobile phone use in the youngest age group to OR = 4.4,

Table 8

Use of mobile phones and acoustic neuroma risk, meta-analysis of Hardell, Carlberg [41] and Interphone [10]. Numbers of exposed cases (Ca) and controls (Co) are given.

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
<i>Latency ≥10 years</i>						
-all	20/99	2.93 (1.57–5.46)	68/141	0.76 (0.52–1.11)	88/240	1.46 (0.39–5.47)
-ipsilateral	13/45	2.97 (1.42–6.21)	44/52	1.18 (0.69–2.04)	57/97	1.81 (0.73–4.45)
-contralateral	6/29	2.38 (0.89–6.35)	17/30	0.69 (0.33–1.42)	23/59	1.22 (0.37–4.11)
<i>Cumulative use ≥1640 h</i>						
-all	10/43	2.86 (1.33–6.14)	77/107	1.32 (0.88–1.97)	87/150	1.81 (0.86–3.81)
-ipsilateral	7/21	3.10 (1.21–7.95)	47/46	2.33 (1.23–4.40)	54/67	2.55 (1.50–4.40)
-contralateral	3/12	2.28 (0.60–8.71)	16/26	0.72 (0.34–1.53)	19/38	1.12 (0.37–3.34)

Random-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1640 h) groups.

95% CI = 1.3–15 for mobile phone use and to OR = 4.3, 95% CI = 1.4–13 for cordless phone use.

Also for acoustic neuroma the risk was highest in the youngest age group with OR = 5.0, 95% CI = 1.5–16 for use of mobile phone increasing to OR = 6.8, 95% CI = 1.4–34 for ipsilateral use. Only one case had first use of cordless phone before the age of 20, so no conclusions could be drawn for cordless phones. Regarding meningioma no clear pattern of age-dependent increased risk was seen.

There are few other studies on brain tumour risk for children from use of wireless phones. Mobikids is one study that is on-going. A multi-centre case-control study was conducted in Denmark, Sweden, Norway, and Switzerland, CEFALO [53]. It included children and adolescents aged 7–19 years and has been commented elsewhere in detail since serious methodological problems exist in the study design and interpretation of the results [54].

In CEFALO a statistically non-significant increased risk for brain tumours among regular users (one call per week for at least 6 months) of mobile phones was found; OR = 1.36, 95% CI = 0.92–2.02. This OR increased somewhat with cumulative duration of subscriptions and duration of calls

[53]. No data for long-term use were given; the longest latency period was 5 years. Interestingly, further support of a true association was found in the results based on operator-recorded use for 62 cases and 101 controls, which for time since first subscription >2.8 years yielded a statistically significant OR of 2.15, 95% CI = 1.07–4.29, with a statistically significant trend ($p = 0.001$).

Use of cordless phones was not well assessed. The authors stated that such use was covered only in the first 3 years of use. No explanation was given for this most peculiar definition. Wireless phone use was not considered, that is use of both mobile phones and cordless phones as the relevant exposure category, as used by the Hardell group and adopted by IARC [1]. Instead Aydin et al. [53] included use of cordless phones in the ‘unexposed’ category when risk estimates were calculated for mobile phone use. Similarly, when use of cordless phones was analysed mobile phone use was regarded as ‘no exposure’. Thus, an increased risk was potentially concealed.

The authors summarised that they “*did not observe that regular use of a mobile phone increased the risk for brain tumors in children and adolescents.*” An editorial in the same journal accompanied that conclusion by stating

Table 9

Odds ratio (OR) and 95% confidence interval (CI) for glioma, meningioma and acoustic neuroma in different age groups for first use of the wireless phone [26–28,40]. Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI-code, year of diagnosis. For glioma adjustment was also made for vital status.

	Glioma (n = 1148)		Meningioma (n = 916)		Acoustic neuroma (n = 243)	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
Wireless phone (mobile and cordless phone)	670/1267	1.3 (1.1–1.5)	461/1172	1.0 (0.9–1.2)	155/1172	1.5 (1.1–2.0)
<20 years old	25/27	2.3 (1.3–4.3)	6/27	1.0 (0.4–2.6)	5/27	2.4 (0.8–7.3)
20–49 years old	377/746	1.3 (1.1–1.6)	276/711	1.3 (1.02–1.6)	103/711	1.8 (1.2–2.6)
≥50 years old	268/494	1.3 (1.1–1.6)	179/434	0.9 (0.7–1.2)	47/434	1.3 (0.9–1.9)
Mobile phone	529/963	1.3 (1.1–1.6)	347/900	1.1 (0.9–1.3)	130/900	1.7 (1.2–2.3)
<20 years old	17/14	3.1 (1.4–6.7)	5/14	1.9 (0.6–5.6)	5/14	5.0 (1.5–16)
20–49 years old	315/581	1.4 (1.1–1.7)	210/555	1.3 (0.99–1.6)	86/555	2.0 (1.3–2.9)
≥50 years old	197/368	1.3 (1.01–1.6)	132/331	1.0 (0.8–1.3)	39/331	1.4 (0.9–2.2)
Cordless phone	402/762	1.3 (1.1–1.6)	294/701	1.1 (0.9–1.4)	96/701	1.5 (1.04–2.0)
<20 years old	16/16	2.6 (1.2–5.5)	2/16	0.5 (0.1–2.2)	1/16	0.7 (0.1–5.9)
20–49 years old	206/437	1.2 (0.9–1.5)	167/416	1.3 (0.98–1.6)	65/416	1.7 (1.1–2.5)
≥50 years old	180/309	1.4 (1.1–1.7)	125/269	1.1 (0.8–1.4)	30/269	1.3 (0.8–2.1)

that the study showed “no increased risk of brain tumors in children and adolescents who are regular cell phone users” [55]. This was echoed by a news release from the Karolinska Institute in Stockholm claiming that the results of no increased risk were ‘reassuring’ (<http://ki.se/ki/jsp/polopoly.jsp?d=130&a=125250&l=en&newsdep=130>). However, these statements go far beyond what the study really showed. In fact, the results indicate a moderately increased risk, in spite of low exposure, short latency period and limitations in study design and analyses. Aydin et al. discussed recall bias – that people tend to overestimate their number of calls – and interestingly they showed that controls overestimated their number of calls more than cases [56]. It was concluded that it was unlikely that a false positive result occurred in CEFALO and that the OR was underestimated for heavy users. Certainly the results in the article [53] cannot be used as reassuring evidence against an association, as discussed in our commentary [54].

3.10. Danish cohort study on mobile phone users

Ideally a cohort study on wireless phone users would be of substantial value. However, several problems exist to establish a cohort with high quality assessed exposure. For example use of both mobile phones and cordless phones vary over time and exposure to RF-EMF emissions also depends on several physical characteristics for different phone types. An attempt to establish a cohort of mobile phone users was made in Denmark in co-operation between the Danish Cancer Society and the International Epidemiology Institute (IEI), Rockville, MD, USA. It was financed by grants from two Danish telecom operation companies (TeleDenmark Mobil and Sonofon), IEI, and the Danish Cancer Society. The source of money for IEI has not been disclosed.

The first results from the Danish study on brain tumour risk among mobile phone subscribers were published in 2001 [57]. It included subjects from January 1, 1982 until December 31, 1995 identified from the computerised files of the two Danish operating companies, TeleDenmark Mobil and Sonofon. A total of 723,421 subscribers were initially identified but the final cohort consisted of only 58% of these subjects. Due to lack of names of individual users 200,507 corporate users were excluded. They were expected to be the heaviest users and such exclusion would underestimate any risk estimates. It should be noted that duration of subscription of a digital phone was at most ≥ 3 years ($n=9$) and that two thirds of the subscriptions began in 1994 and 1995. In other words, the majority of the cohort members had two years or less of subscription time. This and other shortcomings in this cohort study have been discussed elsewhere in detail [58]. The Danish study was part of the IARC evaluation but it was concluded that the methods used could have resulted in considerable misclassification in exposure assessment [1].

The first update of the Danish study gave follow-up data until 2002 [59]. The median time since first subscription was this time 8.0 years. It was now stated that the cohort

members were excluded from the reference population, which seems not to have been the case in the first publication. The Standardised Incidence Ratio (SIR) for glioma was close to unity, SIR = 1.01, 95% CI = 0.89–1.14. The highest SIR was found for glioma in the temporal lobe where RF-EMF exposure from a mobile phone would be highest, SIR = 1.21, 95% CI = 0.91–1.58 ($n=54$ cases).

After the outcome of the IARC-evaluation was made public in June 2011 [1] two additional reports on the Danish cohort were soon published. Both were new up-dates of mobile phone subscribers and included more information on risk related to longer follow-up. One focused on acoustic neuroma [60] while the other gave results both for all cancers and separately for glioma and meningioma [61].

Approximately 2.9 million of the Danish population of 5.5 million in total was included in the record linkage study on acoustic neuroma [60]. Of the 2.9 million subjects 420,095 were mobile phone subscribers that started their subscription 1987–1995 and in accordance with the aim of the study had lasted for ≥ 11 years, i.e., 1998–2006 during which period the tumour cases were ascertained. No evidence of an increased risk was found for ≥ 11 years of subscription; adjusted Incidence Rate Ratio (IRR) was 0.87, 95% CI = 0.52–1.46.

The analysis of long-term exposure (≥ 11 years) was based on only 15 exposed cases with acoustic neuroma all of which were men. Analysis of tumour size was based on even fewer cases; 8 had a subscription for ≥ 11 years. As for the risk related to laterality Schüz et al. [60] compared the location of acoustic neuroma in long-term mobile phone subscribers with shorter use (< 11 years) and non-subscribers to see if tumours occurred more frequently on the side which was assumed to be the mostly exposed. This assumption was based on ecological data from the prospective study, COSMOS, as proxy for laterality [62]. Due to these facts the argument of no laterality risk is not very impressive, especially when applied to only 15 exposed cases.

The fourth report on the Danish mobile phone cohort on tumours of the central nervous system showed no overall increased risk [61]. This was true also when restricted to the individuals with the longest mobile phone use, ≥ 13 years of assumed subscription.

This time the number of the cohort was reduced to 358,403 (49.5%) of the initially identified subscribers ($n=723,421$). This number was also used in the study on acoustic neuroma [60]. The major additional exclusion ($n=54,350$) was due to record linkage with the Danish so-called CANULI cohort on socioeconomic factors [63]. That register started 1990 and included subjects from the age of 30. Subscription holders aged 18–29 years were excluded from the mobile phone cohort; this was also the case for the third publication (acoustic neuroma), see above. Follow-up of cancer started at January 1, 1990, or at the age of 30 if occurred later, and ended December 31, 2007.

The study period was 1990–2007 [61] but the cohort was established during 1982–1995. Cancer cases before 1990 were disregarded since the CANULI cohort started in 1990.

The authors did not discuss the impact of the exclusion of these subscribers on the results. This exclusion would include the early users of analogue phones, which seem to have had higher emissions of RF-EMF than the later digital system. The authors themselves also stated the following in their discussion: “. . . we found indications that early subscription holders before 1995 were in fact heavier users (based on outgoing calls) compared with all subscription holders in the years 1996–2002.” Analysis of any early effect in the group who used phones with the highest emissions was most likely hampered. Moreover, also the youngest users, aged 18–29 years that had previously been included, were now excluded from the cohort. The fully adjusted model had no substantial effect on the risk estimates, so results adjusted for age and calendar period should be possible also for the youngest users. The exclusion of young subscribers could be of importance since as discussed above studies have indicated highest risk in subjects that started the use of a mobile or cordless phone before the age of 20 [28,41].

Some of the many shortcomings of the Danish cohort study include: (a) no individual exposure data (e.g. on cumulative exposure, side of head mostly used, and use of cordless phones); including users of cordless phones in the reference category; (b) no control for use of mobile phones in the population after the establishment of the cohort; and (c) no operator-verified data on years of subscription was available. These limitations are likely to have led to an underestimate of any risk in this study. One would expect considerable misclassification of mobile phone use both among subscribers and the reference population since no new subscribers were included in the exposed cohort after 1995.

The publication of the latest update of the Danish study [61] was accompanied by an editorial by Ahlbom and Feychting from the Karolinska Institute in Sweden [64]. It began with the statement: “Evidence is reassuring, but continued monitoring of health registers and prospective cohorts is still warranted.” They pointed out methodological advantages, such as elimination of non-response and selection bias, but did forget to mention that less than 50% of the initial cohort remained for analysis. However, they were more lenient on the methodological limitations that they had previously pointed out as serious. In a letter to the Editor in 2007 on an earlier publication of the same cohort [59] they pointed out that several methodological shortcomings undermined the authors’ conclusion that “any large association of risk of cancer and cellular telephone use can be excluded” [65]. Although more long-term data was now available and adjustment for socioeconomic factors could be made, the update by Frei et al. [61] suffers from basically the same methodological limitations – mainly related to exposure assessment – as the first one did. Instead of addressing the limitations of the Danish cohort study in full, Ahlbom and Feychting [64] used their space to selectively report on results in the Hardell group studies choosing the time period 2000–2003 [23,24] although the whole investigation period was 1997–2003 [27,40]. They discussed incidence data on

brain tumours in Sweden instead of Denmark, which would have been more appropriate regarding a Danish cohort study.

The authors of the Danish study have themselves pointed out the main causes of such considerable exposure misclassifications [61]: mobile phone subscription holders not using the phone were classified as ‘exposed’, non-subscribers using the mobile phone were classified as ‘unexposed’; corporate subscribers of mobile phones (200,507 people), which are likely to have been heavy users, were classified as ‘unexposed’; persons with a mobile phone subscription later than 1995 were classified as ‘unexposed’ and users of cordless phones not using a mobile phone were also classified as ‘unexposed’.

Other limitations are the absence of analysis by laterality (the side of head where the phone is used in relation to the side of the tumour) and the complete absence of actual exposure data. These and other shortcomings in the cohort study have been discussed elsewhere in more detail [58,65].

It is clear from these limitations that the authors’ conclusion that: “In this update of a large nationwide cohort study of mobile phone use, there were no increased risks of tumours of the central nervous system, providing little evidence for a causal association” is not soundly based [61].

3.11. Hazard ratio (HR) for survival of patients with glioma

A poorer survival among children with acute lymphoblastic leukaemia exposed to ELF-EMF has been reported in two studies [66,67]. These findings certainly strengthen a causal association between exposure to ELF-EMF and childhood leukaemia. Thus, a carcinogenic effect of RF-EMF emissions would be strengthened if exposure might correlate with survival of glioma patients. To further elucidate that possibility we analysed survival of all cases with malignant brain tumour ($n = 1251$) in our case-control studies [26–28]. Most cases were diagnosed with glioma ($n = 1132$ in this study) so in the following results for glioma are presented in short, for further details see Hardell and Carlberg [68].

Hazard ratio (HR) for survival was close to unity for all glioma cases for use of wireless phones, HR = 1.1, 95% CI = 0.9–1.2. However, latency >10 years increased HR to 1.2, 95% CI = 1.002–1.5. Increased ratio was found for both mobile phone use, HR = 1.3, 95% CI = 1.0005–1.6, and cordless phone use, HR = 1.3, 95% CI = 0.9–1.9. HR increased also with cumulative number of hours of use of mobile phone and cordless phone with statistically significant trend for tertiles ($p = 0.01$) of use of both phone types.

Regarding different types of astrocytoma wireless phone use gave a decreased HR = 0.5, 95% CI = 0.3–0.9 for low-grade astrocytoma, WHO grades I–II. Similar results were found for both mobile and cordless phones. Latency did not change these results. Also cumulative numbers of hours for use yielded decreased HR for both mobile and cordless phone use.

For anaplastic astrocytoma, WHO grade III, there was no clear pattern of an association for latency or cumulative number of hours for use. On the contrary, for glioblastoma multiforme, WHO grade IV, long-term use >10 years latency of mobile phone increased the ratio, HR = 1.3, 95% CI = 0.9–1.7, and cordless phone, HR = 1.8, 95% CI = 1.2–2.8.

This study showed elevated HR, indicating decreased survival of all glioma cases with long-term and high cumulative use of wireless phones. For astrocytoma WHO grade IV an increased HR was found indicating a survival disadvantage. On the other hand HR was decreased for low-grade astrocytoma, WHO grades I–II, indicating a survival benefit in that group of cases. This could be caused by RF-EMF exposure leading to tumour-associated symptoms and earlier detection and surgery with better prognosis in that patient group [69].

3.12. Brain tumour incidence

It has been suggested that overall incidence data on brain tumours for countries may be used to qualify or disqualify the association between mobile phones and brain tumours observed in the case-control studies [53,64,70,71]. As mentioned above, in support of the cohort findings that Frei et al. [61] presented for Denmark, Ahlbom and Feychting [64] refer to data on overall brain tumour incidence from the Swedish Cancer Registry rather than from the Danish Cancer Registry, which would have been more relevant.

In Denmark a statistically significant increase in incidence rate per year for brain and central nervous system tumours (combined) was seen during 2000–2009; in men +2.7%, 95% CI = +1.1 to 4.3% and in women +2.9%, 95% CI = +0.7 to 5.2% (<http://www-dep.iarc.fr/NORDCAN/english/frame.asp>). Updated results for brain and central nervous system tumours have been released in Denmark. The age-standardised incidence of brain and central nervous system tumours increased with 40% among men and 29% among women during 2001–2010 (<http://www.sst.dk/publ/Publ2011/DAF/Cancer/Cancerregisteret2010.pdf>). A more recent news release based on the Danish Cancer Register stated that during the last 10 years there has been an increasing number of cases with the most malignant glioma type, glioblastoma multiforme (astrocytoma WHO grade IV), especially among men (<http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftig+stigning+i+hjern-esvulster.htm>). So far these incidence data are not generally available.

Also in the CEFALO study including Denmark, Sweden, Norway and Switzerland [53] only data from the Swedish Cancer Registry were used on time trends for brain tumour incidence. As we have displayed elsewhere [54] annual change in incidence in the age group 5–19 years differs between the Nordic countries. Thus, for the time period 1990–2008 in Norway a yearly increase in incidence with +3.3%, 95% CI +0.8 to 5.9% in boys and +2.5%, 95% CI +0.2 to 4.9% in girls was seen, whereas in Sweden there was

a decline in boys and slight increase in girls. Thus, it would have been more appropriate in CEFALO to discuss trends in all included countries.

The quality of the Swedish Cancer Registry for reporting central nervous system tumours, particularly high-grade glioma, has been seriously questioned [72,73]. In the Deltour et al. [70] article on cancer incidence in the Nordic countries Sweden accounted for about 40% of the population and cases. Thus, under-reporting of brain tumour cases to the Swedish Cancer Register would make the conclusions of the Deltour et al. study less valid.

Little et al. [71] studied the incidence rates of glioma during 1992–2008 in the United States and compared with ORs for glioma associated with mobile phone use in the 2010 Interphone publication [9] and our pooled results published in 2011 [28]. Since our results are discussed and questioned by Little et al., their study needs to be reviewed in more detail. Our response to the journal (BMJ) was never accepted for publication in paper version and cannot be found via PubMed, only on the web (<http://www.bmj.com/content/344/bmj.e1147/rr/578564>).

First, one important methodological issue that was not stated in the abstract or in Figs. 2–4 in the article by Little et al. [71], but can be found in the web appendix, is that observed rates were based on men aged 60–64 years from the Los Angeles SEER registry as the baseline category. These data were used to estimate rates in the entire dataset, men and women aged ≥ 18 years and all 12 SEER registries. Thereby numerous assumptions were made as pointed out by Kundi [74] and Davis et al. [75].

Using only men, as Little et al. [71] did, ignores the fact that women had less frequent use of mobile phones than men in our studies, Table 10. Overall 31% of women reported such use versus 57% of men. Furthermore, use varies with age group with a large difference according to age, as we have explored in our publications [28,41]. Thus, the age group 60–64 year old men is not valid to use for these calculations.

Little et al. [71] do not explain how they obtained different results on incidence trends based on the Hardell group results and Interphone on the risk for mobile phone use. They ignored that the Hardell group assessed also use of cordless desktop phones in contrast to Interphone. As pointed out by IARC and the Hardell group the appropriate exposure category for wireless phone RF-EMF is use of both mobile and cordless phones [1]. We have compared our results with Interphone regarding different age groups and exposure categories in these studies. Thereby the results are similar for both study groups [14]. We have now updated the results based on our 2011 publication, Table 11 [14]. We restricted cases and controls to the age group 30–59 years and disregarded use of cordless phones as in Interphone. Odds ratios are in fact somewhat lower in our study than in Interphone. It is thus remarkable that the projected incidence rates by Little et al. are so different based on our results compared with Interphone although ORs are similar. It should be added that Little et al. [71] present

Table 10

Gender and age distribution for use of mobile phones among glioma cases aged 20–80 years in the Hardell group studies [28]; $n = 1148$.

Age, diagnosis	Men		Women		Total	
	No use/ ≤ 1 year latency, mobile phones	Use > 1 year latency, mobile phones	No use/ ≤ 1 year latency, mobile phones	Use > 1 year latency, mobile phones	No use/ ≤ 1 year latency, mobile phones	Use > 1 year latency, mobile phones
20–24	8	7 (47%)	3	8 (73%)	11	15 (58%)
25–29	10	15 (60%)	5	10 (67%)	15	25 (63%)
30–34	11	26 (70%)	19	8 (30%)	30	34 (53%)
35–39	9	23 (72%)	8	13 (62%)	17	36 (68%)
40–44	10	26 (72%)	16	11 (41%)	26	37 (59%)
45–49	14	37 (73%)	12	16 (57%)	26	53 (67%)
50–54	22	61 (73%)	26	27 (51%)	48	88 (65%)
55–59	35	65 (65%)	59	20 (25%)	94	85 (47%)
60–64	41	51 (55%)	53	15 (22%)	94	66 (41%)
65–69	55	46 (46%)	57	13 (19%)	112	59 (35%)
70–74	43	16 (27%)	41	5 (11%)	84	21 (20%)
75–80	27	8 (23%)	35	2 (5%)	62	10 (14%)
All	285	381 (57%)	334	148 (31%)	619	529 (46%)

wrong latency periods for the results in our studies both in the publication and in the web appendix.

There are several other points that may be added. The results by Little et al. [71] for oligodendroglioma > 10 year latency in our study are wrong in the web appendix, should be OR = 2.2, 95% CI = 0.9–5.4 and not OR = 1.4, 95% CI = 0.9–2.3. Another example is that the results for anatomical localisations and tumour grade [in Table 5 in the article] by Little et al. are based on numerous assumptions from SEER data, Interphone and the Hardell group studies. The authors seem not to have paid attention to the fact that the fraction of mobile phone users differs for gender and age groups, see Table 10. Furthermore, in the final Interphone Study Group [9] publication only results for the whole glioma group were presented in contrast to our published results for both low-grade and high-grade astrocytoma [27], results that are ignored by Little et al. We have now analysed the data further using our 2011 publication, Table 12 [28]. Obviously the risk is higher for high-grade (mostly glioblastoma multiforme) than low-grade astrocytoma for latency time > 10 years. This is of interest considering the statistically significant yearly increasing incidence of high-grade glioma in the SEER data for 1992–2008, +0.64%, 95% CI = +0.33 to 0.95% published by Little et al. [71] without any further comments. On the contrary, the incidence of low-grade glioma decreased with

–3.02%, 95% CI = –3.49 to –2.54%. Increasing yearly trend for glioma in the temporal lobe, +0.73%, 95% CI = +0.23 to 1.23% was also found [71]. Certainly these findings should have been explored in more detail in the study.

In summary the conclusion by Little et al. that “*Raised risk of glioma with mobile phone use, as reported by one (Swedish) study. . . are not consistent with observed incidence trends in the US population data. . .*” goes far beyond scientific evidence and what would be possible to show with the faulty methods used in the study. We agree with Kundi [74] that there is much room for improvement of the BMJ review process, as we have exemplified [54] regarding another recent BMJ publication by Frei et al. [61], as also discussed above.

One should be careful about using data on the incidence of brain tumours, like in Aydin et al. [53] and Deltour et al. [70], to dismiss results in analytical epidemiology. There might be other factors that influence the incidence rate like changes in exposure to other risk factors for brain tumours that are not assessed in descriptive studies. Cancer incidence depends on initiation, promotion and progression of the disease [76]. The mechanism for RF-EMF carcinogenesis is unclear which adds to the view that descriptive data on brain tumour incidence are of limited value.

There are in fact other studies that show an increasing incidence of brain tumours. In Australia the incidence of

Table 11

Odds ratio (OR) and 95% confidence interval (CI) for glioma in the Interphone study [9] and Hardell et al. [14] for the age group 30–59 years. Use of cordless phones disregarded in the Hardell group studies as was done in Interphone. Numbers of exposed cases (Ca) and controls (Co) are given.

	Interphone Appendix 2			Hardell et al.		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Unexposed ^a	93/159	(1.0)	–	241/660	(1.0)	–
<i>Latency</i>						
2–4 years	460/451	1.68	1.16–2.41	128/322	1.09	0.84–1.41
5–9 years	468/491	1.54	1.06–2.22	121/258	1.11	0.84–1.47
10+ years	190/150	2.18	1.43–3.31	84/103	1.75	1.23–2.50

^a Unexposed Interphone Appendix 2: Latency 1–1.9 years; unexposed Hardell et al.: No use + latency ≤ 1 year.

Table 12

Odds ratio (OR) and 95% confidence interval (CI) for mobile phone use and astrocytoma, cf. Hardell et al. [28].

	>1–5 year latency		>5–10 year latency		>10 year latency		Total, >1 year latency	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Astrocytoma, high grade ($n = 820$)	1.2	0.9–1.5	1.5	1.1–1.9	3.0	2.1–4.2	1.5	1.2–1.8
Astrocytoma, low grade ($n = 132$)	1.4	0.8–2.2	1.3	0.7–2.4	1.7	0.7–4.0	1.4	0.9–2.2

primary brain tumours was studied in two areas, the state of New South Wales and Australian Capital Territory, with about 7 million inhabitants [77]. The study covered the time period 2000–2008 and all diagnoses had a histopathological verification. It included 13 pathology databases servicing 24 neurosurgical centres. Adults aged ≥ 65 years recorded the largest proportion of malignant brain tumours, 52%. The Annual Percentage Change (APC) for malignant tumours increased statistically significant +3.9%, 95% CI +2.4 to 5.4%. An increase was seen among both men and women. The APC for benign tumours increased with +1.7%, 95% CI –1.4 to +4.9%, thus not statistically significant.

From urban Shanghai an increasing incidence of brain and nervous system tumours for the time period 1983–2007 was reported with APC +1.2%, 95% CI +0.4 to 1.9% in males and APC +2.8%, 95% CI +2.1 to 3.4% in females [78]. No results were given for different tumour types, e.g. malignant and benign brain tumours, or anatomical site. The authors concluded that “*The study did not support an association between cellular telephone use and increased risk of brain and nervous tumours.*” However, that statement goes far beyond what is scientifically justified from this register based study and what was actually investigated.

Certainly it is more informative to analyse incidence trends by anatomical site and histology of the tumour. de Vocht et al. [79] reported in England for the time period 1998–2007 a statistically significant increasing incidence of brain tumours, the majority glioma, in the temporal lobe for men ($p < 0.01$) and women ($p < 0.01$), and frontal lobe for men ($p < 0.01$). The incidence increased also for women in the frontal lobe, although not statistically significant ($p = 0.07$). The incidence decreased in other parts of the brain.

Zada et al. [80] studied incidence trends of primary malignant brain tumours in the Los Angeles area during 1992–2006. APC was calculated for microscopically confirmed histological subtypes and anatomic sub sites. The overall incidence of primary malignant brain tumours decreased over the time period with the exception of glioblastoma multiforme (astrocytoma WHO grade IV). The annual age adjusted incidence rate of that tumour type increased statistically significant in the frontal lobe with APC +2.4% to +3.0% ($p \leq 0.001$) and temporal lobe APC +1.3% to +2.3% ($p \leq 0.027$) across all registries. In the California Cancer Registry the incidence of glioblastoma multiforme increased also in cerebellum, APC +11.9% ($p < 0.001$). In the parietal and occipital lobes or in overlapping lobes no statistically significant changes in incidence were seen. For lower grade astrocytoma decreases of annual age adjusted incidence rates

were observed. The authors concluded that there was a real increase in the incidence of glioblastoma multiforme in frontal and temporal lobes and cerebellum. These results by Zada et al. [80] are of interest since the highest absorbed dose of RF-EMF emissions from mobile phones has been calculated to occur in these parts of the brain [6].

It should be noted that also Deltour et al. [70] reported increasing glioma incidence rates in Denmark, Finland, Norway, and Sweden for the time period 1979–2008. APC increased for men with +0.4%, 95% CI +0.1 to 0.6% and for women with +0.3%, 95% CI +0.1 to 0.5%. Unfortunately no data were given for subtypes of glioma and anatomical sites of the tumours, which would certainly have been informative. The authors did not consider these and other limitations when they conclude that “*Our data indicate that, so far, no risk associated with mobile phone use has manifested in adult glioma incidence trends...many increased or decreased risks reported in case-control studies are implausible, implying that biases and errors in the self-reported use of mobile phone have likely distorted the findings.*” It should be noted that regarding Sweden we reported increasing incidence of astrocytoma WHO grades I–IV during 1970–2007. In the age group >19 years the annual change was +2.16%, 95% CI +0.25 to 4.10% during 2000–2007 [41].

4. Discussion

The most comprehensive results on use of wireless phones and the association with brain tumours come from the Hardell group in Sweden and the international Interphone study. As pointed out by IARC [1] other studies as discussed above are too small with short latency times, usually in the range of at most 5 years. Both the Hardell group studies and Interphone give results for latency time of 10 years or more. Thus, a summary evaluation will mainly be based on results from these two study groups.

Both were case-control studies and the cases were recruited during similar time periods, 1997–2003 in the Hardell group and during 2000–2004 in Interphone, with somewhat different years in the varying study regions. There was no overlapping of cases in the Hardell group studies and the Swedish part of Interphone. Cases were ascertained from Regional Cancer Registries in the Hardell group studies and all diagnoses were based on histopathological verification. Thus, all cases had been operated or undergone biopsy of the tumour for diagnosis. In contrast, in Interphone cases were identified from neurological or neurosurgical facilities in the

study regions; in some centres also from cancer registries. The diagnoses of glioma, meningioma and acoustic neuroma were based on histopathology or diagnostic imaging. It should be pointed out that the diagnosis of both meningioma and acoustic neuroma has a rather high precision using CT and/or MRI. Regarding glioma it is certainly more difficult to establish a valid diagnosis without histopathology, especially when it comes to subgroups such as different grades of astrocytoma (WHO grades I–IV). In the publication by Lähkölä et al. [81] most glioma diagnoses were based on histopathology, whereas this has not been published for Interphone in total. It is notable that Interphone [9] has not presented separate results for astrocytoma in total in contrast to the Hardell group. Especially results for high-grade glioma including the most common glioma type, glioblastoma multiforme (WHO grade IV), would be of value since the highest risk was found for that subtype by Hardell et al., Table 12 [27,28]. It is also of interest that we found higher risk for use of mobile and cordless phones for astrocytoma grades III–IV than for grades I–II [82]. Some results were published for glioblastoma multiforme from the 5 North European countries [81]. Certainly the total result for glioma and >10 years since first ipsilateral mobile phone use with OR = 1.39, 95% CI = 1.01–1.92 (p for trend 0.04) would have been of interest for glioblastoma multiforme separately in Lähkölä et al. [81].

The Hardell group included cases aged 20–80 years whereas eligible cases in Interphone were aged 30–59 years at diagnosis. This difference is important since the highest incidence of astrocytoma WHO grade IV (glioblastoma multiforme) is found in the age group 45–75 years with mean age 61 years and 80% older than 50 years [83]. As can be seen in Table 10, the highest prevalence of use of mobile phones in the Hardell group studies was up to the age of 54 years, so limiting the age to 59 years as in Interphone diminishes the possibility to find an increased risk taking a reasonable tumour induction period. It seems as if the age distribution in Interphone was more decided by prevalence of mobile phone use in the population than age distribution for glioma cases. Excluding the age group 20–29 years, as in Interphone, makes also an evaluation of young users more difficult, see Table 9.

Meningioma is a slow growing benign tumour with a peak incidence in the sixth and seventh decade of life with a 3:2–2:1 female:male ratio [84]. As pointed out by Interphone [10] the incidence peak of acoustic neuroma is in the age group 50–65 years. Thus, again limiting upper age to 59 years for cases in Interphone excluded a large proportion of cases with meningioma or acoustic neuroma taking a reasonable latency period.

One control subject matched on age, gender and geographical area (region) to each case in the Hardell group studies was drawn from the national population register. The register covers the whole population and each person is assigned a unique id-number making it possible to trace current address for all inhabitants. In Interphone one control was selected for each case from a 'locally appropriate population-based sampling frame'. In Germany the centres used individual

matching or frequency matching. The matching variables were age within 5 years, gender and region of residence; in Israel also ethnic origin. When stratified matching was used individual matching was made afterwards from the whole control sample with cases being assigned one control subject (two in Germany) interviewed as close as possible in time to the case [9]. Regarding the Interphone study on acoustic neuroma some centres sampled special controls to the cases, other draw controls from the pool of controls in the glioma and meningioma studies, or used a mixture of both methods.

The Nordic countries have population registers that were used in Denmark, Norway and Finland for recruitment of controls in Interphone. Also Germany used a population register [85]. However, UK used general practitioners' lists [86] and in Japan random digit dialling was used [44,87]. Certainly the methods used in Interphone may introduce selection bias. Patient lists are usually selective to use for drawing of controls and do not represent the whole population which is the source of the cases. Also random digit dialling has the potential to introduce selection bias since persons that are registered to subscribe a phone are usually wealthier than non-subscribers. Furthermore, it seems not to be the most appropriate method for selection of controls in a study on mobile phone use, and certainly not regarding cordless phones, since phone subscribers are selected as controls. Furthermore, later selection of controls from a pool with individual matching may give the possibility for selection bias if this is not done in a blinded manner as to exposure status.

These methods contrast to the Hardell group where controls were drawn consequentially to the cases and all controls that answered the questionnaire were included in the analyses. In Interphone proxy interviews were performed for 13% of glioma cases but only 1% of controls [9]. This is in contrast to the Hardell group study on deceased cases with malignant brain tumours [26]. Deceased controls were drawn from the Death Registry in Sweden. Relatives to both deceased cases and deceased controls were interviewed, thereby creating the same condition for assessment of exposure among cases and controls. Although using proxy interviews for both cases and controls is the more appropriate method exclusion of proxy interviews in Interphone had little impact on the overall result in the sensitivity analysis.

Use of wireless phones was carefully assessed by a self-administered questionnaire in the Hardell et al. studies. The information was supplemented over the phone by trained interviewers thereby using a structured protocol. This was done blinded as to case or control status. The ear that had mostly been used during calls with mobile phone and/or cordless phone was assessed by separate questions; >50% of the time for one side, or equally for both sides. This information was checked during the supplementary phone calls. Moreover every person that had used a mobile phone received after that a letter asking them again to specify the ear that had been used during phone calls and to what extent that side of the head was mostly used. There was a very good agreement of the results using these three methods to assess these data. Also

other exposures were assessed in the questionnaire. After the interviews all personal data like names and addresses were removed from the questionnaires so that only an id-number that did not disclose if it was a case or a control was shown. Thus, coding of the data for statistical analysis was performed without personal data on the individual.

We investigated in more detail the possibility of recall and observational bias in our second case-control study [21]. Reporting a previous cancer or if a relative helped to fill in the questionnaire did not change the results, i.e., were no confounding factors. Potential observational bias during phone interviews was analysed by comparing change of exposure in cases and controls after these interviews. No statistically significant differences were found, showing that our results could not be explained by observational bias, for further details see discussion in that publication [21].

On the contrary information on past mobile phone use was mostly collected during face-to-face interviews in Interphone obviously disclosing if it was a case or a control that was interviewed. These interviews were performed by a large number of interviewers at different participating centres. In the personal interviews a computer program that guided the interview with questions read by the interviewer from a laptop computer screen was used. The interviews in the Swedish part lasted for about 45 min. The answers were entered directly into the computer by the interviewer. Cards were shown to if possible identify the model of the mobile phone [88]. The purpose of the study was thereby obviously disclosed to the cases and controls. This was in contrast to the Hardell group mailed questionnaire that contained a large number of other questions without special attention to wireless phones.

We regard hospital based interviews of cases, as in the Interphone study, to be a major disadvantage and ethically questionable. At that time the patient has not fully recovered from e.g. surgery, may not have been fully informed about the diagnosis, treatment and prognosis and may even be under sedation by drugs. Using computer based face-to-face interviews may also be a stressful situation for the patient. In fact patients scored significantly lower than controls due to recalling of words (aphasia), problems with writing and drawing due to paralysis in the Danish part of Interphone [89]. Obviously observational bias could have been introduced by the interview methods in Interphone. Only Finland used a paper version of the questionnaire, but Finland has never published country specific results on the different tumour types, which would certainly have been of interest. For unclear reasons the results on glioma were only included as part of the results for the 5 North European countries [81] and as part of the whole Interphone study [9]. Furthermore, it has not been disclosed how the personal interviews were performed in sparsely populated areas, e.g. in the Northern Sweden. Did the interviewers travel long distances for interviews of controls in rural areas or were all controls living in the largest cities thereby creating selection bias?

It should be noted that the number of participating cases and controls from each centre in Interphone was quite low. It

varied for glioma from 60 (Japan) to at most 421 (UK North), for meningioma from 52 (New Zealand) to 350 (Israel) and for acoustic neuroma from 18 (New Zealand) to 152 (UK South). Similarly the number of controls varied according to centre [9,10]. It is obvious that with so low number of interviewed subjects by many different interviewers the quality may have been hampered in Interphone by low training and experience of certain interviewers. Experienced interviewers were defined as those who conducted at least 20 interviews. In fact, in the sensitivity analysis the risk increased for glioma for cumulative mobile phone use ≥ 1640 h from OR = 1.40, 95% CI = 1.03–1.89 to OR = 1.50, 95% CI = 1.10–2.06 if ‘experienced interviewers only’ were considered. In the Hardell group studies few persons conducted all interviews of the 1251 participating cases with malignant brain tumour, 1254 cases with benign brain tumour, and 2438 controls (total 4942; note one case had both a malignant and a benign brain tumour). All interviewers were first educated; they used a defined protocol and gained considerable experience as interviewers. In fact, they were obliged to carry out the interviews extensively to fulfil the quality in data assessment according to the structured protocol. It is obvious that the few interviewers in the Hardell group study must have been much more experienced than the diversity of interviewers in Interphone. The higher risk restricting analysis to ‘experienced interviewers’ in Interphone indicates observational bias during assessment of exposure decreasing the risk. Furthermore, 20 interviews as the definition was in Interphone to be an experienced interviewer, is after all a very low number.

Several other sensitivity analyses were performed in Interphone without any major impact on the results. It is discussed in the Interphone study [9] that the increased risk for glioma in the highest decile of cumulative exposure was caused by a number of subjects reporting >5 h call time per day. This number may be real in e.g. certain occupations using the phone as a working tool. Furthermore, if call time was truncated to 5 h per day no statistically significant difference of the risk was found, OR = 1.38, 95% CI = 1.02–1.87 for glioma and OR = 3.03, 95% CI = 1.62–5.67 for acoustic neuroma (exposure up to 5 years before reference date). Certainly it is not justified to exclude these subjects from the analysis as was done in some of the calculations in Interphone [9,10].

It is always essential to have a high response rate in case-control studies to get as valid results as possible. In the Hardell group studies the response rate was 85% ($n = 1251$) for cases with malignant brain tumour, 88% ($n = 1254$) for cases with benign brain tumour, and 84% ($n = 2438$) for controls [29,40]. Lower response rates were obtained in the Interphone study, 64%, range by centre 36–92%, ($n = 2765$) for glioma cases, 78%, range 56–92%, ($n = 2425$) for meningioma cases, 82%, range 70–100% ($n = 1121$) for acoustic neuroma cases, and 53%, range 42–74%, ($n = 7658$) for controls [9,10]. Certainly these low response rates, less than half of the cases and controls in some centres, may have created the possibility of considerable selection bias and are examples of the multiple methodological problems in Interphone. As has been

discussed elsewhere not responding controls in Interphone tended to be less frequent users of mobile phone than participating controls leading to underestimation of the risk [32].

There are other differences between the Hardell group studies and Interphone study such as restricting age to 30–59 years in Interphone compared with 20–80 years in the Hardell-group studies and considering use of cordless phones as no exposure to RE-EMF in Interphone. Even if the prevalence of mobile phone use is highest in the age group 30–59 years, excluding older cases diminishes the possibility to find an increased risk, assuming a reasonable latency time. As discussed above the peak incidence of most brain tumours is at a higher age. In a case series from Canada all brain tumours showed a bimodal age distribution with one peak in the 0–4 age group and the other in the 60–69 age group [90]. As shown elsewhere [14] step-wise exclusion of the age group 20–29 years, 60–80 years and including cordless phone use among unexposed reduced OR in the Hardell-group studies to similar results as in Interphone [see Tables 1 and 2 in the publication]. Thus, Interphone seems to have underestimated the risk also for these reasons.

Survival of patients with glioma has only been presented by the Hardell group [68]. Decreased survival of glioma cases with long-term and high cumulative use of wireless phones was found. We found a survival disadvantage for astrocytoma WHO grade IV among cases using mobile phone or cordless phone indicating a worse prognosis in that patient group. On the contrary, a survival benefit for astrocytoma WHO grades I–II was observed. The fact that there was no clear trend with intensity or duration of wireless phone use for low-grade astrocytoma does not speak in favour of an effect of RF-EMF from such use. The exposure might, however, produce awareness bias in these cases. RF-EMF may give tumour promotion [91] inducing disease related personality disturbances and habit changes leading to earlier tumour diagnosis than among unexposed patients. This would result in earlier treatment with a better prognosis after surgery in this patient group [69]. These findings indicate a complex biological effect from RF-EMF exposure and strengthen a causal association between these tumour types, e.g. astrocytoma WHO grade IV (glioblastoma multiforme), and use of wireless phones.

By placing a strong emphasis on incidence data an association between use of wireless phones and brain tumours has been challenged [92]. The authors considered that, if the increased risks seen in case-control studies reflect a causal relationship, there would already be an increase in incidence of brain and central nervous system tumours, for which there seemed to be little evidence. This belief is unfounded for two reasons. The first relates to latent periods for glioma and acoustic neuroma development, typically 10–40 years [93,94]. The results on long-term use of wireless phones are scanty and at most latency period of 10+ years have been studied. Furthermore, we know little about the earliest events in the genesis of glioma in humans for obvious reasons. However, progression of glioma has been studied in large series of

tumours of different malignancy grades. Patients with low-grade glioma have been followed with later progression to high-grade glioma [95]. Thus, since the natural history of most glioma from earliest events to clinical manifestation is unknown, but most likely several decades, the exposure duration in most studies is incompatible with a tumour initiating effect. An initiating effect is what would have the most direct effect on the incidence. The other reason concerns the possibility of an effect on tumour development (promotion) and its consequences on the increase in incidence that can possibly occur. If the exposure acts as a promoter, this would decrease latency time for already existing tumours, giving a temporary but not a continuous increase in incidence. In addition it has to be pointed out that any such effect on tumour development is limited by the magnitude of the shift of the age-incidence function and its slope for the respective tumour type [91]. It should be noted that studies on tumour type and anatomical localisation indicate by now an effect from RF-EMF on the incidence of brain tumours [71,77,79,80].

5. Conclusions

There is a consistent pattern of increased risk of glioma and acoustic neuroma associated with use of mobile phones and cordless phones. The epidemiological evidence comes mainly from two study centres, the Hardell group and the Interphone study group. In the same studies by the Hardell group and Interphone study group no consistent pattern of an increased risk was found for meningioma. These results strengthen the other findings, i.e., increased risk for glioma and acoustic neuroma, since a systematic bias in the studies would also have been inherited for meningioma. Furthermore, a causal association between use of mobile phone and glioma and acoustic neuroma comes from the meta-analyses as presented in this publication and also reviewed elsewhere [96]. Supportive evidence comes also from anatomical localisation of the tumour to the most exposed area of the brain, cumulative exposure and latency time that all add to the biological relevance of an increased risk. In addition risk calculation based on estimated absorbed dose gives strength to the findings as well as the impact on survival of glioma patients relating to their use of mobile and cordless phones.

Evidence is increasing that workers with heavy use of wireless phones who develop glioma or acoustic neuroma should be compensated. In fact, the first case with such compensation has now been established in court. The Italian Supreme Court affirmed a previous ruling that the Insurance Body for Work (INAIL) must grant worker's compensation to a businessman who had used wireless phones for 12 years and developed a neuroma in the brain (www.applelettrosmog.it; www.microwavenews.com). He had used both mobile and cordless phones for five to six hours per day preferably on the same side as the tumour developed. The neuroma was located in the trigeminal Gasser's ganglion in the brain. This fifth cranial nerve controls facial sensations and muscles. It is

the same type of tumour as the acoustic neuroma in the eighth cranial nerve located in the same area of the brain. The Italian case fulfils the criteria for a causal association; more than 10 years use of wireless phones, high cumulative exposure on the same side as the tumour appeared, and a tumour type that would be predicted based on previous research on use of wireless phones and brain tumour risk. No further appeal of the Supreme Court decision is possible.

In summary there is reasonable basis to conclude that RF-EMFs are bioactive and have a potential to cause health impacts. There is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of wireless phones (mobile phones and cordless phones) mainly based on results from case-control studies from the Hardell group and Interphone Final Study results. Epidemiological evidence gives that RF-EMF should be classified as a human carcinogen. The current safety limits and reference levels are not adequate to protect public health. New public health standards and limits are needed.

Authors' contributions

Lennart Hardell was responsible for drafting of the manuscript and Michael Carlberg made all statistical calculations. Michael Carlberg and Kjell Hansson Mild read and gave valuable comments on the manuscript. All authors have read and approved the final version. No conflicts of interest reported.

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Pooled Analysis of Two Swedish Case–Control Studies on the Use of Mobile and Cordless Telephones and the Risk of Brain Tumours Diagnosed During 1997–2003

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Here we present the pooled analysis of 2 case–control studies on the association of brain tumours with mobile phone use. Use of analogue cellular phones increased the risk for acoustic neuroma by 5%, 95% confidence interval (CI) = 2–9% per 100 hrs of use. The risk increased for astrocytoma grade III–IV with latency period with highest estimates using >10-year time period from first use of these phone types. The risk increased per one year of use of analogue phones by 10%, 95% CI = 6–14%, digital phones by 11%, 95% CI = 6–16%, and cordless phones by 8%, 95% CI = 5–12%. For all studied phone types OR for brain tumours, mainly acoustic neuroma and malignant brain tumours, increased with latency period, especially for astrocytoma grade III–IV.

malignant tumours benign tumours acoustic neuroma astrocytoma cellular phones

1. INTRODUCTION

The use of wireless phone communication has increased dramatically during the past decade. Today almost everyone in working life has a mobile or a cellular phone and the amount of time spent on the phone is increasing. There is concern over adverse health effects especially those caused by the use of mobile phones since the development has been technology driven rather than based on laboratory and clinical studies on potential

adverse health effects. So far most human studies have been limited in their conclusions due to low numbers of long-term users. The brain is a main target organ for exposure to microwaves during the use of both mobile and desktop cordless phones. Our case–control studies on brain tumours are among the first in the world to give results for long-term users, ≥ 10 years, with large enough numbers of exposed subjects to estimate long-term cancer risk.

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Nordic countries were among the first in the world to introduce this new technology. Analogue (Nordic Mobile Telephone System, NMT) phones operating at 450 MHz were introduced in Sweden in 1981 but portable NMT 450 phones were first introduced in 1984. Analogue phones using 900 MHz were used in Sweden between 1986 and 2000. The digital system (GSM) started in 1991 and is presently the most common phone type. This system uses dual band, 900 and 1 800 MHz. Universal Mobile Telecommunication System (UMTS) or 3G started in Sweden in 2003 operating at 1 900 MHz.

Desktop cordless phones also use wireless technology. First the analogue system in the 800–900 MHz radiofrequency (RF) radiation was used when these phones were available in Sweden in 1988. Digital cordless telephones (DECT) that operate at 1 900 MHz have been used since 1991.

The use of mobile and desktop cordless telephones results in exposure to microwaves. The different types of phones have different output power. An NMT phone operates with a maximum power of 1 W and very seldom down regulates this; a GSM 900 phone operates with a maximum peak power of 2 W but can down regulate this to some milliwatts depending on the distance to the base station, adaptive power control (APC) and a typical value would be a few tens of milliwatts, giving a mean output power of less than 10 mW. Cordless phones lack APC and operate with a peak power of 250 mW, and with a duty cycle of 1/24 giving a mean output power of about 10 mW. The anatomical area with the highest exposure is the ipsilateral (same) side of

the brain that is used during the call. If a hands-free device is used and a cellular telephone is placed at another part of the body that anatomical area receives the highest RF exposure.

We have performed six case–control studies since the 1990s on the use of mobile or cordless phones and different tumour types, i.e., brain tumours, salivary gland tumours, non-Hodgkin lymphoma and testicular cancer. Three studies concerned brain tumours and they are presented in the following with some further analysis of the study material.

The first case–control study on brain tumours was rather small [1, 2]. This was followed by two larger case–control studies on brain tumours [3, 4, 5, 6]. Here we present results from the pooled analysis of these two studies [7, 8]. In the following a short description of the studies is given; further details can be found in the various publications. In principle the same epidemiological methods were used in all studies. A summary of our six case–control studies on this topic can be found elsewhere [9].

2. MATERIALS AND METHODS

Ethical committees approved all studies. They were performed in various health service regions in Sweden and at somewhat different time periods for recruitment of cases and controls (Table 1). The cases were reported by Cancer Registries in Sweden, which has a very good coverage of all incident cancer cases. The current address was checked using the national Population Registry.

TABLE 1. Description of Case–Controls Studies by Hardell et al. [1, 2, 3, 4, 5, 6] on the Use of Mobile and Cordless Telephones and the Risk for Brain Tumour

Study	Geographical Area	Years	Included Persons	Response Rate
CNS [1, 2]	Uppsala/Örebro, Stockholm	1994–1996 1995–1996	233 cases 466 controls	209 (90%) cases 425 (91%) controls
CNS [3, 4]	Uppsala/Örebro, Stockholm, Linköping, Göteborg	Jan 1, 1997– June 30, 2000	1 617 cases* 1 617 controls	1 429 (88%) cases 1 470 (91%) controls
CNS, benign [5]	Uppsala/Örebro, Linköping	July 1, 2000– Dec 31, 2003	462 cases** 820 controls	413 (89%) cases 692 (84%) controls
CNS, malignant [6]	Uppsala/Örebro, Linköping	July 1, 2000– December 31, 2003	359 cases** 820 controls	317 (88%) cases 692 (84%) controls

Notes. CNS—central nervous system; *—one case had two benign brain tumours, **—one case had both a malignant and a benign brain tumour.

Deceased cases were excluded in order to get as good assessment of exposure as possible. The controls were drawn from the Swedish Population Registry, thereby matched to the cases on gender, age and geographical area.

3. ASSESSMENT OF EXPOSURE

Exposures to cellular and cordless phones were assessed with a mailed questionnaire including also exposure to certain chemical agents and X-ray investigations and lifetime work history whereby the socioeconomic index (SEI) was assessed since adjustment was made for SEI-code in the statistical analyses. Detailed questions were asked on the use of mobile and cordless phones including years of use, mean use per day in minutes, use of a hands-free device, external antenna in a car and ear most frequently used during phone calls. It was possible to separate the use of analogue and digital mobile phones since different prefixes are used for the phone numbers in Sweden, 010 and 07, respectively. The answers were supplemented over the phone by a trained interviewer using a structured protocol if some details were unclear. The interviews as well as the coding of the answers for statistical analyses were blinded as to case or control status. Details have been further explored in the various publications.

4. STATISTICAL ANALYSIS

Unconditional logistic regression analysis (Stata/SE 8.2 for Windows; StataCorp, College Station, TX, USA) was used to calculate odds ratios (OR) and 95% confidence intervals (CI). The unexposed category consisted of subjects who had not used cellular or cordless phones. The exposed cases and controls were divided according to phone type, analogue, digital or cordless. In the assessment of exposure the use of a mobile or cordless phone that started in the year of diagnosis (corresponding year for the matched control) was disregarded. Thereby the same year of diagnosis of the case was used for the corresponding control as cut-off for exposure. Adjustment was made in the analysis for gender, age, SEI-code and year of diagnosis [7, 8].

We used age as a continuous variable in the analysis. Latency or tumour induction period was analysed using three time periods, >1–5 years, >5–10 years and >10 years from the first use of a cellular or cordless telephone until diagnosis. Note that overall results for all latency groups were calculated in one analysis. The calculations of the combinations of lifetime use in hours (1–1 000, 1 001–2 000 and >2 000 hrs) and latency (>1–5, >5–10 and >10 years) were done separately for each latency category. Duration of use and latency period were used as continuous variables. We calculated OR and 95% CI per 100 hrs of use of the phones and also per one year of use and one-year latency period.

5. RESULTS

The pooled analysis of the two case–control studies on brain tumours was based on answers from 1 254 (88%) cases with benign brain tumour, 905 (90%) with malignant brain tumour and 2 162 (89%) controls. Details from the separate studies can be found elsewhere [3, 4, 5, 6].

Regarding meningioma the risk increased with latency period. With latency of >10 years analogue phones yielded OR = 1.6, 95% CI = 1.02–2.5, digital phones OR = 1.3, 95% CI = 0.5–3.2 and cordless phones OR = 1.6, 95% CI = 0.9–2.8. However, in the multivariate analysis adjusted for the different phone types lower odds ratios were found and none were statically significant [7] (Table 2).

All phone types increased the risk for acoustic neuroma. Regarding analogue phones odds ratio increased with latency period and was highest in the category with latency period of >15 years yielding OR = 3.5, 95% CI = 1.4–10 [7]. Increased risk was also found for digital mobile phones and cordless phones. However, in the multivariate analysis only analogue phones were significant risk factors with OR 2.2, 95% CI = 1.3–3.8 using >10-year latency period [7].

In Table 3 results are displayed per 100 hrs of use, one year of use and latency. Regarding meningioma the risk did not increase significantly per 100 hrs of use. However, per one year of use analogue phones yielded

TABLE 2. Use of Mobile and Cordless Phones and Odds Ratio (OR) and 95% Confidence Intervals (CI) for Different Tumour Types. Adjustment Was Made for Age, Gender, SEI-Code and Year of Diagnosis. Results Are Given for Different Latency Periods

Study	>1-5-Year Latency			>5-10-Year Latency			>10-Year Latency		
	Analogue	Digital	Cordless	Analogue	Digital	Cordless	Analogue	Digital	Cordless
	OR CI	OR CI	OR CI	OR CI	OR CI	OR CI	OR CI	OR CI	OR CI
CNS (1997-2003) [7, 8]									
All	1.3 0.9-1.7	1.1 0.97-1.3	1.2 0.97-1.4	1.4 1.1-1.9	1.4 1.1-1.8	1.4 1.1-1.7	2.1 1.5-2.9	2.1 1.1-3.9	1.6 1.1-2.4
Benign, all	1.4 0.9-2.0	1.1 0.9-1.4	1.1 0.9-1.4	1.7 1.2-2.3	1.2 0.9-1.7	1.4 1.1-1.7	1.8 1.2-2.6	1.6 0.8-3.5	1.4 0.8-2.3
Meningoma	1.2 0.8-1.8	1.0 0.8-1.3	1.0 0.8-1.3	1.2 0.8-1.8	1.1 0.8-1.6	1.3 1.01-1.8	1.6 1.02-2.5	1.3 0.5-3.2	1.6 0.9-2.8
Acoustic neuroma	2.3 1.2-4.1	1.4 1.01-2.1	1.5 1.01-2.1	3.4 2.1-5.5	1.8 1.1-3.0	1.5 0.96-2.4	3.1 1.7-5.7	0.6 0.1-5.0	1.0 0.3-2.9
Malignant, all	1.2 0.8-1.8	1.2 0.96-1.5	1.2 0.9-1.5	1.1 0.8-1.6	1.7 1.2-2.2	1.5 1.1-2.0	2.4 1.6-3.4	2.8 1.4-5.7	1.8 1.1-3.0
Astrocytoma, grade I-II	1.1 0.4-2.8	1.4 0.8-2.3	1.3 0.7-2.2	1.1 0.4-2.6	1.6 0.8-3.4	1.6 0.9-3.0	1.6 0.6-4.1	1.3 0.2-11	1.6 0.5-4.6
Astrocytoma, grade III-IV	1.3 0.8-2.2	1.3 0.97-1.7	1.2 0.9-1.7	1.3 0.8-2.0	2.2 1.6-3.1	1.8 1.3-2.5	2.7 1.8-4.2	3.8 1.8-8.1	2.2 1.3-3.9

Notes. SEI—socioeconomic index, CNS—central nervous system.

OR = 1.05, 95% CI = 1.01-1.09 and cordless phones OR = 1.04, 95% CI = 1.01-1.07. Similar results were found for latency period. For acoustic neuroma the risk increased per 100 hrs of use of analogue phones with OR = 1.05, 95% CI = 1.02-1.09. Odds ratio also increased significantly per one year of use and latency for analogue phones. Digital mobile phones and cordless phones did not increase the risk significantly in these calculations.

For astrocytoma grade I-II there was no clear trend of increasing odds ratio with increasing latency period (Table 2) and the risk was not significantly increased. Nor did odds ratio increase significantly per 100 hrs of use, one year of use or one-year latency period for any phone type (Table 3).

On the contrary, for astrocytoma grade III-IV (high grade) odds ratio increased with latency period and was highest with >10-year latency for all phone types. In that latency group analogue phones yielded OR = 2.7, 95% CI = 1.8-4.2, digital phones OR = 3.8, 95% CI = 1.8-8.1 and cordless phones OR = 2.2, 95% CI = 1.3-3.9 (Table 2). In the multivariate analysis analogue phones gave OR = 2.0, 95% CI = 1.4-2.9, digital phones OR = 2.4, 95% CI = 1.1-4.9 and cordless phones OR = 1.3, 95% CI = 0.8-2.3 [8].

The risk increased significantly for astrocytoma grade III-IV per 100 hrs of use, for analogue phones OR = 1.06, 95% CI = 1.03-1.09, digital phones OR = 1.04, 95% CI = 1.02-1.06 and cordless phones OR = 1.02, 95% CI = 1.01-1.03 (Table 3). Also per one year of use and latency period odds ratio increased significantly for all phone types.

In Table 4 analyses are presented for the three different latency periods and in each period three groups of use; 1-1 000, 1 001-2 000 and >2 000 hrs. Increased odds ratios were found for benign tumours in the latency groups of >5-10 and >10 years. These results were mainly explained by the increased risk for acoustic neuroma. There was no obvious dose-response in the three categories of cumulative hours of use, although in several calculations highest risk was found in the category with highest cumulative use in hours.

Clearly for malignant brain tumours the use of mobile phones increased odds ratio in all categories in the latency period of >10 years. All mobile phone use (analogue and digital combined) gave for 1-1 000 hrs OR = 2.0, 95% CI = 1.3-3.0 increasing to OR = 6.4, 95% CI = 3.0-14 in the group of >2000 hrs of cumulative use. Regarding cordless phones use of >1 000 hrs increased odds ratio significantly both for the latency period >5-10 and >10 years.

TABLE 3. Odds Ratio (OR) and 95% Confidence Interval (CI) per 100 hrs of Use, One-Year Use and One-Year Latency Period, Respectively, for Mobile (Analogue, Digital) or Cordless Phones in Brain Tumour Studies [7, 8]. Adjustment Was Made for Age, Gender, SEI-Code and Year of Diagnosis

	Analogue Phone		Digital Phone		Cordless Phone	
	OR	95% CI	OR	95% CI	OR	95% CI
OR per 100 hrs of use						
Benign tumour	1.03	1.003–1.060	1.00	0.98–1.03	1.01	0.998–1.020
Meningioma	1.02	0.99–1.05	0.99	0.96–1.02	1.01	0.997–1.020
Acoustic neuroma	1.05	1.02–1.09	1.03	0.998–1.060	1.01	0.997–1.020
Malignant tumour	1.05	1.02–1.07	1.03	1.01–1.05	1.01	1.01–1.02
Astrocytoma, grade I–II	1.04	0.996–1.100	1.03	0.99–1.06	1.01	0.99–1.03
Astrocytoma, grade III–IV	1.06	1.03–1.09	1.04	1.02–1.06	1.02	1.01–1.03
OR per one year of use						
Benign tumour	1.06	1.03–1.10	1.04	1.0004–1.0700	1.04	1.01–1.06
Meningioma	1.05	1.01–1.09	1.02	0.98–1.06	1.04	1.01–1.07
Acoustic neuroma	1.12	1.06–1.17	1.06	0.995–1.130	1.04	0.99–1.10
Malignant tumour	1.08	1.04–1.11	1.08	1.04–1.12	1.06	1.03–1.09
Astrocytoma, grade I–II	1.03	0.94–1.13	1.06	0.97–1.16	1.05	0.98–1.12
Astrocytoma, grade III–IV	1.10	1.06–1.14	1.11	1.06–1.16	1.08	1.05–1.12
OR per one-year latency period						
Benign tumour	1.05	1.03–1.08	1.04	1.001–1.070	1.04	1.01–1.07
Meningioma	1.03	1.004–1.060	1.02	0.98–1.06	1.04	1.01–1.07
Acoustic neuroma	1.10	1.06–1.14	1.06	0.99–1.13	1.04	0.99–1.09
Malignant tumour	1.06	1.03–1.08	1.08	1.04–1.12	1.05	1.02–1.08
Astrocytoma, grade I–II	1.03	0.96–1.09	1.06	0.97–1.16	1.04	0.98–1.11
Astrocytoma, grade III–IV	1.07	1.04–1.10	1.11	1.06–1.16	1.08	1.04–1.11

Notes. SEI—socioeconomic index.

TABLE 4. Odds Ratio (OR) and 95% Confidence Interval (CI) for Latency Periods and Cumulative Use in Hours of Mobile or Cordless Phones in Brain Tumour Studies [7, 8]. Adjustment Was Made for Age, Gender, SEI-Code and Year of Diagnosis

	>1–5-Year Latency		>5–10-Year Latency		>10-Year Latency	
	Cases Controls	OR CI	Cases Controls	OR CI	Cases Controls	OR CI
Benign tumours						
Analogue phone						
1–1 000 hrs	51 86	1.3 0.9–1.9	85 120	1.6 1.2–2.3	50 75	1.8 1.2–2.8
1 001–2 000 hrs	0 0	—	5 4	3.6 0.9–14	2 4	1.5 0.3–8.4
>2 000 hrs	1 0	—	0 3	—	5 5	2.5 0.7–8.9
Digital phone						
1–1 000 hrs	315 562	1.2 0.96–1.4	87 157	1.3 0.9–1.7	12 12	3.2 1.3–7.6
1 001–2 000 hrs	6 14	1.1 0.4–2.8	8 15	1.4 0.6–3.4	1 4	0.6 0.1–6.1
>2 000 hrs	2 5	1.1 0.2–5.7	6 5	4.0 1.2–13	0 2	—

TABLE 4. (continued)

	>1-5-Year Latency		>5-10-Year Latency		>10-Year Latency	
	Cases Controls	OR CI	Cases Controls	OR CI	Cases Controls	OR CI
Benign tumours (cont.)						
Mobile phone						
1-1 000 hrs	286 531	1.1 0.9-1.4	150 229	1.4 1.1-1.9	49 68	1.9 1.3-2.9
1 001-20 00 hrs	2 7	0.7 0.2-3.6	15 19	2.2 1.1-4.4	7 20	1.0 0.4-2.5
>2 000 hrs	2 3	1.7 0.3-10	6 12	1.4 0.5-3.9	8 11	2.1 0.8-5.4
Cordless phone						
1-1 000 hrs	228 399	1.1 0.9-1.4	102 166	1.4 1.02-1.8	9 34	0.8 0.3-1.6
1 001-2 000 hrs	14 26	1.0 0.5-2.0	25 23	2.3 1.2-4.1	6 3	4.3 1.03-18
>2 000 hrs	8 12	1.4 0.5-3.4	18 30	1.3 0.7-2.4	13 8	3.5 1.4-8.8
Malignant tumours						
Analogue phone						
1-1 000 hrs	39 86	1.1 0.7-1.1	54 120	1.1 0.8-1.6	54 75	1.8 1.2-2.7
1 001-2 000 hrs	0 0	—	1 4	0.5 0.1-4.9	9 4	5.7 1.7-19
>2 000 hrs	0 0	—	2 3	1.4 0.2-8.8	19 5	9.6 3.5-27
Digital phone						
1-1 000 hrs	254 562	1.2 0.96-1.5	86 157	1.5 1.04-2.0	15 12	4.1 1.7-9.7
1 001-2 000 hrs	9 14	1.5 0.6-3.5	17 15	2.7 1.3-5.6	0 4	—
>2 000 hrs	2 5	0.9 0.2-4.6	15 5	6.5 2.3-19	4 2	5.9 1.01-34
Mobile phone						
1-1 000 hrs	237 531	1.2 0.95-1.5	107 229	1.2 0.9-1.6	52 68	2.0 1.3-3.0
1 001-2 000 hrs	5 7	1.6 0.5-5.0	13 19	1.5 0.7-3.2	16 20	2.0 0.99-4.0
>2 000 hrs	1 3	0.8 0.1-7.7	9 12	1.6 0.6-3.8	28 11	6.4 3.0-14
Cordless phone						
1-1 000 hrs	173 399	1.2 0.9-1.5	79 166	1.3 0.96-1.8	13 34	1.0 0.5-2.0
1 001-2 000 hrs	12 26	1.2 0.6-2.5	20 23	2.5 1.3-4.8	10 3	11 2.9-43
>2 000 hrs	8 12	1.9 0.7-4.7	25 30	2.3 1.3-4.0	10 8	3.9 1.5-10

Notes. SEI—socioeconomic index.

6. DISCUSSION

The results in this pooled analysis were based on a fairly high number of long-term users of mobile

and cordless phones. Cases were ascertained from the Swedish Cancer Registry that has a good coverage of all new cases. Controls were enrolled from the Swedish Population Registry that covers

the whole population. Thus, no selection bias was introduced in the enrolment of cases and controls in the various studies. Regarding brain tumours assessment of exposure was made about 2 months after histopathological diagnosis. One advantage was that the cases were informed about their diagnoses and that they could answer the questionnaires and phone interviews at home in a more relaxed setting than in a hospital.

A high response rate was obtained for both cases and controls. All assessment of exposures and coding of the data were made without knowing if it was a case or a control, thereby avoiding observation bias. In the statistical analysis adjustment was made for potential confounding factors such as age, gender, year of diagnosis of the case and corresponding year for the matched control, and SEI. Since the prevalence of the use of mobile and cordless phones increases over the years it was of importance to adjust for year of diagnosis. The incidence of meningioma is higher in women than in men, thus adjustment for gender was necessary.

The main result was an increased risk for acoustic neuroma and high-grade astrocytoma (grade III–IV). Especially for high-grade astrocytoma the risk increased both with latency and the number of hours of use of the studied phone types, and the results seem to be of biological relevance. Odds ratio per years of use and latency was rather similar indicating that most subjects use a phone continuously over the years, merely changing the type of the phone. Obviously the use of analogue phones has declined over the years, whereas the use of digital phones has increased in the Swedish population.

Acoustic neuroma might be a “signal” tumour type for increased brain tumour risk from microwave exposure, since it is located in an anatomical area with high exposure during calls with mobile or cordless phones. In fact, an increasing incidence of acoustic neuroma has been noted in Sweden [9]. The risk increased significantly by 5% (95% CI = 2–9%) for acoustic neuroma per 100 hrs of analogue phones. The risk increased also significantly, 12% (95% CI = 6–17%) per years of use of

analogue phones, and similar results were obtained per years of latency period. However, for digital mobile phones or cordless phones the risk did not increase significantly per 100 hrs of use, years of use or latency period. Regarding the three categories of latency time that we analysed we found no clear trend. Increased odds ratio was also found in the shortest latency group, >1–5 years. This might indicate an effect in the late stage of carcinogenesis by microwaves from analogue phones. However, as we have discussed elsewhere [11], longer latency period has been found in other studies on the use of mobile phones and the risk for acoustic neuroma. Clearly further studies are necessary on brain tumours and the use of wireless communication.

Regarding meningioma and astrocytoma grade I–II (low-grade) no clear association was found. However, for astrocytoma grade III–IV (high-grade) the risk increased significantly per 100 hrs of use of all phone types, and also per years of use; 10% (95% CI = 6–14%) for analogue phones, 11% (95% CI = 6–16%) for digital phones and 8% (95% CI = 5–12%) for cordless phones. Thus, these results were similar regardless of the type of phone. As presented elsewhere [8] both analogue and digital mobile telephones were statistically significant risk factors for astrocytoma grade III–IV in the multivariate analysis.

It should be noted that the highest risk for malignant brain tumours was calculated in the >10-year latency group and >2000 hrs of cumulative use (Table 4). Obviously our results indicate a longer latency period for malignant brain tumours than for acoustic neuroma. It may depend on an effect by microwaves in different stages of carcinogenesis for these tumour types. It is certainly noteworthy and worrying that a very high risk was calculated for malignant brain tumours for use of analogue phones in the >10-year latency group and >2 000 hrs of cumulative use, OR = 9.6, 95% CI = 3.5–27. High odds ratios were also calculated for digital mobile phones and cordless phones.

Recall bias might be a problem in assessment of exposure in case–control studies. Our results with increasing risk with latency period and the time

of cumulative use, especially for astrocytoma grade III–IV, indicate that the findings are not explained by recall bias, but are of biological relevance. Furthermore, different results were found for different tumour types, which would not be expected if recall bias existed.

However, in studies of tumour risk and mobile phone use exposure assessment is a greater problem than for the acute effects since for this type of disease it is the exposure 5–10 years or more ago that is of interest. Most users of mobile phones have not been using just one single telephone. It is even more likely that if they have been using a mobile phone for more than a few years, they will also have changed their phone a few times. Many users will also have been using different phone systems such as analogue and digital, and probably many of them have also been using a cordless phone at home or at work. The problem we are facing is then how to integrate the various specific absorption rate (SAR) distributions from the different devices and add up the different times on these phones to one exposure measure? At the moment it is not clear how to combine the use of different phones with different power output, different systems, different frequencies and different anatomical SAR distribution, into one exposure and dose measure. The difficulties lie in the fact that we do not know the interacting mechanism(s) between the electromagnetic fields emitted from the phone and the biological organism.

7. CONCLUSION

In our series of studies on tumour risk associated with the use of mobile or cordless telephones the consistent finding for all studied phone types was an increased risk for brain tumours, mainly acoustic neuroma and malignant brain tumours. Using a latency period of >10 years odds ratios increased especially for astrocytoma grade III–IV. Our studies were among the first to indicate an association between the use of mobile phones and cordless phones and brain tumours. These results seem to have been corroborated in later studies from other research groups. In a recent review of currently published studies on this

topic, one cohort study and 13 case–control studies, we concluded that the use of mobile phones for ≥ 10 years gives a consistent pattern of an increased risk for acoustic neuroma and glioma, most pronounced for high-grade glioma. The risk is highest for ipsilateral exposure [11].

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Thermal and non-thermal health effects of low intensity non-ionizing radiation: An international perspective[☆]

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ABSTRACT

Exposure to low frequency and radiofrequency electromagnetic fields at low intensities poses a significant health hazard that has not been adequately addressed by national and international organizations such as the World Health Organization. There is strong evidence that excessive exposure to mobile phone-frequencies over long periods of time increases the risk of brain cancer both in humans and animals. The mechanism(s) responsible include induction of reactive oxygen species, gene expression alteration and DNA damage through both epigenetic and genetic processes. *In vivo* and *in vitro* studies demonstrate adverse effects on male and female reproduction, almost certainly due to generation of reactive oxygen species. There is increasing evidence the exposures can result in neurobehavioral decrements and that some individuals develop a syndrome of “electro-hypersensitivity” or “microwave illness”, which is one of several syndromes commonly categorized as “idiopathic environmental intolerance”. While the symptoms are non-specific, new biochemical indicators and imaging techniques allow diagnosis that excludes the symptoms as being only psychosomatic. Unfortunately standards set by most national and international bodies are not protective of human health. This is a particular concern in children, given the rapid expansion of use of wireless technologies, the greater susceptibility of the developing nervous system, the hyperconductivity of their brain tissue, the greater penetration of radiofrequency radiation relative to head size and their potential for a longer lifetime exposure.

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1. Introduction

Electromagnetic fields (EMFs) are packets of energy that have no mass. They vary in frequency and wavelength. At the high end of the electromagnetic spectrum there are cosmic and X-rays that have enough energy to cause ionization, and therefore are known

as ionizing EMFs. Below in frequency and energy are ultraviolet, visible light and infrared EMFs. Excessive exposure to ultraviolet EMFs poses clear danger to human health, but life on earth would not be possible without visible light and infrared EMFs. Below these forms of EMF are those used for communications (radiofrequency or RF-EMFs, 30 kHz–300 GHz) and those generated by electricity (extremely low-frequency or ELF-EMFs, 3 Hz–3 kHz). These EMFs do not have sufficient energy to directly cause ionization, and are therefore known as non-ionizing radiation. RF-EMFs at sufficient intensity cause tissue heating, which is the basis of operation of the microwave oven. However the question to be addressed here is human health effects secondary to exposures to non-ionizing EMFs at low intensities that do not cause measureable heating.

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In spite of a large body of evidence for human health hazards from non-ionizing EMFs at intensities that do not cause measurable tissue heating, summarized in an encyclopedic fashion in the Bioinitiative Report (www.bioinitiative.org), the World Health Organization (WHO) and governmental agencies in many countries have not taken steps to warn of the health hazards resulting from exposures to EMFs at low, non-thermal intensities, nor have they set exposure standards that are adequately health protective. In 2001 the International Agency for Research on Cancer (IARC, 2002), part of the WHO, declared ELF-EMFs to be “possibly carcinogenic to humans”, and in 2011 they made a similar declaration for RF-EMFs (Baan et al., 2011; IARC, 2013). The classification of RF-EMFs as a “possible” human carcinogen was based primarily on evidence that long-term users of mobile phones held to the head resulted in an elevated risk of developing brain cancer. One major reason that the rating was not at “probable” or “known” was the lack of clear evidence from animal studies for exposure leading to cancer. The US National Toxicology Program has released preliminary results of a study of long term exposure of rats to cell phone radiation which resulted in a statistically significant increase in brain gliomas, the same cancer found in people after long-term cell phone use, and schwannomas, a tumor similar to the acoustic neuroma also seen after intensive mobile phone use (Wyde et al., 2016). Similar results in rats have been reported in an independent study at the Ramazzini Institute with exposures similar to those from a mobile phone base station (Falcioni et al., 2018). This evidence, in conjunction with the human studies, demonstrates conclusively that excessive exposure to RF-EMF results in an increased risk of cancer. In light of this new evidence for cancer in rodents in response to prolonged exposure to mobile phone frequencies, the IARC rating should be raised at least to “probable” (Group 2A) if not “known” (Group 1).

Unfortunately the International EMF Project of the WHO, which is part of the Department of Public Health, Environment and Social Determinants of Health in Geneva, has consistently minimized health concerns from non-ionizing EMFs at intensities that do not cause tissue heating (WHO, 2014). In this regard WHO has failed to provide an accurate and human health-protective analysis of the dangers posed to health, especially to the health of children, resulting from exposure to non-thermal levels of electromagnetic fields. The Department of Public Health, Environment and Social Determinates of Disease takes its advice on the issues related to human health effects of non-ionizing EMFs from the International Commission on Non-ionizing Radiation Protection (ICNIRP). Almost all members of the core group preparing the new Environmental Health Criteria (EHC) document for the WHO are members of ICNIRP (Starkey, 2016; Hardell, 2017), a non-government organization (NGO) whose members are appointed by other members. In spite of recent efforts to control for conflicts of interest, ICNIRP has a long record of close associations with industry (Maisch, 2006). When queried as to why the WHO would take recommendations from such a group, WHO staff replied that ICNIRP is an official NGO which works closely with the WHO. Why this should exclude other scientific research groups and public health professionals is unclear, particularly since most members of ICNIRP are not active researchers in this field. We are particularly concerned that a new WHO EHC document on RF-EMFs is scheduled to be released soon, and that the members of the EHC Core Group and the individuals whose assistance has been acknowledged are known to be in denial of serious non-thermal effects of RF-EMFs in spite of overwhelming scientific evidence to the contrary (Starkey, 2016; Hardell, 2017).

Others have dismissed the strong evidence for harm from ELF- and RF-EMFs by arguing that we do not know the mechanism whereby such low energetic EMFs might cause cancer and other diseases. We have definitive evidence that use of a mobile phone

results in changes in brain metabolism (Volkow et al., 2011). We know that low-intensity ELF- and RF-EMFs generate reactive oxygen species (ROS), alter calcium metabolism and change gene expression through epigenetic mechanisms, any of which may result in development of cancer and/or other diseases or physiological changes (see www.bioinitiative.org for many references). We do not know the mechanisms behind many known human carcinogens, dioxins and arsenic being two examples. Given the strength of the evidence for harm to humans it is imperative to reduce human exposure to EMFs. This is the essence of the “precautionary principle”.

There are a number of reasons for our concern. In the past the major exposure of the general population to RF-EMFs came from radio and television signals. Now there are almost as many mobile phones as there are people in the world, all of them being exposed to RF-EMFs. There are mobile phone towers everywhere, and in many developing countries there are no land-lines that allow communication without exposure to RF-EMFs. There is rapid movement in many developed countries to place small cell transmitting devices (5G) operating at higher frequencies (24–70 GHz) every approximately 300 m along sidewalks in residential neighborhoods. There are other significant sources of exposure, coming from WiFi, smart meters and soon from automobiles operating without a human driver. Therefore human exposure has increased dramatically in recent years, and continues to increase rapidly. While we already are seeing harm from these exposures, the degree of harm will only increase with time because of the latency that is known to occur between exposure and development of diseases such as cancer.

Standards for protection of human health from EMFs vary greatly around the world. Many countries set standards based on the false assumption that there are no adverse health effects of RF-EMFs other than those that are caused by tissue heating. This is the case in North America, Australia and some European countries. Many countries from the former Soviet Union have much more restrictive standards. However information from cellular and human studies show biological effects that constitute hazards to human health at exposure levels that are often exceeded during daily life.

This report follows a recent non-official meeting in Geneva with WHO representatives, where the authors urged WHO to acknowledge low intensity effects of ELF-EMFs and non-thermal health effects of RF-EMFs. This report does not attempt to present a complete overview of the subject [see the Bioinitiative Report (www.bioinitiative.org) for that] but rather to provide a holistic picture of the processes explaining most or all of the adverse effects of EMF exposures. It summarizes the evidence for cancer resulting from exposure to EMFs, and identifies other diseases or pathological conditions such as Alzheimer's disease and hypofertility that have been shown to be associated with excessive exposure to low-intensity EMFs. We also focus on electrohypersensitivity (EHS) in both children and adults and cognitive and behavioural problems in children resulting from the increasing exposure. Finally we discuss what is known about the mechanisms whereby non-thermal EMF radiation can cause disease with special reference to EMF-related free radical production and epigenetic and genetic mechanisms.

2. Mobile phone use and the risk for glioma, meningioma and acoustic neuroma

The brain is the main target for exposure to RF-EMF radiation during use of handheld wireless phones, both mobile and cordless phones (Cardis et al., 2008; Gandhi et al., 2012). An increased risk for brain tumors has been of concern for a long time. The results of the Swedish National Inpatient Register have documented an

increasing incidence of brain tumors in recent years (Carlberg and Hardell, 2017). In May 2011 RF radiation in the frequency range 30 kHz–300 GHz was evaluated to be a Group 2B, i.e. a “possible” human carcinogen, by IARC (Baan et al., 2011; IARC, 2013). This was based on an increased risk for glioma and acoustic neuroma in human epidemiological studies. In the following an updated summary is given of case-control studies on brain and head tumors; glioma, meningioma and acoustic neuroma. The Danish cohort study on ‘mobile phone users’ (Johansen et al., 2001; Schüz et al., 2006) is not included due to serious methodological shortcomings in the study design, including misclassification of exposure (see Söderqvist et al., 2012a).

2.1. Glioma

Glioma is the most common malignant brain tumor and represents about 60% of all central nervous system (CNS) tumors. Most of these are astrocytic tumors that can be divided into low-grade (WHO grades I-II) and high-grade (WHO grades III-IV). The most common glioma type is glioblastoma multiforme (WHO grade IV) with peak incidence in the age group 45–75 years and median survival less than one year (Ohgaki and Kleihues, 2005). Three research groups have provided results in case-control studies on glioma (Interphone, 2010; Coureau et al., 2014; Hardell and Carlberg, 2015). Hardell and colleagues have published results from case-control studies on use of wireless phones and brain tumor risk since the end of the 1990s (Hardell et al., 1990; for more discussion see Carlberg and Hardell, 2017).

A random effects model was used for meta-analyses of published studies, based on test for heterogeneity in the overall group (“all mobile”). Note that only the Hardell group also assessed use of cordless phones. Thus their reference category included cases and controls with no use of wireless phones in contrast to the other studies investigating only mobile phone use. In Table 1 results for highest cumulative use in hours of mobile phones is given. All studies reported statistically significant increased risk for glioma and the meta-analysis yielded an odds ratio (OR) = 1.90 [95% confidence interval (CI) = 1.31–2.76]. For ipsilateral mobile phone use the risk increased further to OR = 2.54 (95% CI = 1.83–3.52) in the meta-analysis based on 247 exposed cases and 202 controls.

Carlberg and Hardell (2014) found shorter survival in patients with glioblastoma multiforme associated with use of wireless phones compared with patients with no use. Interestingly mutation of the p53 gene involved in disease progression has been reported in glioblastoma multiforme in patients with mobile phone use ≥ 3 h per day. The mutation was statistically significantly correlated with shorter overall survival time (Akhavan-Sigari et al., 2014). Further support for the increased risk of glioma associated with mobile phone use has been obtained in additional analyses of parts of the Interphone study (Cardis et al., 2011; Grell et al., 2016; Momoli

et al., 2017).

2.2. Meningioma

Meningioma is an encapsulated, well-demarcated and rarely malignant tumor. It is the most common benign tumor and accounts for about 30% of intracranial neoplasms. It develops from the pia and arachnoid membranes that cover the CNS. It is slowly growing and gives neurological symptoms by compression of adjacent structures. The most common symptoms are headaches and seizures. The incidence is about two times higher in women than in men. Meningioma develops mostly among middle aged and older persons (Cea-Soriano et al., 2012). Carlberg and Hardell (2015) included meningioma in their case-control studies. The results of the meta-analysis for cumulative exposure in the highest category are given in Table 2. In total there was an increased (but not statistically significant) risk for cumulative exposure but the increased risk was statistically significant for ipsilateral use of mobile phones (OR = 1.49, 95% CI = 1.08–2.06).

2.3. Acoustic neuroma

Acoustic neuroma, also called vestibular schwannoma, is a benign tumor located on the eighth cranial nerve from the inner ear to the brain. It is usually encapsulated and grows in relation to the auditory and vestibular portions of the nerve. It grows slowly and due to the narrow anatomical space may give compression of vital brain stem structures. First symptoms of acoustic neuroma are usually tinnitus and hearing problems. Results for use of mobile phones in Interphone (2011) and Hardell et al. (2013) are given in Table 3. Statistically significant increased risk was found for cumulative ipsilateral use ≥ 1640 h yielding OR = 2.71 (95% CI = 1.72–4.28).

The study by Moon et al. (2014) was not included in the meta-analysis because data on cumulative mobile phone use with numbers of cases and controls were not given. Support of an increased risk was seen in the case-case part of the study (Moon et al., 2014) and also in the report by Sato et al. (2011). Pettersson et al. (2014) made a case-control study on acoustic neuroma in Sweden not overlapping the Hardell et al. (2013) study. An increased risk for the highest category of cumulative use of both mobile phone (≥ 680 h OR = 1.46, 95% CI = 0.98–2.17) and cordless phone (≥ 900 h OR = 1.67, 95% CI = 1.13–2.49) was found. Pettersson et al. (2014) was not included in the meta-analysis due to the many scientific shortcomings in the study, e.g. laterality analysis was not made for cordless phone, the numbers in the laterality analysis for mobile phone are not consistent in text and tables and the ‘unexposed’ reference category included subjects using either mobile and cordless phone, which is clearly not correct (Hardell and Carlberg, 2014).

Table 1

Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95% confidence interval (CI) for glioma in case-control studies in the highest category of cumulative hours of mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone 2010						
Cumulative use ≥ 1640 h	210/154	1.40	1.03–1.89	100/62	1.96	1.22–3.16
Coureau et al., 2014						
Cumulative use ≥ 896 h	24/22	2.89	1.41–5.93	9/7	2.11	0.73–6.08
Carlberg and Hardell, 2015						
Cumulative use ≥ 1640 h	211/301	2.13	1.61–2.82	138/133	3.11	2.18–4.44
Meta-analysis						
Longest cumulative use	445/477	1.90	1.31–2.76	247/202	2.54	1.83–3.52

Table 2
Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95% confidence interval (CI) for meningioma in case-control studies in the highest category of cumulative hours of mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone 2010						
Cumulative use ≥ 1640 h	130/107	1.15	0.81–1.62	46/35	1.45	0.80–2.61
Coureau et al., 2014						
Cumulative use > 896 h	13/9	2.57	1.02–6.44	6/4	2.29	0.58–8.97
Carlberg and Hardell 2015						
Cumulative use ≥ 1640 h	141/301	1.24	0.93–1.66	67/133	1.46	0.98–2.17
Meta-analysis						
Longest cumulative use	284/417	1.27	0.98–1.66	119/172	1.49	1.08–2.06

Table 3
Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95% confidence interval (CI) for acoustic neuroma in case-control studies in the highest category of cumulative hours of mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone 2011						
Cumulative use ≥ 1640 h	77/107	1.32	0.88–1.97	47/46	2.33	1.23–4.40
Hardell et al., 2013						
Cumulative use ≥ 1640 h	27/301	2.40	1.39–4.16	19/133	3.18	1.65–6.12
Meta-analysis						
Cumulative use ≥ 1640 h	104/408	1.73	0.96–3.09	66/179	2.71	1.72–4.28

2.4. In summary

Based on case-control studies there was a consistent finding of increased risk for glioma and acoustic neuroma associated with use of mobile phones. Similar results were found for cordless phones in the Hardell group studies, although such use was not reported by the other study groups. The findings are less consistent for meningioma although somewhat increased risk was seen in the meta-analysis of ipsilateral mobile phone use. A longer follow-up time is necessary for this type of slow growing tumor.

The results on glioma and acoustic neuroma are supported by results from animal studies showing co-carcinogenic and tumor promoting effects from RF-EMF ([Tillmann et al., 2010](#); [Lerchl et al., 2015](#)). Recent results from the National Toxicology Program (NTP) study showed genotoxicity of RF radiation in rats and mice exposed to RF-EMF ([Smith-Roe et al., 2017](#)). That result supports previous findings of DNA strand breaks in rat brain cells exposed to RF-EMF ([Lai and Singh, 1997](#)).

Of importance also is that the results in the NTP and Ramazzini studies both demonstrated an increased incidence of tumors of the same type, glioma and malignant schwannoma, as has been seen in humans with mobile phone use ([Wyde et al., 2016](#); [Falcioni et al., 2018](#)). Acoustic neuroma (vestibular schwannoma) is a similar type of tumor as malignant schwannoma, although benign. In fact, rates of brain tumors are increasing in Sweden and use of wireless phones has been suggested to be the cause ([Hardell and Carlberg, 2017](#)).

3. Other diseases and pathological conditions attributed to exposure to low-intensity EMFs

The evidence for harm from RF-EMF is strongest for cancer as a consequence of intensive mobile phone use, especially gliomas, glioblastomas and acoustic neuromas. But there is other evidence for elevation in risk of leukemia among children living near to very high intensity radio transmission towers ([Michelozzi et al., 2002](#); [Ha et al., 2007](#)). This is particularly interesting because leukemia is the cancer most associated with elevated exposure to ELF-EMFs

arising from power lines ([Ahlbom et al., 2000](#); [Greenland et al., 2000](#)). There is some evidence for elevations in breast cancer risk among women who wear their mobile phones in their bra ([West et al., 2013](#)). Heavy use of a mobile phone was associated with significantly elevated rates of ipsilateral parotid tumors in studies from both Israel ([Sadetzki et al., 2007](#)) and China ([Duan et al., 2011](#)). No increased risk was found in a Swedish study, but the results were limited by low number of participants and lack of data on heavy and long-term use of wireless phones ([Söderqvist et al., 2012b](#)).

There are other significant human health hazards of concern. There is strong animal and human evidence that exposure to RF-EMFs as well as ELF-EMFs reduces fertility in both males (reviewed by [McGill and Agarwal, 2014](#)) and females ([Roshangar et al., 2014](#)). An association between spontaneous abortion and non-thermal EMF exposure including ELF-EMFs was reported in several case-control studies ([Dodge, 1970](#); [Juutilainen et al., 1993](#); [Li et al., 2017](#)). The increased use of mobile phones and increased exposure coming from WiFi, smart meters and other wireless devices has been paralleled in time with male hypofertility and sperm abnormalities in semen ([Rolland et al., 2013](#)). These effects may be related to holding an active wireless laptop in a man's lap or having an active mobile phone on their belt, but more study is needed. There is evidence that isolated human sperm exposed to RF-EMFs are damaged by generation of reactive oxygen species ([Agarwal et al., 2009](#)).

There are other diseases or physiologic alterations which have been reported to be associated with exposure to non-thermal EMFs in humans and in animals ([Belyaev et al., 2016](#)). Alzheimer disease has been shown to be significantly associated with chronic ELF-EMF occupational exposure in prospective epidemiological studies ([García et al., 2008](#); [Davanipour and Sobel, 2009](#)). Exposure to RF-EMFs has been reported to increase neuropsychiatric and behavioural disorders ([Johansson et al., 2010](#); [Divan et al., 2012](#)), trigger cardiac rhythm alteration and peripheral arterial pressure instability ([Havas, 2013](#); [Saili et al., 2015](#)), induce changes in immune system function ([Lyle et al., 1983](#); [Grigoriev et al., 2010](#); [Sannino et al., 2011, 2014](#)) and alter salivary ([Augner et al., 2010](#)) and

thyroid (Koyu et al., 2005; Mortavazi et al., 2009; Pawlak et al., 2014) function. There is an urgent need for more study of these diseases or biological alterations in relation to exposure to both ELF- and RF-EMFs.

4. An emerging concern: cognitive and neurobehavioral problems in children

Children, and especially fetuses, are more vulnerable than adults for most environmental exposures (Sly and Carpenter, 2012). This is because their cells are rapidly dividing and their organ systems are not mature. As a result, events that perturb cellular function early in life can result in abnormalities that last. There is a building body of evidence indicating that exposure to RF-EMFs has adverse effects on cognition and neurobehavior, especially in children and adolescents. Concern about the particular sensitivity of children to RF-EMFs emitted from mobile phone was first raised in 2000 by a British independent expert group (IEG, 2000) that noted that the increased sensitivity to EMFs of children could be due not only to the natural vulnerability of the developing nervous system, but also to the smaller head size and thickness of the skull. These factors, plus the higher conductivity of the young nervous system, result in greater penetration of RF-EMFs into the brain (Gandhi et al., 1996). Of concern is the fact that any adverse effects during development may have life-long consequences and that young people, because they will have a longer life span, will receive a greater cumulative exposure than adults (Kheifets et al., 2005; Hansson Mild et al., 2006).

There are several reasons to be concerned. Animal studies have shown that *in utero* RF-EMF exposure from mobile phones affects fetal programming and leads to alteration in neurodevelopment and behavior of offspring (Aldad et al., 2012; Zhang et al., 2015). Exposure of young rats to non-thermal intensities impairs learning and spatial memory secondary to a deleterious impact of EMFs on hippocampal, pyramidal or cortical neurons. Similar detrimental cognitive and behavioural defects were also observed in adult animals exposed to low-intensity.

EMFs (Bas et al., 2009; Deshmukh et al., 2015; Kumari et al., 2017; Shahin et al., 2017). The exposure induces markers of oxidative stress and inflammation in the brain (Dasdag et al., 2012; Megha et al., 2015).

There are human data consistent with these animal studies. Divan et al. (2008) reported that prenatal and to a lesser degree postnatal exposure to cell phones is associated with emotional and hyperactivity problems in 7-year old children. This finding was confirmed in a second replicative study involving different participants (Divan et al., 2012). Birks et al. (2017) used data from studies in five cohorts from five different countries (83,884 children) and concluded that maternal mobile phone use during pregnancy increased the risk that the child will show hyperactivity and inattention problems. A meta-analysis involving 125,198 children (mean age 14.5 years) reported statistically significant associations between access to and use of portable screen-based media devices (e.g. mobile phones and tablets) and inadequate sleep quality and quantity and excessive daytime sleepiness (Carter et al., 2016). Early life exposure to lead has long been known to cause a reduction in cognitive function and shortened attention span (Needleman et al., 1979). Two studies have shown that prenatal (Choi et al., 2017) or postnatal (Byun et al., 2017) mobile phone exposure results in greater neurobehavioral effects in children with elevated lead levels than those seen with elevated lead alone. These results raise concern that EMFs may have synergistic actions with other environmental contaminants known to cause a reduction in intelligence quotient (IQ) and attention, such as polychlorinated biphenyls, methyl mercury, environmental tobacco smoke and probably others (Carpenter, 2006).

Finally the problem should be considered at the societal, worldwide level. Many adolescents (Lenhart, 2015) and even very young children and infants (Kabali et al., 2015) use cordless devices immoderately, to such a point that the common intensive use of devices in children and adolescents has been ascribed as an addiction (Paz de la Puente and Balmori, 2007; Roberts et al., 2014).

The specific absorption rate (SAR)-based ICNIRP safety limits were established on the basis of simulation of EMF energy absorption using standardized adult male phantoms, and designed to protect people only from the thermal effects of EMFs. These assumptions are not valid for two reasons. Not only do they fail to consider the specific morphological and bioclinical vulnerabilities of children, but also they ignore the effects known to occur at non-thermal intensities. The same criticisms apply to other so called “independent” advisory groups or agencies, such as the Advisory Group of Non-Ionizing Radiation in the UK (AGNIR, 2012), the French Agency for Food, Environmental and Occupational Health & Safety in France (ANSES, 2013), and the Scientific Committee on Emerging Newly Identified Health Risk (SCENIHR, 2009), all of whom deny the detrimental health effects of low intensity, non thermal EMF exposure and make recommendations based only on thermal SAR considerations.

Although several scientific authorities, such as the US American Academy of Pediatrics (AAP, 2013), and the Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP, 2011) have made specific recommendations to not allow the use of mobile phones by children and to limit their use by adolescents, unfortunately these age categories remain a target for marketing of mobile phone devices [<http://www.who.int/peh-emf/project/mapnatreps/RUSSIA%20report%202008.pdf>]. The RNCNIRP has warned that if no rational, health-based safety limits are adopted for children and adolescents and no measures are taken to limit the use of cordless devices, we can expect disruption of memory, decreases in learning and cognitive capabilities, increases in irritability, sleep disturbance, and loss of stress adaptation in this population. There will also be long-term effects, including an increase in brain cancer, infertility, EHS, Alzheimer disease and other neurodegenerative diseases (RNCNIRP, 2011; Markov and Grigoriev, 2015). National and international bodies, particularly the WHO, will bear major responsibility for failing to provide specific science-based guidance and recommendations so as to avoid such global health threats.

5. Electrohypersensitivity, microwave illness or idiopathic environmental intolerance attributed to electromagnetic fields

There is a segment of the human population that is unusually intolerant to EMFs. The term “electromagnetic hypersensitivity” or “electrohypersensitivity (EHS)” to describe the clinical conditions in these patients was first used in a report prepared by a European group of experts for the European Commission (Bergqvist et al., 1997). Santini et al. (2001, 2003) reported similar symptoms occurring in users of digital cellular phones and among people living near mobile phone base stations.

In 2004, because of the seemingly increasing worldwide prevalence, WHO organized an international scientific workshop in Prague in order to define and characterize EHS. Although not acknowledging EHS as being caused by EMF exposure, the Prague working group report clearly defined EHS as “a phenomenon where individuals experience adverse health effects while using or being in the vicinity of devices emanating electric, magnetic or electromagnetic fields” (www.who.int/pehemf/EHS_Proceedings_June2006.pdf). Following this meeting, WHO acknowledged EHS as an adverse health condition (WHO, 2005).

According to the Prague Workshop recommendations, it was proposed to use the term “idiopathic environmental intolerance (IEI) attributed to electromagnetic fields” (IEI-EMF) because of the lack of a proven causal link with EMF exposure (Hansson Mild et al., 2006). This pathological disorder is identical to what has been previously described under the term “microwave illness” (Carpenter, 2015).

This syndrome is characterized by fatigue, chronic pain and impaired cognitive function (see the Paris appeal, <http://appel-de-paris.com/?lang=en>). The precise mechanism(s) whereby environmental exposure to either ELF- or RF-EMFs can cause the development of this syndrome are still uncertain. However several lines of experimental and clinical data are sufficiently strong so as to indicate that ELF-EMFs and RF-EMFs exposure is associated with adverse biological and clinical health effects in humans as well as animals (Rea et al., 1991; McCarty et al., 2011; Belpomme et al., 2015; Hedendahl et al., 2015; Irigaray et al., 2018a). The prevalence of EHS has been estimated to range 1–10% in developed countries (Hallberg and Oberfeld, 2006) but appears today to be around 3% (Huang et al., 2018).

Since WHO official reports on mobile phone exposure and public health (WHO, 2014) and more particularly on EHS (WHO, 2005), much clinical and biological progress has been made to identify and objectively characterize EHS, as was summarized during the international scientific consensus meeting of the 5th Paris Appeal Congress that took place in May 2015 in Brussels at the Royal Belgium Academy of Medicine (ISD, 2015). EHS has many characteristics in common with other IEI pathological disorders, including chronic fatigue syndrome, fibromyalgia, Gulf War Illness and especially the syndrome of multiple chemical sensitivity (MCS), which Belpomme et al. (2015) have shown to be associated with EHS in many patients who report being electrohypersensitive.

5.1. Bioclinical identification and characterisation of electrohypersensitivity

In a prospective study involving systematic face-to-face questionnaire-based interviews and clinical physical examinations of nearly two thousand patients who self-reported having EHS or EHS and MCS, Belpomme and colleagues reported that EHS is a well-defined clinico-biological entity, characterized by the progressive occurrence of neurologic symptoms, including headache, tinnitus, hyperacusis, superficial and/or deep sensibility abnormalities, fibromyalgia, vegetative nerve dysfunction and reduced cognitive capability. These symptoms are repeatedly reported by the patients to occur each time they are exposed to EMFs, even of weak intensity. They result in chronic insomnia, fatigue, emotional lability and depressive tendency (Belpomme et al., 2015; Irigaray et al., 2018b).

Table 4 presents the detailed symptomatic picture which was obtained during face-to-face interviews with subjects with EHS in comparison to those with both EHS and MCS and to a series of apparently healthy control subjects that showed no evidence of EHS and/or MCS. As shown in the Table, the symptoms reported are consistent with those in other published questionnaire-based studies of EHS patients (Dodge, 1970; Johansson et al., 2010; Nordin et al., 2014; Medeiros and Sanchez, 2016; Rööslä, 2008). The clinical symptoms observed in EHS or EHS/MCS patients are statistically significantly much more frequent than those in apparently normal controls. Although many of these symptoms are non-specific, the general clinical picture resulting from their association and frequency strongly suggests that EHS can be recognized and identified as a specific neurological disorder.

Because of the multiple and relatively common symptoms and the lack of recognized objective diagnosis criteria, studies on EHS

were left with only the patient's self-reported interpretation for many years. As a result, EHS has unfortunately been considered to be a psychiatric disease of unknown origin. This helps explain why most mainstream public health and societal bodies claim there is not sufficient data proving that the clinical symptoms experienced and reported by EHS patients are caused by EMF exposure. Therefore they refuse to acknowledge EHS as a true neuropathological disorder. This negative point of view was supported by some blind or double blind studies showing that most individuals who report they suffer from EHS were not able to identify when they were exposed to either EMFs or sham controls (Rubin et al., 2011; Eltiti et al., 2015). However other studies have found that EHS subjects can identify EMF exposure in a statistically significant manner when they are blinded to whether or not the exposure was on (Rea et al., 1991; McCarty et al., 2011).

To account for these seemingly negative results a nocebo effect was suggested (ANSES, 2017). However there is presently no consensus on a biological mechanism through which a nocebo effect could occur (Medeiros and Sanchez, 2016; Chrousos and Gold, 1992; Jakovljevic, 2014). Moreover, results obtained in a carefully designed psycho-clinical study in self-reporting EHS patients are not consistent with an initial nocebo response to perceived EMF exposure, even though it is plausible that after the onset of the disease such phenomena may intervene secondarily through an acquired learning and conditioning process (Dieudonné, 2016). In addition, a meta-analysis of cross sectional studies has documented a 38% greater risk of development of headaches among mobile phone users than non-users, and an increasing risk of headache with longer daily call duration (Wang et al., 2017).

Belpomme, Irigaray and colleagues recently identified several biomarkers in EHS and/or MCS patients which allow physicians to identify and objectively characterize EHS as a true somatic pathological disorder, discounting the hypothesis of a causal psychosomatic or nocebo-related process. These came in part from a prospective clinical and biological analysis of a series of several hundred consecutive cases of individuals who self-reported that they suffered from EHS or both EHS and MCS (Belpomme et al., 2015) and more recently from the prospective analysis of an additional series of EHS patients (Irigaray et al., 2018a). Table 5 summarizes the different biomarkers that have been measured in the peripheral blood of these patients and the results which have been obtained based on the EHS and EHS/MCS patient groups. Note that among the different markers, the 6-hydroxymelatonin sulfate/creatinine ratio in urine appears to be the best marker to be used in medical practice since it has been found to be decreased in all cases evaluated to date (Belpomme et al., 2015).

By measuring different major oxidative stress-related biomarkers, such as thiobarbituric acid reactive substances (TBARS), oxidized glutathione (GSSG) and nitrotyrosine (NTT) in EHS patients, Irigaray et al. (2018b) have recently shown that near 80% of the EHS patients present with detectable oxidative stress biomarkers (Fig. 1). More than 40% of EHS patients present with at least one positive biomarker, 20% with two and 15% will all three of the biomarkers investigated. This indicates that in addition to the inflammation-related biomarkers previously associated with EHS, EHS patients are also characterized by exhibiting biomarkers of oxidative stress (Belpomme et al., 2015; Irigaray et al., 2018a,b).

The significance of the different biomarkers measured in the peripheral blood of EHS and EHS/MCS patients is that these results imply that these patients present with some degree of oxidative/nitrosative stress, inflammation and autoimmune response. Increased levels of several of these markers (notably protein S100B and NTT) may reflect hypoxia-associated oxidative stress-induced blood brain barrier (BBB) opening. It has been previously hypothesized that opening of the BBB can be caused by environmental

Table 4Clinical symptom occurrence in EHS and EHS/MCS patients in comparison with normal controls^a.

	EHS	EHS/MCS	p ^b	Normal controls	p ^c	p ^d
Headache	88%	96%	0.065	0%	<0.0001	<0.0001
Dysesthesia	82%	96%	0.002	0%	<0.0001	<0.0001
Myalgia	48%	76%	<0.0001	6%	<0.0001	<0.0001
Arthralgia	30%	56%	<0.001	18%	0.067	<0.0001
Ear heat/otalgia	70%	90%	<0.001	0%	<0.0001	<0.0001
Tinnitus	60%	88%	<0.0001	6%	<0.0001	<0.0001
Hyperacusis	40%	52%	0.118	6%	<0.0001	<0.0001
Dizziness	70%	68%	0.878	0%	<0.0001	<0.0001
Balance disorder	42%	52%	0.202	0%	<0.0001	<0.0001
Concentration/Attention deficiency	76%	88%	0.041	0%	<0.0001	<0.0001
Loss of immediate memory	70%	84%	0.028	6%	<0.0001	<0.0001
Confusion	8%	20%	0.023	0%	0.007	<0.0001
Fatigue	88%	94%	0.216	12%	<0.0001	<0.0001
Insomnia	74%	92%	0.001	6%	<0.0001	<0.0001
Depression tendency	60%	76%	0.022	0%	<0.0001	<0.0001
Suicidal ideation	20%	40%	0.003	0%	<0.0001	<0.0001
Transitory cardiovascular abnormalities	50%	56%	0.479	0%	<0.0001	<0.0001
Occular deficiency	48%	56%	0.322	0%	<0.0001	<0.0001
Anxiety/Panic	38%	28%	0.176	0%	<0.0001	<0.0001
Emotivity	20%	20%	1	12%	0.176	0.176
Irritability	24%	24%	1	6%	<0.001	<0.001
Skin lesions	16%	45%	<0.0001	0%	<0.0001	<0.0001
Global body dysthermia	14%	8%	0.258	0%	<0.0001	<0.007

^a This data results from the clinical analysis of the 100 first clinically evaluated cases issued from the already published series of EHS and/or MCS patients who have been investigated for biological markers [Belpomme et al., 2015]. It has been compared symptomatically with data obtained from a series of 50 apparently normal subjects matched for age and sex, used as controls.

^b Significance levels (p values) obtained for comparison between the EHS and EHS/MCS groups.

^c Significance levels (p values) obtained for comparison between the EHS and normal control groups.

^d Significance levels (p values) obtained for comparison between the EHS/MCS and normal control groups.

Table 5

Patient mean values and standard deviations of biomarker levels in comparison with normal reference values as well as the percentage of patients with abnormal values in the peripheral blood in subjects with EHS or both EHS and MCS (Belpomme et al., 2015).

Biomarker and Normal reference values	Patients groups			
	EHS Mean \pm SD % Above normal		EHS/MCS Mean \pm SD % Above Normal ^a	
hs-CRP < 3 mg/l	10.3 \pm 1.9	15%	6.9 \pm 1.7	14.3%
Vitamine D > 30 ng/ml	20.6 \pm 0.5	69.3%	14.5 \pm 1.3	70.1%
Histamine < 10 nmol/l	13.6 \pm 0.2	37%	13.6 \pm 0.4	41.5%
IgE < 100 UI/ml	329.5 \pm 43.9	22%	385 \pm 70	24.7%
S100B < 0.105 μ g/l	0.20 \pm 0.03	14.7%	0.17 \pm 0.03	19.7%
Hsp 70 < 5 ng/ml	8.2 \pm 0.2	18.7%	8 \pm 0.3	25.4%
Hsp 27 < 5 ng/ml	7.3 \pm 0.2	25.8%	7.2 \pm 0.3	31.8%
Anti-O-myelin auto-antibodies ^b	Positive	22.9%	Positive	23.6%
24-h urine 6-OHMS/creatinine ratio >0.8 ^c	0.042 \pm 0.003	100%	0.048 \pm 0.006	100%

hs-CRP, high-sensitivity C-reactive protein; IgE, Immunoglobulin E; S100B, S 100 calcium binding protein B; Hsp 27, heat shock protein 27; Hsp 70, heat shock protein 70; anti-O-myelin auto-antibodies, auto-antibodies against O-myelin; 6-OHMS, 6-hydroxymelatonin sulfate.

^a There is no statistically significant difference between the two groups of patients for the different biomarkers analyzed, suggesting that EHS and MCS share a common pathological mechanism for genesis.

^b Qualitative test.

^c Data restricted to those not on neuroleptic medication as the simultaneous use of several psychotherapeutic drugs may also be associated with a decrease of this 24-h urine ratio by modifying melatonin metabolism.

stressors, be they chemicals or EMFs. This may have occurred in these patients, as has been shown to occur in several (but not all) animal experiments involving EMF exposure (Oscar and Hawkins, 1977; Persson et al., 1997; Eberhardt et al., 2008; Sirav and Seyhan, 2009). Comparable data using metabolic and genetic biomarkers were also obtained in another large series of EHS patients (De Luca et al., 2014). Overall these data indicate that the clinical use of biomarkers allows the objective characterisation and identification of EHS and MCS as two etiopathologic facets of a unique

pathological disorder, and also allows insight into the genesis of these two diseases.

The development of new imaging techniques has also greatly increased our ability to objectively characterize EHS and MCS. Using ultrasonic cerebral tomography (UCTS) (Parini et al., 1984), EHS- and EHS/MCS-patients were found to have a statistically significant decrease in mean pulsometric index in several middle cerebral artery-dependant portions of the temporal lobes, especially in the capsulo-thalamic area, which is part of the limbic

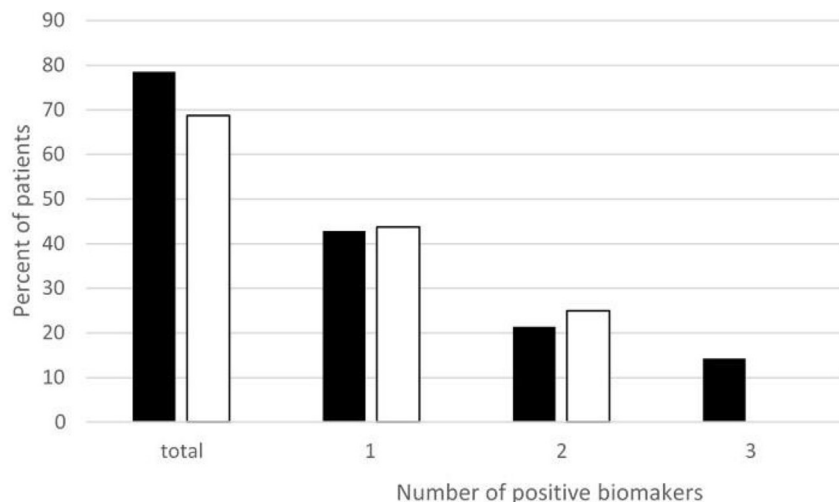


Fig. 1. Percentage of EHS self-reporting patients having positive TBARS, GSSG and/or NTT oxidative stress biomarkers measured in the peripheral blood. “Positive” biomarkers correspond to marker levels above the upper normal limit; “total” corresponds to the patients with one or more positive biomarker levels. Black bars show the percentage of patients with one, two or all three of the biomarkers for TBARS, GSSG and NTT. The white bars show the percentage of patients with either TBARS or GSSG or both oxidative stress markers.

system and the thalamus. This suggests that EHS and EHS/MCS may be associated with a brain blood flow (BBF) deficiency and/or neuronal dysfunction in these brain structures (Belpomme et al., 2015; Irigaray et al., 2018a,b). Irigaray et al. (2018c) have recently confirmed that UCTS is the best imaging technique to diagnose EHS and to follow patients treated for EHS and/or MCS.

In addition, using positron emission tomography (PET) it has been shown that short term exposure to pulse-modulated RF-EMF causally affects regional BBF in normal subjects using a mobile phone (Aalto et al., 2006; Huber et al., 2005), a finding that may account for the modifications observed in the sleep and waking EEG (Huber et al., 2002). By use of functional MRI (fMRI) in EHS patients exposed chronically to ELF-EMFs, regional BBF changes have been reported in the frontal lobes, such as abnormal default mode network and more particularly a decrease in BBF and cerebral metabolism. These observations indicate that fMRI may also be a tool for diagnosis of EHS and clinical follow up of patients (Heuser and Heuser, 2017). A decreased BBF-associated pulso-metric index decrease in both hemispheres was also recently observed by the Belpomme group by using transcranial Doppler ultrasound (TDU) (Purlaustja and Sorond, 2012) applied to the middle cerebral artery in a study involving 120 EHS and/or MCS patients. This study revealed a decrease in pulsatility index and an increase in diastolic flow velocity in 70% of the 120 cases investigated to date.

In summary it is the strong opinion of the authors that there is presently sufficient clinical, biological and radiological data emanating from different independent international scientific research groups for EHS, whatever its causal origin, to be acknowledged as a well-defined, objectively characterized pathological disorder. As a result, patients who self-report that they suffer from EHS should be diagnosed and treated utilizing presently available objective biological tests, among which are the concentration of peripheral blood biomarkers and the use of imaging techniques such as PET, fMRI and TDU and, when available, UCTS. Whatever its etiological origin and mechanism of action, EHS should be acknowledged by the WHO as a real and distinct neurological and pathological disorder (McCarty et al., 2011; Hedendahl et al., 2015) and thus be included in the International Classification of Diseases.

5.2. Possible etiopathogenic processes involved in genesis of electro-hypersensitivity

EMFs, both RF-EMFs at non-thermal intensities and ELF-EMFs, have been found to cause persistent adverse biological effects in microorganisms (Fojt et al., 2004), plants (Roux et al., 2008; Maffei, 2014), birds (Balmori, 2005; Balmori and Hallberg, 2007; Frey, 1993), and mammals. Therefore the effects observed in humans cannot be due to only a placebo or psychosomatic effect. These biological effects may be due both to the pulsed and polarised characteristics of man-made EMFs emitted by electric or wireless technologies as opposed to the terrestrial non-polarised and continuously emitted natural EMFs (Blackman, 2009; Belyaev, 2015; Panagopoulos et al., 2015).

The inflammatory and oxidative/nitrosative states that have been documented in EHS patients are remarkable since they confirm the data obtained experimentally in animals exposed to non-thermal EMFs (Esmekaya et al., 2011; Burlaka et al., 2013), and especially in the brain (Megha et al., 2015; Kesari et al., 2011). The limbic system-associated capsulo-thalamic abnormalities that the Belpomme group has observed by using UCTS in EHS and/or MCS patients (Belpomme et al., 2015; Irigaray et al., 2018a,c) may likely correspond to the hippocampal neuronal alterations caused by EMF exposure in the rats (Bas et al., 2009; Furtado-Filho et al., 2015; Deshmukh et al., 2013). Fig. 2 summarizes our hypothesis regarding the inflammation and oxidative stress-related mechanisms which may account for EMF- and/or chemically-related health effects in the brain and consequently for EHS genesis.

6. Mechanisms whereby low intensity electromagnetic fields cause biological effects and harm

Arguments used in the past to attempt to discount the evidence showing deleterious health effects of ELF-EMFs and RF-EMF exposure at non-thermal SAR levels were based on the difficulties encountered in understanding the underlying biological effects and the lack of recognized basic molecular mechanisms accounting for these effects. This is no longer the case. There are a number of well-documented effects of low intensity EMFs that are the mechanistic basis behind the biological effects documented above (www.who.int).

bioinitiative.org). These include induction of oxidative stress, DNA damage, epigenetic changes, altered gene expression and induction including inhibition of DNA repair and changes in intracellular calcium metabolism. Both low-intensity ELF-EMF and non-thermal RF-EMF effects depend on a number of physical parameters and biological variables and physical parameters, which account for the variation in health outcomes (Belyaev, 2015; Belyaev et al., 1999). Importantly, the most severe health effects are observed with prolonged chronic exposures even when intensities are very low (Belyaev, 2017). The physics of non-equilibrium and non-linear systems and quantum mechanics are at least in part the basis of the physical mechanisms responsible for the non-thermal molecular and biological effects of non-thermal EMF radiation (Belyaev, 2015), although a detailed report on these actions is beyond the scope of this review.

Lower RF-EMF intensity is not necessarily less bioactive or less harmful. Non-thermal EMF effects can be observed at intensities which are very close to ordinary background levels and quite similar to intensities emitted by mobile phone base stations. There are time windows for observation of non-thermal EMF effects which may be dependent upon the endpoint measured, the cell type and the duration and power density of exposure. Non-thermal RF-EMF effects are affected by static magnetic fields and electromagnetic stray fields, which result in the variation of non-thermal EMF effects from mobile phones because of adjacent electrical appliances, power lines and other sources of ELF and static magnetic fields, including changes in the geomagnetic field (Gapeev et al., 1999a and b).

Cell-to-cell interactions potentiate the response to non-thermal EMFs (Belyaev et al., 1996). Biological responses to EMFs have been shown to be influenced by sex and age (Zhang et al., 2015; Sirav and Seyhan, 2016). Physiological parameters such as the stage of cell growth, oxygen, divalent ions and temperature are important

variables affecting cellular responses to EMFs (Liburdy and Vanek, 1987; Sannino et al., 2011).

6.1. Combined exposures

EMFs at non-thermal intensities may interfere with other environmental stressors, showing an interplay of molecular pathways and resulting in either beneficial or detrimental health effects, depending on the nature and conditions of co-exposures (Novoselova et al., 2017; Ji et al., 2016). One example is the demonstration that RF-EMF exposure modulates the DNA damage and repair induced by ionizing radiation (Belyaev et al., 1993). Another example is the synergistic of exposure to lead and EMFs on cognitive function in children described above (Choi et al., 2017; Byun et al., 2017). These co-exposure factors should be considered when assessment of detrimental effects, including carcinogenicity, is performed.

Not all of the effects of EMFs on the nervous system and other organs are necessarily harmful. The best example of a positive effect is the well-documented and clinically useful benefit of applied magnetic fields to promote bone healing (Bassett, 1994). Both ELF-EMF (Zhang et al., 2015) and RF-EMF (Arendash et al., 2010) have been reported to slow cognitive decline in rodent models of Alzheimer's disease. Some human studies report a facilitating effects of cognitive performance (Lee et al., 2001) while Koivisto et al. (2000) reported an increase in response time and vigilance tasks but a decrease in mental arithmetic tasks. These studies clearly show that EMFs have biological effects at non-thermal intensities, but suggest that not all biological effects are necessarily harmful.

6.2. Duration of exposure and dose intensity

Such parameters as power density, dose, and duration of exposure have been analyzed for development of reliable safety standards, which would protect against the detrimental health effects of chronic exposure to RF-EMFs at non-thermal intensities. Some studies show no effect under fixed short-term exposures, but this does not imply that there are no effects from longer-term exposures (Choi et al., 2014). Exposure in studies showing RF-EMF effects was on average twice the duration as those with no significant effects (Cucurachi et al., 2013). The response to non-thermal EMFs depends on both power density and duration of exposure. Importantly, the same response is observed with lower power density but prolonged exposure as at higher power density and shorter exposure (Nordenson et al., 1994). While SAR is a good surrogate for thermal RF effects from acute exposures, many studies have shown that SAR should be either replaced by "dose-specific absorption" or power density complimented by duration of exposure for description of non-thermal RF effects (Belyaev, 2015). Recent studies have provided more evidence for the greater importance of dose and duration of exposure than SAR alone for biological and health effects from long-term exposures to non-thermal RF-EMFs (Furtado-Filho et al., 2015).

6.3. Oxidative stress

Non-ionizing radiation does not have sufficient energy to directly break chemical bonds, and therefore the DNA damage that occurs with non-ionizing EMF exposures is primarily a consequence of generation of reactive oxygen species (ROS), resulting in oxidative stress. There are numerous animal experiments which clearly demonstrate that non thermal EMFs can cause oxidative stress (Esmekaya et al., 2011; Burlaka et al., 2013), particularly in the brain (Shahin et al., 2017; Dasdag et al., 2012; Megha et al., 2015; Furtado-Filho et al., 2015). Oxidative stress is known to

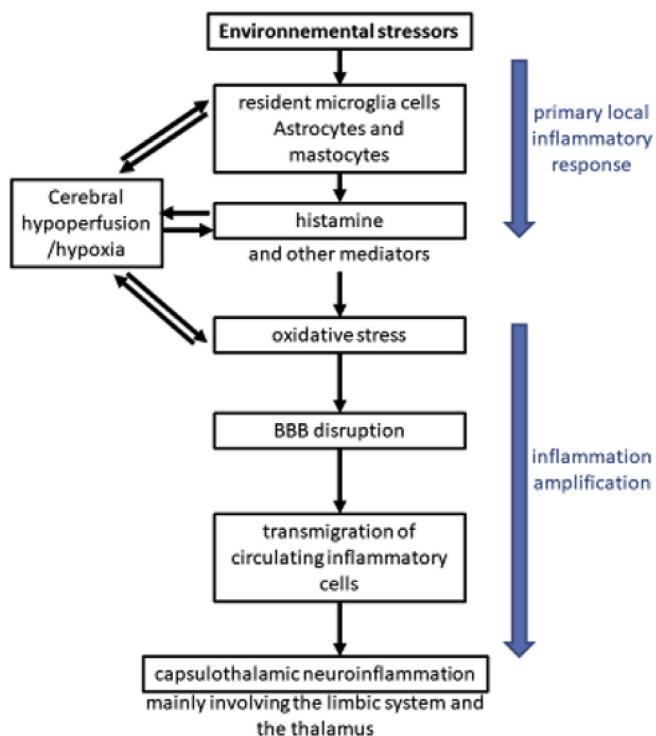


Fig. 2. Hypothetical EHS/MCS common etiopathogenic model based on neuro-inflammation and oxidative/nitrosative stress-induced blood brain barrier disruption (Belpomme et al., 2015).

play a central role in development of cancer and aging and serves as a signaling agent in the inflammatory response (Holmstrom and Finkel, 2014).

The brain is a particularly important organ for sensitivity to EMFs. Brain cancer resulting from EMF exposures is a serious concern, and EHS is a disease of the central nervous system. Several mechanisms at the cellular and molecular levels have been reported that may be the basis of these non-thermal RF-EMF effects on brain function. ELF- and/or RF-EMF exposure at embryonic or early postnatal stages can alter *in vivo* synaptic efficacy and plasticity of neurons (Balassa et al., 2014), a finding which was further supported by *in vitro* studies showing a significant decrease in the differentiation of neural stem cells into neurons (Eghlidospour et al., 2017), the alteration of transcript levels of neuronal differentiation-related genes and impairment of neurite outgrowth of embryonic neural stem cells exposed to ELF- or RF-EMFs (Ma et al., 2014). These observations support the conclusion that low-intensity but prolonged exposure to non-thermal EMFs may have adverse effects on neurogenesis during development and indicate how important it is to protect the fetus and young child from excessive exposure to all mobile devices.

Animal studies have documented that 900 MHz or 2.45 GHz non-thermal RF-EMF exposure in rats, either short term or chronic, can trigger neuronal dysfunction and even apoptosis of hippocampal pyramidal cells (Bas et al., 2009; Shahin et al., 2017) and cerebellum Purkinje cells (Sonmez et al., 2010) through induction of oxidative stress. Exposure of pregnant dams elicited EMF oxidative stress-induced neuronal pathologic changes in offspring (Odaci et al., 2016). Such pathological changes could be due to ROS-induced opening of the BBB (Nordal and Wong, 2005) and/or to ROS-associated brain hypoxia caused by a decrease in EMF-induced BBF and/or EMF-induced hemoglobin deoxygenation (Mousavy et al., 2009; Muehsam et al., 2013). The resulting hypoxia may induce metabolic neuronal dysfunction as in the case of EHS patients (Belpomme et al., 2015) but also neuronal cell death by either apoptosis or necrosis as in the case of Alzheimer's disease and other forms of dementia (Bell and Zlokovic, 2009).

While some consider the laboratory data on EMFs as being inconsistent, showing either detrimental or no effects and on occasion even beneficial effects, the vast majority still show detrimental effects. For example Henry Lai in the Bioinitiative Report Research Summaries Update of November 2017, Chapter 6 on Genotoxic Effects, reported that i) of 46 studies on ELF genotoxicity with the comet assay as the end point, 34 studies (74%) showed detrimental effects, ii). Of 189 total studies on ELF and oxidative stress, 162 (87%) showed a positive correlation, and iii) of 200 studies on RF and free radicals, 180 (90%) showed detrimental effects. One reason for variability between laboratory studies is the strong dependence on low-threshold EMF effects on a number of physical and biological variables (Belyaev, 2010).

6.4. Genetic and epigenetic mechanisms

Genetic effects are the most direct cause for carcinogenicity. This is true both for genotoxic changes caused by exposure to EMFs and existing polymorphic genetic differences within a population that increase susceptibility to cancer. DNA can no longer be considered to be unaffected by environmental EMF levels, as many studies have shown that DNA can be activated and damaged by EMFs at levels that have been considered to be safe (Blank and Goodman, 1999).

The primary mechanism through which low-intensity EMFs can alter DNA is through ROS production. Lai and Singh (2004) first reported that a 2 h exposure of rats to 60 Hz EMFs at 0.1–0.5 mT resulted in DNA strand breaks in neurons, and provided evidence

that this effect was mediated by free radical formation and blocked by free radical scavengers. Vijayalaxmi and Prihoda (2009) in a meta-analysis of 87 publications found a biologically small but statistically significant difference between DNA damage in ELF-EMF-exposed somatic cells as compared to controls, and reported evidence for epigenetic changes for some outcomes. For ELF-EMFs this breakage effect was stronger when exposure was intermittent rather than continuous (Nordenson et al., 1994).

Yang et al. (2008) have reported an OR = 4.31 (95% CI = 1.54–12.08) for leukemia in children living within 100 m of a high voltage powerline if they had a certain polymorphism of a DNA repair gene.

Exposure to RF-EMFs can also induce DNA damage under specific conditions (Markova et al., 2005). Tice et al. (2002) and Vijayalaxmi et al. (2013) reported DNA damage and micronuclei formation in cultured human leukocytes and lymphocytes upon exposure to RF-EMF signals of at least 5 W/kg. Not all cell types showed similar responses. Schwartz et al. (2008) reported micronucleus changes in fibroblasts but not lymphocytes exposed to 1950 MHz EMFs. Kesari et al. (2014) also demonstrated DNA strand breaks in the brains of rats exposed for 2 h per day for 60 days to a 3G mobile phone. Changes in DNA secondary structure (Semin, 1995; Diem et al., 2005) and chromosome instability (Mashevich, 2003) have been observed upon exposure to RF-EMFs emitted by mobile phones.

Epigenetic changes, rather than genetic changes in DNA, may underlie many or even most of the biological effects of non-thermal EMFs (Sage and Burgio, 2017). Non-thermal EMFs are epigenetic stressors which can alter gene expression by acting through physical or biochemical processes and be reflected as chromatin remodeling (Belyaev et al., 1997), histone modification (Wei et al., 1990) or altered microRNA (Dasdag et al., 2015) at intensities far below those that cause measurable tissue heating.

Chromatin plays a key regulatory role in controlling gene expression and, more particularly, the access of transcription factors to DNA. It has been shown that extremely low intensity RF-EMF exposure, i.e. at intensities comparable to that of mobile phone and towers, results in changes in chromatin conformation and gene expression (Belyaev et al., 1997; Belyaev and Kravchenko, 1994; Belyaev et al., 2006; Belyaev et al., 2009). In a large number of cells and tissues, compaction of chromatin in specific loci may lead to gene silencing, loss of histone regulatory effects and DNA repair capacity (Wei et al., 1990). Belyaev and collaborators (Markova et al., 2005; Belyaev et al., 2009) have shown that exposure to RF-EMFs emitted by GSM mobile phone alters chromatin conformation in human lymphocytes and inhibits formation of p53-binding protein 1 (53BP1) and phosphorylated histone H2AX (γ -H2AX) DNA repair foci.

EMFs in both the ELF and RF ranges may epigenetically affect DNA by inducing the expression of stress response genes and consequently the synthesis of chaperone stress proteins (Blank and Goodman, 2011a and b). A specific gene sequence has been identified that acts as a sort of antenna, specifically sensitive and responsive to EMFs (Blank and Goodman, 2011b). This is a gene sequence coding for HSP70, a protein belonging to a family of conserved, ubiquitously expressed "heat shock proteins" that sense danger signals and protect cells from the most disparate stress conditions. This is an unambiguous demonstration that EMF exposure even at non-tissue heating intensities has the potential to be harmful to cells and organisms. The HSP70 promoter contains different DNA regions that are specifically sensitive to diverse stressors, thermal and non-thermal. The EMFs are specifically perceived by the sequences sensitive to non-thermal stimuli. During the process of HSP70-response induction, EMFs can activate directly the HSP70 gene promoter (Rodríguez-De la Fuente et al.,

2010) which contains a magnetic field-responsive domain (Lin et al., 1999, 2001).

EMF-related HSP70 and HSP27 stress responses have been detected in the hippocampus of rats exposed to non-thermal EMFs (Yang et al., 2012). Shahin et al. (2017) reported that mice exposed to 2G mobile phones continuously for four months showed elevated ROS, lipid peroxidation, total nitrate and nitrite concentrations and malondialdehyde levels in homogenates of different tissues, and decreased levels of several antioxidant enzymes. These observations justify the use of these markers to characterize EHS in patients who report that they are sensitive to EMFs.

The EMF effects have been suggested to be mediated by the mitogen-activated protein kinase (MAPK) cascades, which is a central signaling transduction pathway which governs all stress-related cellular processes occurring in response to extracellular stimuli (Friedman et al., 2007). It has been shown that long term exposure of cells to mobile phone frequencies or to ELF-EMFs (Goodman et al., 2009) activates the extracellular-signal regulated kinase (ERK), which is one of the four MAPK cascades so far identified.

Non-thermal RF-EMFs may also alter expression of other genes. As long ago as Byus et al., 1988 showed that 450 MHz RF increased ornithine decarboxylase activity in hepatoma cells. Markova et al. (2005) exposed human fibroblasts and mesenchymal stem cells to mobile phone RF-EMFs with analysis of tumor suppressor p53 binding protein 1. Formation of 53BP1 foci was inhibited in both cells types, but the stem cells always showed a greater response. Fragopoulou et al. (2011) exposed mice to either a typical mobile phone or a wireless DECT base station and analyzed the brain proteome. They found significant alteration in 143 specific proteins (ranging from a 0.003 fold downregulation to up to a 114-fold overexpression.) Luo et al. (2013) exposed pregnant women undergoing a first trimester abortion to a mobile phone applied to the abdomen and performed a proteomic analysis of placental villous tissue. They report 15 proteins which were significantly altered by at least 2- to 2.5-fold in exposed women as compared to control women. Twelve of these proteins were identified. Yan et al. (2008) exposed rats to mobile phones 6 h per day for 126 days, and found upregulation of specific mRNAs that regulated several proteins, including calcium ATPase, neural cell adhesion molecule, neural growth factor and vascular endothelial growth factor. EMFs at non thermal levels may not only alter the expression of many proteins but also may directly affect protein conformation (Fragopoulou et al., 2011; Bohr and Bohr, 2013; Beyer et al., 2013) and modify enzyme activity (Vojisavljevic et al., 2010), so altering the regulating capacity of the epigenome. These are epigenetic, not genetic, effects (Sage and Burgio, 2017).

Non-thermal EMF exposure can epigenetically interfere with the differentiation and proliferation programs of stem cells in fetal and adult tissues through ROS production (Wolf et al., 2007; Falone et al., 2007; Ayşe et al., 2010; Park et al., 2014). Stem cells are the most sensitive cells to EMF exposure (Eghlidospour et al., 2017; Markova et al., 2010) and this is particularly the case for neural stem cells of the hippocampus (Leone et al., 2014).

The endogenous natural ionic currents and electrical fields in the human body (Jaffe and Nuccitelli, 1977) are vulnerable to the oscillatory properties of non-thermal EMFs. These consequently may cause detrimental effect on cell differentiation and proliferation in adult tissues (Levin, 2003) in addition to the effects on cell differentiation, proliferation and migration in the fetus (Wolf et al., 2007; Ayşe et al., 2010; Leone et al., 2014). Fetal programming cannot be reduced to only genetic programs. Developmental processes are essentially epigenetic (Leone et al., 2014), and exposure to epigenetic stressors such as non-thermal EMFs are much more dangerous for the fetus than for the adults.

6.5. Calcium regulation

There has long been evidence that EMFs alter several aspects of calcium function. This is important because calcium regulates many different aspects of cell function. Bawin and Adey (1976) reported that very weak ELF-EMFs trigger efflux of calcium from isolated chick brain, although the implications of this observation were not clear. Later they reported a similar action of RF-EMFs (Adey et al., 1982). Pulsed low-frequency EMFs promote bone healing and promote calcium uptake into bone (Spadaro and Bergstrom, 2002) and osteoblasts (Zhang et al., 2010). 50 Hz EMFs increase the number of voltage-gated calcium channels in neuroendocrine cells (Grasso et al., 2004) and presynaptic nerve cell terminals (Sun et al., 2016). Wei et al. (2015) found that ELF-EMFs also altered the frequency of calcium transients in cardiomyocytes and decreased calcium concentrations in sarcoplasmic reticulum. These changes in calcium in heart muscle may be the basis for the cardiovascular effects reported in humans on exposure to EMFs (Havas, 2013). In spite of numerous studies reporting altered calcium metabolism upon exposure to both ELF- and RF-EMFs, the overall implications of these effects are still not clear. However, some have suggested (Ledoigt and Belpomme, 2013) that calcium activation of proteins could be the initial event that results in altered protein configuration, leading to generation of ROS and ultimately activating the molecular pathways to cancer.

7. Public Health Implications of Human Exposure to EMFs

The incidence of brain cancer in children and adolescents has increased between 2000 and 2010 (Ostrom et al., 2015). Gliomas are increasing in the Netherlands (Ho et al., 2014), glioblastomas are increasing in Australia (Dobes et al., 2011) and England (Philips et al., 2018) and all brain cancers are increasing in Spain (Etxeberrua et al., 2015) and Sweden (Hardell and Carlberg, 2017). The latency period between initial exposure and clinical occurrence of brain cancer is not known but is estimated to be long. While not all reports of brain cancer rates show an increase, some do. The continually increasing exposure to EMFs from all sources may contribute to these increases. The prevalence of EHS is unknown, but various reports suggest that it is between 1 and 10% of the population (Hallberg and Oberfeld, 2006; Huang et al., 2018). Male fertility has been declining (Geoffroy-Siraudin et al., 2012; Levine et al., 2017). EMFs increase the risk of each of these diseases and others. Alzheimer's disease is increasing in many countries worldwide and its association with ELF-EMF occupational exposure has been clearly demonstrated through several independent epidemiological studies (Davanipour and Sobel, 2009; Sobel et al., 1996; Qiu et al., 2004) and a meta-analysis of these studies (García et al., 2008). A recent meta-analysis (Huss et al., 2018) has reported an increased risk of amyotrophic lateral sclerosis in workers occupationally exposure to ELF-EMFs.

Safety limits for RF exposure have been based (until today) on the thermal effects of EMFs. But these standards do not protect people, particularly children, from the deleterious health effects of non-thermal EMFs (Naziroglu et al., 2013; Mahmoudabadi et al., 2015). Each of these diseases is associated with decrements in health and quality of life. Brain cancer patients often die in spite of some improvement in treatment, while EHS patients present with increased levels of distress, inability to work, and progressive social withdrawal. The ability for humans to reproduce is fundamental for the maintenance of our species.

The scientific evidence for harm from EMFs is increasingly strong. We do not advocate going back to the age before electricity or wireless communication, but we deplore the present failure of public health international bodies to recognize the scientific data

showing the adverse effects of EMFs on human health. It is encouraging that some governments are taking action. France has removed WiFi from pre-schools and ordered Wi-Fi to be shut off in elementary schools when not in use (<http://www.telegraph.co.uk/news/2017/12/11/france-ipose-total-ban-mobile-phones-schools/>). The State of California Department of Public Health has issued a warning on use of mobile phones and offered advice on how to reduce exposure (State of California, 2017). There are many steps that are neither difficult nor expensive that can be taken to use modern technology but in a manner that significantly reduces threats to human health.

It is urgent that national and international bodies, particularly the WHO, take this significant public health hazard seriously and make appropriate recommendations for protective measures to reduce exposures. This is especially urgently needed for children and adolescents. It is also important that all parts of society, especially the medical community, educators, and the general public, become informed about the hazards associated with exposure to EMFs and of the steps that can be easily taken to reduce exposure and risk of associated disease.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.envpol.2018.07.019>.

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Mobile phones, cordless phones and the risk for brain tumours

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Abstract. The Hardell-group conducted during 1997-2003 two case control studies on brain tumours including assessment of use of mobile phones and cordless phones. The questionnaire was answered by 905 (90%) cases with malignant brain tumours, 1,254 (88%) cases with benign tumours and 2,162 (89%) population-based controls. Cases were reported from the Swedish Cancer Registries. Anatomical area in the brain for the tumour was assessed and related to side of the head used for both types of wireless phones. In the current analysis we defined ipsilateral use (same side as the tumour) as $\geq 50\%$ of the use and contralateral use (opposite side) as $< 50\%$ of the calling time. We report now further results for use of mobile and cordless phones. Regarding astrocytoma we found highest risk for ipsilateral mobile phone use in the >10 year latency group, OR=3.3, 95% CI=2.0-5.4 and for cordless phone use OR=5.0, 95% CI=2.3-11. In total, the risk was highest for cases with first use <20 years age, for mobile phone OR=5.2, 95% CI=2.2-12 and for cordless phone OR=4.4, 95% CI=1.9-10. For acoustic neuroma, the highest OR was found for ipsilateral use and >10 year latency, for mobile phone OR=3.0, 95% CI=1.4-6.2 and cordless phone OR=2.3, 95% CI=0.6-8.8. Overall highest OR for mobile phone use was found in subjects with first use at age <20 years, OR=5.0, 95% CI 1.5-16 whereas no association was found for cordless phone in that group, but based on only one exposed case. The annual age-adjusted incidence of astrocytoma for the age group >19 years increased significantly by +2.16%, 95% CI +0.25 to +4.10 during 2000-2007 in Sweden in spite of seemingly underreporting of cases to the Swedish Cancer Registry. A decreasing incidence was found for acoustic neuroma during the same period. However, the medical diagnosis and treatment of this tumour type has changed during recent years and underreporting from a single center would have a large impact for such a rare tumour.

Introduction

During the last decade there was a rapid increase in the use of wireless phones and the prevalence has reached 100% in many countries. Concerns about different health risks have been raised, particularly an increased risk for brain tumours (1). The ipsilateral brain (same side as the mobile phone has predominantly been used) is most exposed, whereas the contralateral side (opposite side to the mobile phone) is much less exposed (2). It is thus of vital importance to have information on the localisation of the tumour in the brain and which side of the head that has predominantly been used during phone calls.

Studies in this area have been hampered by rather short latencies for the different types of wireless phones. In general carcinogenesis usually takes decades from first exposure to manifest cancer, although shorter latencies have been implicated for promoters and certain types of diseases, e.g. ionising radiation and leukemia (3-5). Sweden was one of the first countries in the world to adopt this new technology so studies with longer latencies are possible and health effects from the wireless technology may be especially pertinent in our country for early warnings. Analogue phones (NMT, Nordic Mobile Telephone System) were introduced on the market in the early 1980s using both 450 and 900 Megahertz (MHz) fields. NMT 450 was used in Sweden beginning in 1981 and ending in December 31, 2007, whereas NMT 900 operated from 1986 to 2000.

The market is now dominated by the digital system (GSM, Global System for Mobile Communication) that started in 1991 and uses dual band, 900 and 1,800 MHz. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900 MHz RF fields has been introduced around the world more recently, in Sweden since 2003. The desktop cordless phones (Digital Enhanced Cordless Telecommunication, cordless phone) have been used in Sweden since 1988, first analogue 800-900 MHz RF fields, but since early 1990s the digital 1,900 MHz system has been used.

Results from the Hardell-group have been published previously on the association between use of mobile or cordless phones and brain tumours. All studies were approved by the local Ethics Committee. These studies are briefly discussed in the following and additional results are presented on e.g. age-dependent brain tumour risk. The aim of this presentation is not to give a review of this area, since such publications can be found elsewhere (6,7). In addition to our studies only a few publications from the so-called Interphone group give results

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for 10-year latency (7). That group includes 13 countries and cases and controls were recruited during 1999-2004, varying for different countries. For unclear reasons the final results have not yet been published.

In 1999 we published results from our first case control study on brain tumours and use of mobile phones (8). In total 209 (90%) of the cases and 425 (91%) of the controls that fulfilled the inclusion criteria answered the mailed questionnaire. Overall we did not find an association. For ipsilateral exposure we saw a somewhat increased risk (9). These results were based on low numbers of exposed subjects and short latency periods, so no firm conclusions could be drawn. Furthermore, in this first study we did not include the use of cordless phone.

This initial study was followed by two larger studies by us on the same topic. The aim of this paper was to report results from further analyses of these large studies, as will be presented below.

The second case control study included cases diagnosed during the time period January 1, 1997 through June 30, 2000 and population-based controls. All cases were reported to a cancer registry and had histopathological verification of tumour diagnosis. The study included the use of cordless phones, as well as asking more questions on e.g. occupational exposures. Use of wireless phones was carefully assessed by a self-administered questionnaire. The information was supplemented over the phone, if necessary. The ear that had mostly been used during calls with mobile phone and/or cordless phone was assessed by separate questions; >50% of the time for one side, or equally both sides. This information was checked during the supplementary phone call. Moreover, every person that had used a mobile phone received after that a letter asking them again to specify the ear that had been used during phone calls and to what extent that side of the head was mostly used, e.g. 100, 70 and 50% etc. There was a very good agreement for the result using these three methods to assess these data.

Separately, tumour localisation was defined by using medical records, such as computer tomography (CT) and/or magnetic resonance imaging (MRI). After that use of the wireless phone was defined as ipsilateral (>50% of the time), equally ipsi/contralateral or contralateral (<50%) in relation to tumour side. The tumour type was defined by using histopathology studies. In the calculation of cumulative hours of use over the years we used information of first and last year for use (time period) and average number of minutes per day during that period. Use in a car with external antenna was disregarded as well as use of a handsfree device. We adopted a minimum latency period of one year. Hence, we could define latency period and cumulative use for the different phone types.

Only living subjects were included in our studies and this second case control study included 1,429 (88%) cases and 1,470 (91%) controls. The results regarding use of wireless phones have been published previously (10-13).

This study was followed by our third case control study on the same topic. The methods were the same as in the second study using an identical questionnaire. The study period was from July 1, 2000 until December 31, 2003. In total 729 (89%) cases and 692 (84%) controls participated, as previously published (14,15).

We made pooled analysis of the two case control studies on brain tumour cases diagnosed 1997-2003, both malignant (16) and benign (17). This was possible since the same methods were used in both studies with an identical questionnaire. For more details about the study design, see our previous publications.

Materials and methods

We have previously reported findings for different age groups at the time of diagnosis in the study with inclusion period 1997-2000 (18). Now we have re-analysed the whole study period 1997-2003, especially in regard to age at the first time for use of a wireless phone and the association with different types of brain tumours. We analysed also type of phone and laterality of tumour according to the method by Inskip *et al* (19). Furthermore, we evaluated the risk for tumour for men and women separately, anatomical localisations in the brain, latency for first use of mobile phone or cordless phone, survival and incidence of brain tumours in Sweden.

We used three age groups for first use of a wireless phone; <20 years, 20-49 years and 50-80 years. For laterality analysis of tumour in relation to phone use one group consisted of ipsilateral and varying ipsi/contralateral use (in the following called ipsilateral), the other of contralateral use. The malignant brain tumours (n=905) were divided into astrocytoma grade I-IV (n=663), oligodendroglioma (n=93), other/mixed glioma (n=78) and other types (medulloblastoma n=6, ependymoma n=19, other types n=46). The benign tumours (n=1,254) were divided into acoustic neuroma (n=243), meningioma (n=916) and other types (n=96). One case had both acoustic neuroma and meningioma and another case had both 'other type' malignant tumour and acoustic neuroma.

Statistical methods. All analyses were done using StataSE 10.1 (Stata/SE 10.1 for Windows; StataCorp., College Station, TX). Odds ratio (OR) and 95% confidence interval (CI) were calculated using unconditional logistic regression analysis. The unexposed category consisted of subjects that reported no use of mobile or cordless phones. Adjustment was made for gender, age (as a continuous variable), socio-economic index (SEI) and year of diagnosis. The same year as for the case was used for the corresponding control. Ipsilateral use of a wireless phone was defined here as $\geq 50\%$ on the tumour side. Note, that laterality of the tumour was not available for all cases, e.g., midline tumours or tumours in both hemispheres.

Results

Malignant brain tumours. For malignant brain tumours we obtained answers from 905 (90%) cases (16). For reference the whole control population of 2,162 (89%) subjects during 1997-2003 was used.

Different malignant tumour types. Regarding mobile phones OR=1.4, 95% CI=1.1-1.7 was calculated for astrocytoma grade I-IV, increasing to OR 2.0, 95% CI=1.5-2.5 for ipsilateral use, whereas no increased risk was found for contralateral use, Table I. Using >10-year latency time yielded higher ORs and

Table I. Odds ratio (OR) and 95% confidence interval (CI) for astrocytoma grade I-IV (n=663).^a

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
All			
Mobile phone, >1 year latency	346/900 1.4 1.1-1.7	229/374 2.0 1.5-2.5	98/308 1.0 0.7-1.4
>10 year latency	78/99 2.7 1.8-3.9	50/45 3.3 2.0-5.4	26/29 2.8 1.5-5.1
Cordless phone, >1 year latency	261/701 1.4 1.1-1.8	167/309 1.8 1.4-2.4	81/235 1.2 0.8-1.6
>10 year latency	28/45 2.5 1.4-4.4	19/15 5.0 2.3-11	8/20 1.4 0.6-3.5
<20, >1 year latency			
Mobile phone	15/14 5.2 2.2-12	8/5 7.8 2.2-28	2/4 2.2 0.4-13
Cordless phone	14/16 4.4 1.9-10	9/6 7.9 2.5-25	1/4 1.1 0.1-10
20-49, >1 year latency			
Mobile phone	208/555 1.5 1.1-2.0	131/221 2.1 1.5-2.9	67/198 1.2 0.8-1.8
Cordless phone	138/416 1.3 0.98-1.8	83/179 1.6 1.1-2.4	50/154 1.2 0.8-1.8
50-80, >1 year latency			
Mobile phone	123/331 1.3 0.97-1.7	90/148 1.8 1.3-2.5	29/106 0.8 0.5-1.3
Cordless phone	109/269 1.5 1.1-2.0	75/124 1.9 1.3-2.7	30/77 1.2 0.8-1.9

^aNumbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI and year of diagnosis.

regarding mobile phone use also contralateral use gave a significantly increased risk. We also analysed astrocytoma grade I-II and III-IV separately with no clear difference, although the >10 year latency group had few exposed cases in these calculations (data not shown).

For different age groups highest OR for astrocytoma was found for the subjects that had started the use of a mobile phone at age <20 years, OR=5.2, 95% CI=2.2-12, higher for ipsilateral use OR=7.8, 95% CI=2.2-28, Table I. Similar results were found for use of cordless phone. Thus, first use at age <20 years yielded OR=4.4, 95% CI=1.9-10 increasing to OR=7.9, 95% CI=2.5-25 for ipsilateral use. Lower ORs were

calculated for both mobile phones and cordless phones in the two older age groups. No significantly decreased or increased risks were found for contralateral use in the analysed age groups.

For oligodendroglioma and other/mixed glioma no significantly increased risks were found, Table II. In the group of 'other' malignant brain tumours significantly increased risk was found for mobile phone use, >10 year latency, OR=3.2, 95% CI=1.2-8.8 increasing for ipsilateral use to OR=4.1, 95% CI=1.03-16. Analysis of different entities in the group of 'other' malignant brain tumours gave significantly increased OR only for a heterogenic group of

Table II. Odds ratio (OR) and 95% confidence interval (CI) for other malignant brain tumours.^a

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
Oligodendroglioma (n=93)			
Mobile phone, >1 year latency	51/900 1.5 0.9-2.4	28/374 1.7 0.9-3.0	21/308 1.3 0.7-2.4
>10 year latency	5/99 1.6 0.5-4.8	3/45 1.6 0.4-6.1	2/29 2.1 0.4-11
Cordless phone, >1 year latency	38/701 1.4 0.8-2.5	16/309 1.1 0.5-2.1	19/235 1.7 0.9-3.2
>10 year latency	3/45 1.8 0.4-7.2	1/15 1.1 0.1-11	2/20 2.5 0.5-13
Other/mixed glioma (n=78)			
Mobile phone, >1 year latency	35/900 1.0 0.6-1.7	22/374 1.1 0.6-2.1	13/308 1.0 0.5-2.0
>10 year latency	5/99 1.8 0.6-5.3	4/45 2.7 0.8-9.2	1/29 1.1 0.1-9.5
Cordless phone, >1 year latency	26/701 1.0 0.5-1.7	17/309 1.1 0.6-2.3	9/235 0.8 0.3-1.8
>10 year latency	1/45 0.9 0.1-7.5	0/15 - -	1/20 1.4 0.1-13
Other malignant (n=71; medulloblastoma - n=6, ependymoma - n=19, other - n=46)			
Mobile phone, >1 year latency	36/900 1.2 0.7-2.1	15/374 1.3 0.6-2.8	5/308 0.4 0.1-1.3
>10 year latency	8/99 3.2 1.2-8.8	4/45 4.1 1.03-16	1/29 1.7 0.2-15
Cordless phone, >1 year latency	25/701 1.1 0.6-2.0	7/309 0.7 0.3-1.8	7/235 0.9 0.3-2.3
>10 year latency	1/45 1.1 0.1-10	0/15 - -	1/20 3.9 0.3-44

^aNumbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI and year of diagnosis.

4 cases with ipsilateral use. Due to low numbers it was not meaningful to make separate calculations for different age groups of first use of a wireless phone.

Benign brain tumours. Our other pooled analysis reported results for the benign brain tumours from the same study period 1997-2003 (17). The questionnaire was answered by 1,254 (88%) cases and the same control group as for malignant brain tumours was used, n=2,162 (89% respondents).

Acoustic neuroma. Use of mobile phones gave for acoustic neuroma OR=1.7, 95% CI 1.2-2.3, and cordless phones OR=1.5, 95% CI=1.04-2.0, Table III. These ORs increased further for ipsilateral use whereas no significantly increased ORs were found for contralateral use. Using >10 year latency period for mobile phones gave OR=2.9, 95% CI=1.6-5.5 and for cordless phones OR=1.3, 95% CI 0.4-3.8.

Regarding different age groups highest risk was found for first use of a mobile phone at age <20 years, OR=5.0, 95% CI=1.5-16, increasing to OR=6.8, 95% CI=1.4-34 for

Table III. Odds ratio (OR) and 95% confidence interval (CI) for acoustic neuroma (n=243).^a

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
All			
Mobile phone, >1 year latency	130/900 1.7 1.2-2.3	80/374 1.8 1.2-2.6	48/308 1.4 0.9-2.1
>10 year latency	20/99 2.9 1.6-5.5	13/45 3.0 1.4-6.2	6/29 2.4 0.9-6.3
Cordless phone, >1 year latency	96/701 1.5 1.04-2.0	67/309 1.7 1.2-2.5	28/235 1.1 0.7-1.7
>10 year latency	4/45 1.3 0.4-3.8	3/15 2.3 0.6-8.8	1/20 0.5 0.1-4.0
<20, >1 year latency			
Mobile phone	5/14 5.0 1.5-16	3/5 6.8 1.4-34	1/4 2.4 0.2-24
Cordless phone	1/16 0.7 0.1-5.9	1/6 1.7 0.2-16	0/4 - -
20-49, >1 year latency			
Mobile phone	86/555 2.0 1.3-2.9	59/221 2.5 1.6-3.9	26/198 1.2 0.7-2.0
Cordless phone	65/416 1.7 1.1-2.5	48/179 2.2 1.4-3.6	16/154 0.9 0.5-1.6
50-80, >1 year latency			
Mobile phone	39/331 1.4 0.9-2.2	18/148 1.1 0.6-1.9	21/106 1.8 1.1-3.2
Cordless phone	30/269 1.3 0.8-2.1	18/124 1.3 0.7-2.2	12/77 1.4 0.7-2.8

^aNumbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI and year of diagnosis.

ipsilateral use, Table III. Only one case had used cordless phone at age <20 years. In the age group 20-49 years highest OR was calculated for ipsilateral use of both mobile phone and cordless phone, whereas no significant association was found in the age group 50-80 years. Contralateral use yielded no significant associations, but for the age group 50-80 years with OR=1.8, 95% CI=1.1-3.2 for mobile phone.

Meningioma. Regarding meningioma mobile phone use gave OR=1.1, 95% CI=0.9-1.3 increasing to OR=1.3, 95% CI=1.01-1.7 for ipsilateral use, Table IV. For cordless phones OR=1.1, 95% CI=0.9-1.4 and for ipsilateral use OR=1.2, 95% CI=0.9-1.6 were calculated. Using >10 year latency period ORs increased for mobile phones to OR=1.5, 95% CI=0.98-2.4, and for cordless phones to OR=1.8, 95% CI=1.01-3.2. Ipsilateral exposure gave for mobile phones

OR=1.6, 95% CI=0.9-2.9, and for cordless phones OR=3.0, 95% CI=1.3-7.2, in the >10 year latency group.

No clear age-dependent effect was found for meningioma, Table IV. The only significant associations were found for ipsilateral use in the age group 20-49 years, for mobile phone use OR=1.6, 95% CI=1.1-2.2 and for cordless phone use OR=1.4, 95% CI=1.002-2.0.

Other benign brain tumours. Regarding other types of benign brain tumours no significant associations were found overall, Table V. In the >10 year latency group ipsilateral mobile phone use gave OR=4.7, 95% CI=1.1-21. Due to low numbers no separate calculations were made for different age groups. All of these four cases belonged to a heterogenic group of 'other' benign brain tumours.

Table IV. Odds ratio (OR) and 95% confidence interval (CI) for meningioma (n=916).^a

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
All			
Mobile phone, >1 year latency	347/900 1.1 0.9-1.3	167/374 1.3 1.01-1.7	125/308 1.1 0.8-1.4
>10 year latency	38/99 1.5 0.98-2.4	18/45 1.6 0.9-2.9	12/29 1.6 0.7-3.3
Cordless phone, >1 year latency	294/701 1.1 0.9-1.4	134/309 1.2 0.9-1.6	101/235 1.1 0.8-1.5
>10 year latency	23/45 1.8 1.01-3.2	11/15 3.0 1.3-7.2	7/20 1.1 0.5-2.9
<20, >1 year latency	5/14	2/5	1/4
Mobile phone	1.9 0.6-5.6	2.2 0.4-13	1.7 0.2-16
Cordless phone	2/16 0.5 0.1-2.2	1/6 0.6 0.1-5.8	1/4 1.0 0.1-9.5
20-49, >1 year latency	210/555	100/221	74/198
Mobile phone	1.3 0.99-1.6	1.6 1.1-2.2	1.2 0.8-1.7
Cordless phone	167/416 1.3 0.98-1.6	79/179 1.4 1.002-2.0	54/154 1.0 0.7-1.5
50-80, >1 year latency	132/331	65/148	50/106
Mobile phone	1.0 0.8-1.3	1.1 0.8-1.5	1.1 0.8-1.6
Cordless phone	125/269 1.1 0.8-1.4	54/124 1.0 0.7-1.4	46/77 1.3 0.9-2.0

^aNumbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI and year of diagnosis.

Age for use of wireless phones and latency. The median age for cases with astrocytoma was 53 years for use of both mobile phone and cordless phone with no significant difference between persons that reported ipsilateral or contralateral use. Median age was 60 years for no use of a mobile or cordless phone. There was no significant difference for latency between ipsilateral or contralateral use.

Regarding acoustic neuroma median age among mobile phone users was 51 years and for use of cordless phones 47 years. Median age was not significantly different between persons that reported ipsilateral or contralateral use. Cases with no use of wireless phones had median age 57 years. Latency period was not significantly different between ipsilateral and contralateral use.

Laterality according to Inskip. Laterality of tumour was significantly associated with self-reported laterality of use of

a mobile phone or cordless phone among cases with astrocytoma or acoustic neuroma, Table VI. Thus, the relative risk (RR) for mobile phone use was 1.7, $p < 0.001$ for astrocytoma and for acoustic neuroma $RR = 1.3$, $p = 0.01$. Cordless phone yielded for astrocytoma $RR = 1.5$, $p < 0.001$ and for acoustic neuroma $RR = 1.7$, $p < 0.001$.

Anatomical tumour localisation. Tumours of the astrocytoma type were located in the frontal lobe (n=214), parietal (n=73), temporal (n=169), occipital (n=29), multiple lobes (frontal, parietal, temporal; n=126), cerebellum (n=16) and 'other' (multiple or not defined; n=36). Clearly ipsilateral use of mobile or cordless phones was associated with an increased risk for astrocytoma in the frontal, parietal or temporal lobe (data not in Table). These results were similar, e.g., for the temporal lobe and >10 year latency for ipsilateral mobile phone use $OR = 3.0$, 95% $CI = 1.4-6.3$ and

Table V. Odds ratio (OR) and 95% confidence interval (CI) for other benign brain tumours (n=96 pituitary adenoma n=34, other n=62).^a

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
All			
Mobile phone, >1 year latency	49/900 1.5 0.9-2.5	11/374 1.4 0.5-3.8	12/308 2.1 0.8-5.3
>10 year latency	7/99 1.8 0.7-4.9	4/45 4.7 1.1-21	1/29 2.6 0.2-30
Cordless phone, >1 year latency	34/701 1.5 0.8-2.5	8/309 1.5 0.5-4.3	9/235 2.0 0.7-5.5
>10 year latency	1/45 1.3 0.1-12	1/15 9.2 0.4-197	0/20 - -

^aNumbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI and year of diagnosis.

Table VI. Analysis of laterality according to the method of Inskip *et al* (19).

Type of phone/laterality of tumour	Laterality of telephone use			Relative risk	P-value ^a
	Left	Right	Total		
Astrocytoma, grade I-IV					
Mobile phone					
-Left	100	58	158	1.7	<0.001
-Right	40	129	169		
-Total	140	187	327		
Cordless phone					
-Left	71	49	120	1.5	<0.001
-Right	32	96	128		
-Total	103	145	248		
Acoustic neuroma					
Mobile phone					
-Left	47	23	70	1.3	0.01
-Right	25	33	58		
-Total	72	56	128		
Cordless phone					
-Left	40	15	55	1.7	<0.001
-Right	13	27	40		
-Total	53	42	95		

^aFisher's exact test. Subjects with equal use of both ears were assigned to the same side of telephone use as the side of the tumour.

cordless phone use OR=5.6, 95% CI=1.9-16. No association was found for astrocytoma in the cerebellum or 'other' localisation. Regarding the occipital lobe ipsilateral use of mobile phone with latency >10 years yielded OR=4.8, 95% CI=1.1-21 (n=4 cases) whereas cordless

phone did not increase the risk. For astrocytoma in the group of tumour growth in more than one lobe mobile phone use with >10 years latency gave OR=3.0, 95% CI=1.2-7.2 (n=9 cases). No association was found for use of cordless phones in this group.

Table VII. Odds ratio (OR) and 95% confidence interval (CI) for gender-specific analysis of astrocytoma grade I-IV.^a

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
Men (n=405)			
Mobile phone, >1 year latency	255/503 1.6 1.2-2.1	168/215 2.2 1.5-3.1	74/165 1.2 0.8-1.7
>10 year latency	69/84 2.5 1.6-3.8	45/38 3.3 1.9-5.7	22/24 2.7 1.3-5.4
Cordless phone, >1 year latency	176/318 1.8 1.3-2.4	112/142 2.1 1.5-3.1	57/104 1.5 0.9-2.3
>10 year latency	19/31 2.1 1.01-4.4	13/13 4.6 1.6-13	6/12 1.4 0.4-4.1
Women (n=258)			
Mobile phone, >1 year latency	91/397 1.2 0.8-1.6	61/159 1.7 1.1-2.5	24/143 0.8 0.5-1.3
>10 year latency	9/15 3.4 1.3-8.4	5/7 3.3 0.9-11	4/5 4.1 1.01-16
Cordless phone, >1 year latency	85/383 1.1 0.8-1.5	55/167 1.5 0.97-2.2	24/131 0.8 0.5-1.4
>10 year latency	9/14 3.6 1.4-9.3	6/2 16 2.7-90	2/8 1.4 0.3-7.0

^aNumbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, SEI and year of diagnosis.

The same calculations were made for meningioma. Regarding >10 year latency and ipsilateral use of mobile phone significant association was found for meningioma in the parietal lobe, OR=3.8, 95% CI=1.2-12 (n=5 cases) and temporal lobe, OR=3.1, 95% CI=1.2-8.2 (n=7 cases). In the same group, cordless phone use significantly increased the risk for meningioma in the temporal lobe, OR=10, 95% CI=3.1-34 (n=6 cases). No significant associations were found for the other localisations.

Gender-specific analysis. We made gender-specific analyses for astrocytoma and acoustic neuroma. We found a clear association for both genders. Mobile phone use increased the risk for astrocytoma in men, OR=1.6, 95% CI=1.2-2.1 increasing further to OR=2.5, 95% CI=1.6-3.8 in the >10 year latency group. The results for women were OR=1.2, 95% CI=0.8-1.6 and OR=3.4, 95% CI=1.3-8.4, respectively, Table VII. Also use of cordless phones increased the risk.

Similar calculations for acoustic neuroma yielded a pattern of an association both for men and women, although some of the calculations were based on low numbers, Table VIII.

Attributable fraction. Attributable fraction (AF) is the proportion of cases that can be attributed to the particular exposure. This is calculated as the exposed case fraction multiplied by [(OR-1)/OR]. For astrocytoma grade I-IV use of mobile phone and/or cordless phone yielded AF=16.8% corresponding to 111 cases (95% CI=39-169 cases). AF for acoustic neuroma was calculated to 20.4%, or 50 cases (95% CI=13-77 cases).

Survival. Survival for patients with astrocytoma is age-dependent with better prognosis for younger individuals. We found differences in age for subjects that used wireless phones compared with non-users, see above. Thus, we compared survival only among cases that reported use of a wireless phone. There was no significant difference in survival between ipsilateral and contralateral use of a mobile phone (p=0.95). Median survival of astrocytoma cases with ipsilateral use of a mobile phone was 460 days and for contralateral 543 days. Similarly, no significant differences were found for astrocytoma grade I-II and astrocytoma grade III-IV in separate calculations.

The same analysis for use of cordless phone gave no significant differences in survival for patients with astrocytoma

Table VIII. Odds ratio (OR) and 95% confidence interval (CI) for gender-specific analysis of acoustic neuroma.^a

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
Men (n=105)			
Mobile phone, >1 year latency	76/503 2.3 1.4-3.8	47/215 2.4 1.3-4.2	28/165 2.1 1.1-4.0
>10 year latency	15/84 2.9 1.3-6.4	10/38 3.2 1.3-8.1	5/24 3.2 0.98-11
Cordless phone, >1 year latency	45/318 2.0 1.1-3.5	32/142 2.1 1.1-4.0	13/104 1.7 0.8-3.8
>10 year latency	1/31 0.6 0.1-5.6	1/13 1.2 0.1-12	0/12 - -
Women (n=138)			
Mobile phone, >1 year latency	54/397 1.3 0.8-1.9	33/159 1.4 0.9-2.4	20/143 1.0 0.6-1.8
>10 year latency	5/15 3.5 1.2-11	3/7 3.1 0.8-13	1/5 1.6 0.2-14
Cordless phone, >1 year latency	51/383 1.2 0.8-1.9	35/167 1.4 0.9-2.4	15/131 0.8 0.4-1.5
>10 year latency	3/14 2.2 0.6-8.5	2/2 7.5 0.97-58	1/8 1.1 0.1-9.2

^aNumbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, SEI and year of diagnosis.

reporting ipsilateral use compared with contralateral use ($p=0.87$). Median survival for ipsilateral use was 529 days and for contralateral 569 days. No significant differences were found in the groups astrocytoma grade I-II and grade III-IV.

Incidence of brain tumours. We analysed the incidence of brain tumours (ICD-7=193.0) using the Swedish Cancer Registry, available on line (<http://www.socialstyrelsen.se/Statistik/statistikdatabas/index.htm>). Results are shown for the whole time period 1970-2007 and for different decades, age adjusted to the world standard population, Table IX. During the whole period the annual age adjusted incidence increased significantly for all brain tumours with +0.28%, 95% CI=+0.04 to +0.52. After declining during 1990-1999 an increasing incidence was found during 2000-2007 (+0.56%, 95% CI=-0.99 to +2.13). The age-adjusted incidence of astrocytoma increased during 2000-2007 yearly with +1.55%, 95% CI=-0.15 to +3.27, significantly so among women. In the age group >19 years the annual change was significant for astrocytoma, +2.16%, 95% CI= +0.25 to +4.10.

The annual age-adjusted incidence of acoustic neuroma increased significantly for the time period 1970-2007 with +2.12%, 95% CI=+1.22 to +3.02. However, during 2000-2007

a significantly decreasing incidence was found, -7.10%, 95% CI=-12.4 to -1.42.

Using data published in 'Cancer Incidence in Sweden' (2000-2007), available on line, it is possible to analyse the incidence of nervous system tumours (ICD-7=193) for the time period 2000-2007 in the 6 different medical regions of Sweden reporting to the Cancer Registry, age adjusted according to the Swedish population January 1, 2000. Interestingly, a significantly increasing incidence was found in Gothenburg region ($p<0.01$) for both men and women whereas all other regions showed for both genders a declining incidence, for example the Stockholm region ($p=0.053$ for men, $p=0.27$ for women), Fig. 1. The age adjusted incidence in the Stockholm medical region was in 2007 for men 8.8 per 100,000 person years and for women 11.0. The corresponding rates in Gothenburg medical region were 19.3 for men and 18.8 for women.

Discussion

The main results in our further analyses are consistent with a finding of an increased risk for ipsilateral astrocytoma and acoustic neuroma for use of both mobile and cordless phone.

Table IX. Estimated change in incidence rate/year (%) and 95% confidence interval (CI) for all brain tumours, astrocytoma grade I-IV and acoustic neuroma in Sweden 1970-2007.^a

	Brain tumour, all		Astrocytoma grade I-IV		Acoustic neuroma	
	Change in incidence rate/year (%)	95% CI	Change in incidence rate/year (%)	95% CI	Change in incidence rate/year (%)	95% CI
Total						
1970-2007	+0.28	0.04, 0.52	+0.05	-0.20, 0.30	+2.12	1.22, 3.02
-1970-1979	-0.15	-1.48, 1.20	-0.16	-1.75, 1.46	-1.66	-9.83, 7.24
-1980-1989	+2.03	0.60, 3.47	+2.53	1.39, 3.69	+4.96	-0.34, 10.5
-1990-1999	-0.32	-1.34, 0.71	-0.33	-1.74, 1.11	+0.72	-2.08, 3.60
-2000-2007	+0.56	-0.99, 2.13	+1.55	-0.15, 3.27	-7.10	-12.4, -1.42
Men						
1970-2007	+0.13	-0.15, 0.41	+0.12	-0.18, 0.42	+2.82	1.78, 3.88
-1970-1979	-0.77	-2.47, 0.96	-1.19	-3.55, 1.23	-1.16	-12.0, 11.0
-1980-1989	+1.41	-0.46, 3.30	+1.72	-0.55, 4.04	+7.29	0.45, 14.6
-1990-1999	-0.93	-1.97, 0.12	-0.21	-1.63, 1.24	-0.29	-2.92, 2.42
-2000-2007	-0.17	-1.94, 1.63	+0.74	-1.67, 3.21	-6.97	-14.5, 1.18
Women						
1970-2007	+0.44	0.20, 0.69	-0.03	-0.35, 0.28	+1.61	0.64, 2.59
-1970-1979	+0.56	-0.86, 2.01	+1.21	-0.78, 3.24	-1.82	-10.4, 7.62
-1980-1989	+2.65	1.26, 4.05	+3.55	2.39, 4.73	+3.31	-2.23, 9.15
-1990-1999	+0.23	-1.21, 1.70	-0.51	-3.02, 2.06	+1.73	-2.63, 6.29
-2000-2007	+1.27	-0.90, 3.48	+2.67	0.69, 4.68	-7.53	-12.7, -2.10
Total, >19 years old						
1970-2007	+0.22	-0.01, 0.46	-0.01	-0.24, 0.22	+2.12	1.24, 3.00
-1970-1979	+0.15	-1.18, 1.51	-0.12	-1.62, 1.41	-1.66	-9.48, 6.83
-1980-1989	+1.54	0.13, 2.96	+2.10	0.75, 3.48	+4.86	-0.37, 10.4
-1990-1999	-0.25	-1.20, 0.71	-0.15	-1.63, 1.34	+0.66	-1.85, 3.23
-2000-2007	+1.26	-0.62, 3.18	+2.16	0.25, 4.10	-7.08	-12.5, -1.30

^aCalculations based on incidence rates age adjusted to the world standard population.

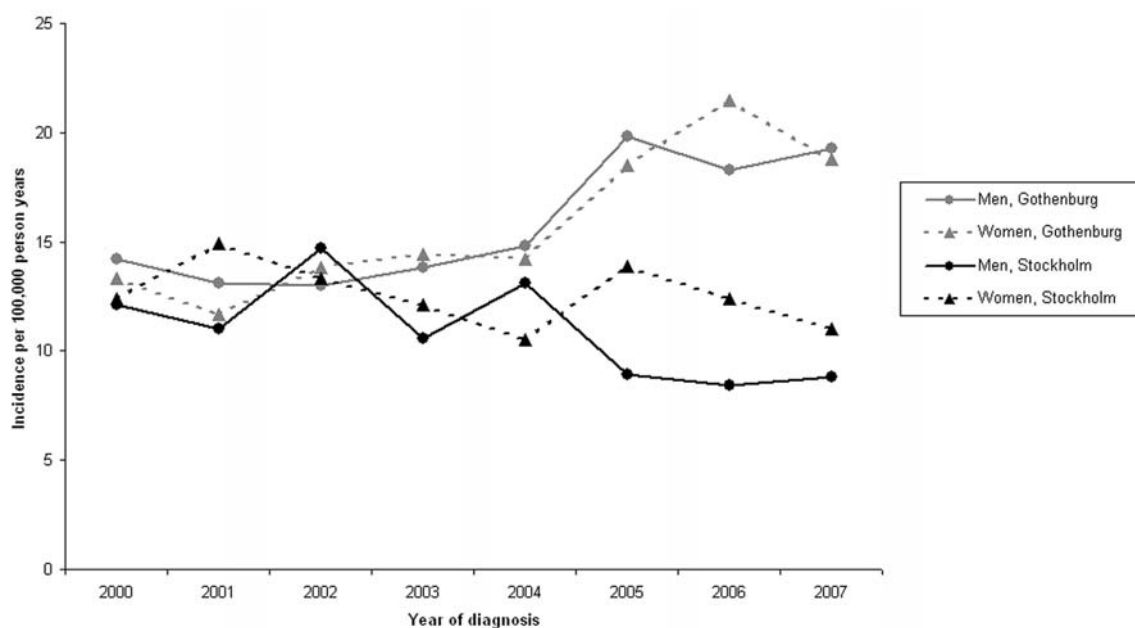


Figure 1. Incidence rates for nervous system tumours (ICD-7=193) in the Gothenburg and Stockholm medical regions, 2000-2007. Age adjusted to the Swedish population January 1, 2000.

Similar results were found when we stratified for gender. For astrocytoma we found an increased risk for tumour in the frontal, parietal or temporal lobe. The risk increased for both tumour types with time since first use and was highest in the group with >10 year latency. This is what one would expect for a carcinogenic effect from radiofrequency fields emitted from wireless phones. The brain is a near-field organ for such exposure, thus all use in a car with external antenna or a handsfree was disregarded. We included in the ipsilateral group all use $\geq 50\%$ on the tumour side of the head. This is in contrast to our previous analyses where ipsilateral was defined as >50% use and contralateral <50% (16,17). With the now used definition we could include in the calculations the subjects with varying side, that is equally both sides during phone calls, previously analyzed separately.

Especially worrying is the finding of highest risk in persons with first use at age <20 years. This was found both for astrocytoma and acoustic neuroma, except use of cordless phone for the latter tumour, however with only one exposed case. This result is of biological significance since a developing organ is more sensitive for carcinogenic agents and the brain is continuing to develop until ~20 years of age. Cases that had used wireless phones were younger than non-users. To evaluate if such microwave exposure influenced astrocytoma growth we analysed age at diagnosis and latency for ipsilateral and contralateral use, however without finding any significant differences. There was no significant difference in survival for cases with astrocytoma with ipsilateral use compared with contralateral use. Thus, these analyses did not indicate that ipsilateral wireless phone use had a major impact on tumour growth or latency compared with contralateral use, but should be interpreted with caution since also contralateral mobile phone use increased the risk in the >10 year latency group.

It is notable with regard to malignant brain tumour that increased risk was only found for astrocytoma as we have published previously. This type of tumour is a glioma and was included in our review and meta-analysis (6,7). Regarding mechanism for microwave carcinogenesis the astrocytoma finding is of interest, as discussed below.

The results were based on our two consecutive population based case control studies on incident brain tumour cases for the time period 1997-2003. Controls were drawn from the population registry. Exposure was assessed by a questionnaire that was supplemented over the phone, if necessary. In order to get good quality on the information only living cases and controls were included. Thus, deceased patients were excluded, but those with a malignant brain tumour have been included in a further case control study with also deceased controls. These results are to be published separately.

Cases were reported from the regional cancer registries in the study areas. All had histopathological verification of the diagnosis, but if it was unclear copies were obtained from the various pathology departments. Also regarding tumour localisation we received detailed information, mostly based on records from radiology departments. In some instances, e.g. side of an acoustic neuroma, this could be obtained from the report to the cancer registry, but usually radiology records were used.

The case participation was good in our studies, 88% for cases with benign brain tumours, 90% for malignant brain

tumour cases and 89% for the controls. One explanation to the high response rate might be that the two studies were hospital-based with many physicians in the research group. Also our study method with questionnaires sent home, usually for cases a couple of months after diagnosis, probably improved the response rate. Thus, cases and controls could answer the questionnaire in a relaxed situation and if necessary give additional information over the phone. Case and control status was obscured during this procedure. Our findings of different risk for different tumour types, increasing risk for latency and ipsilateral use of the wireless phone and no protective effect (decreased OR) for contralateral use strongly argue against both observational and recall bias as an explanation of the findings.

Our method has been judged to be quite superior to the methods in the Interphone studies where computer aided personal interviews were performed, even bedside for the cases (20). Obviously the many different interviewers knew if it was a case or a control that was interviewed. Case participation varied from 37 to 93% and control participation from 42 to 75% in the Interphone studies. Low participation rates for cases and controls might give selection bias and influence the results in the Interphone studies. We have discussed these and other shortcomings in the Interphone studies elsewhere (7,21).

All use of wireless phones using >1-year latency period were included in our studies. Time period for use was assessed including type of phone. Average number of minutes per day was asked for so that total number of hours over the years could be calculated. The unexposed group included subjects with no use or use of wireless phones with ≤ 1 year latency period. On the contrary, mobile phone use in the Interphone studies was defined as 'regular use' on average once per week during at least 6 months, less than that was regarded as unexposed including also all use within <1 year before diagnosis. This definition of 'regular use' seems to have been arbitrary chosen and might have created both observational and recall bias in the interpretation of such a vague definition.

Use of cordless phones was not assessed in most Interphone studies, in a couple of studies said to have been assessed but with no results clearly presented (22,23). Cordless phones have a median power in the same magnitude as GSM phones (24). They are also used for longer calls than mobile phones (16,17). Including use of cordless phones in the 'unexposed' group, as in the Interphone studies, would thus underestimate the risk and bias OR against unity.

Of interest is our consistent finding of an increased risk for astrocytoma associated with use of both mobile phones and cordless phones. Several animal studies have shown dysfunction of the blood-brain barrier (BBB) caused by radiofrequency fields (25,26). Leakage of albumin into the brain has been demonstrated. The BBB consists of endothelial cells and endfeets of astrocytes. Thus, one mechanism might be that microwaves induce BBB dysfunction so that carcinogenic substances may leak into the brain whereby especially the astrocytes might be exposed. There is some support for that mechanism in our study since we found an increased risk for astrocytoma but not consistently so for other types of malignant brain tumours. Of course also an

interaction with microwaves *per se* might exist since microwaves have been shown to induce several non-thermal effects in experimental studies, including free radicals (27).

Clearly an association between use of mobile or cordless phone and acoustic neuroma was also found. This tumour type is of interest since it is located in an anatomical area with high ipsilateral exposure. One of the first signs of an acoustic neuroma is hearing difficulties. This leads usually to a shift of the ear used during phone calls. Thus it is of importance to assess laterality of phone use for the whole time period and not only most recent use. We were careful about this point for all tumour types. Regarding meningioma there was a tendency to higher OR in the >10 year latency group. However, the results were of borderline significance. It is thus pertinent to wait for results from studies with longer latency periods.

In an editorial in the Swedish Medical Association Journal it was claimed that not much confidence can be attributed to our results of an association between mobile phones and brain tumours since the incidence has not been rising according to the Swedish Cancer Registry (28). However, the completeness of the Swedish Cancer Registry has been seriously questioned (29). Thus, in the year 1998 as many as 13.9% of nervous system tumours were reported to the Hospital Discharge Registry only, but not to the Cancer Registry. From county hospitals 121.1% were never reported and university hospitals missed to report 48.2% to the Cancer Registry. In males aged >70 years 43.9% were never reported and the corresponding frequency for females aged >70 years was 29.6%.

With such large deficits the Swedish Cancer Registry is not reliable to use to determine time trends for brain tumours. Interestingly, in spite of this deficit in the Cancer Registry we found significantly increasing incidence for brain tumours during the time period 1970-2007. We found for astrocytoma grade I-IV a sharp and significant increase of the incidence during 2000-2007 for subjects >19 years. Considering a tumour induction period of mostly at least 10 years it seems to be justified to analyse that age group and exclude the younger ones. Use of mobile and cordless phones increased rapidly from mid 1990s in Sweden, so these results strengthen our results of an association between wireless phones and brain tumours, since there is no other known risk factor for brain tumours that has been recently introduced in Sweden. It is noteworthy that we found an attributable fraction of 16.8% for astrocytoma.

Taking the still relatively short time for use of wireless phones on a broad scale (30,31) the results showing increasing brain tumour incidence may be early warning of future public health problems, especially considering the large deficit in the Swedish Cancer Registry. It is striking that during 2000-2007 the incidence of nervous system tumours increased significantly in the Gothenburg medical region, which seems to have better reporting than other medical regions in Sweden. The incidence in that region was in 2007 about two times higher than in Stockholm medical region, and there is no other explanation for that than missing data from the Stockholm region. Similar results were also found comparing Gothenburg area with the other four medical regions in Sweden. In spite of this we found significantly increasing incidence for astrocytoma during 2000-2007 in Sweden which is worrying since due to missing data the true increase would even be higher.

The annual age-adjusted incidence of acoustic neuroma increased significantly during 1970-2007, but in contrast to the finding for astrocytoma decreased significantly during 2000-2007. Today the diagnosis is usually based on CT and MRI, so surgery to determine histopathology is thus not always necessary. This is a rare tumour type and centralisation of therapy using e.g. the γ knife (32,33) may partly explain these findings especially since it seems as if some brain tumours from the Stockholm area are apparently omitted from the Cancer Registry. Another possibility is also that patients with this often slowly growing tumour may be on surveillance with MRI without active treatment and might thus not be reported to the Cancer Registry. Thus these results from analysis of incidence data are not consistent with an association between use of wireless phones and acoustic neuroma. We calculated the attributable fraction to be 20.4% in our studies. However, our results are of biological relevance and considering the large deficit in reporting of nervous system tumours to the Swedish Cancer Registry makes a comparison of incidence data with our results less reliable for such a rare tumour type.

In summary, we report a consistent association between use of mobile or cordless phones and astrocytoma grade I-IV and acoustic neuroma. The risk is highest for ipsilateral exposure to microwaves using >10 year latency period. We found an especially high risk for persons that started use of mobile or cordless phones before the age of 20 years, although based on low numbers. The results are supported by increasing incidence of astrocytoma during 2000-2007 in Sweden, significantly so for subjects >19 years old.

Acknowledgements

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Cancer - Cell Phones; Cell Phones and Risk of Brain
Tumor, Dr. Paul Dart MD. (Petitioner); 2013

Cell Phones and Risk of Brain Tumor



INTERPHONE Study 2010

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International Journal of Epidemiology 2010;39:675–694
doi:10.1093/ije/dyq079

THEME: CANCER

Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case–control study

The INTERPHONE Study Group*

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*List of members of this study group is available in the Appendix.

Accepted 8 March 2010

Background The rapid increase in mobile telephone use has generated concern about possible health risks related to radiofrequency electromagnetic fields from this technology.

Methods An interview-based case–control study with 2708 glioma and 2409 meningioma cases and matched controls was conducted in 13 countries using a common protocol.

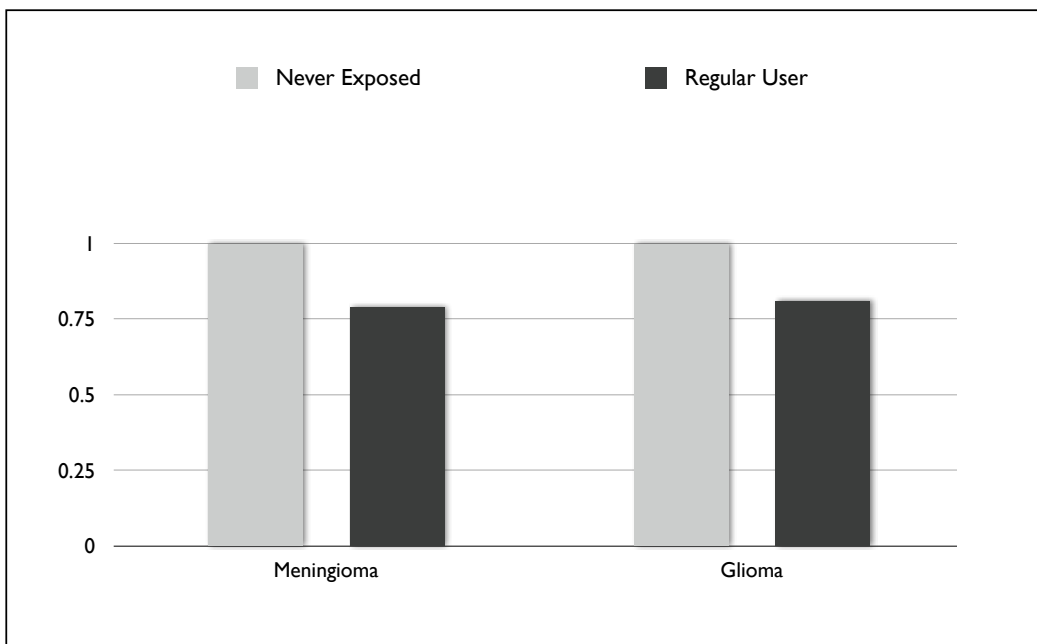
Large case–control study at multiple centers.

Funded in significant part by the telecommunications industry.

Conclusions Overall, no increase in risk of glioma or meningioma was observed with use of mobile phones.

From the authors' published conclusions.

Odds Ratio for Meningioma and Glioma



In the 2010 Interphone Study combined analysis of data for all levels of exposure found that “regular cell phone users” were less likely to have brain tumors than non-users.

This is what was reported in the media about this study.

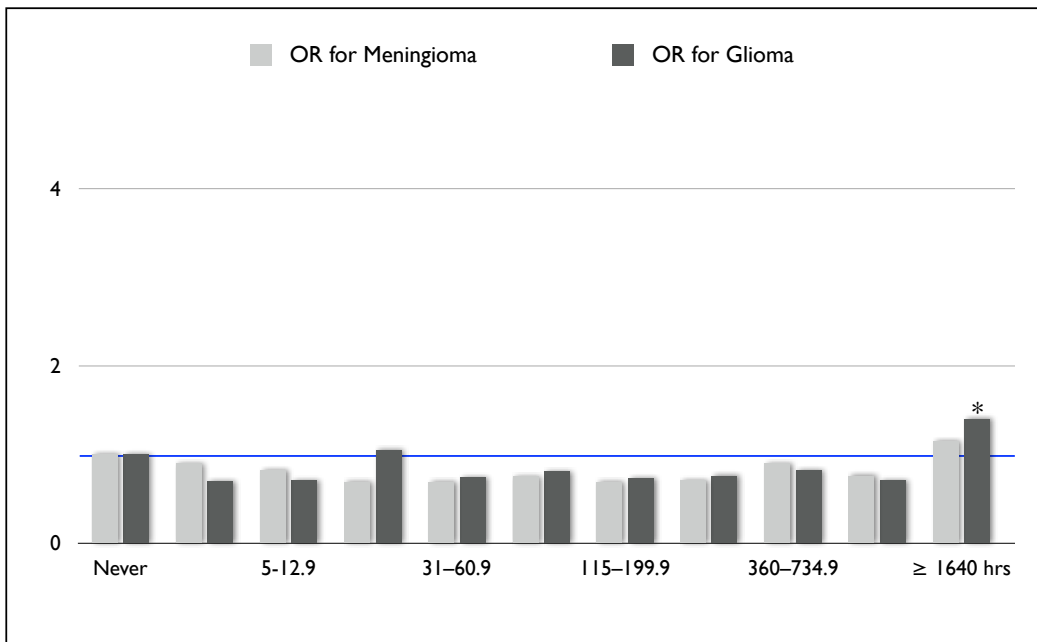
A reduced odds ratio (OR) related to ever having been a regular mobile phone user was seen for glioma [OR 0.81; 95% confidence interval (CI) 0.70–0.94] and meningioma (OR 0.79; 95% CI 0.68–0.91)

INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* (2010); 39(3):675-694.

if the subject had ever been a regular user of a mobile phone (had an average of at least one call per week for a period of ≥ 6 months).²⁶

However, “regular use” was defined as a minimum of one call for week for at least 6 months. In other words, anyone who had made at least 26 cell phone calls in their lifetime was categorized as a “regular user” and placed in the risk group.

Odds Ratio for Meningioma and Glioma with Cell Phone Use



Cumulative call time without hands-free devices, **divided into deciles.**

Blue line is Odds Ratio of 1.0 (equal to control group).

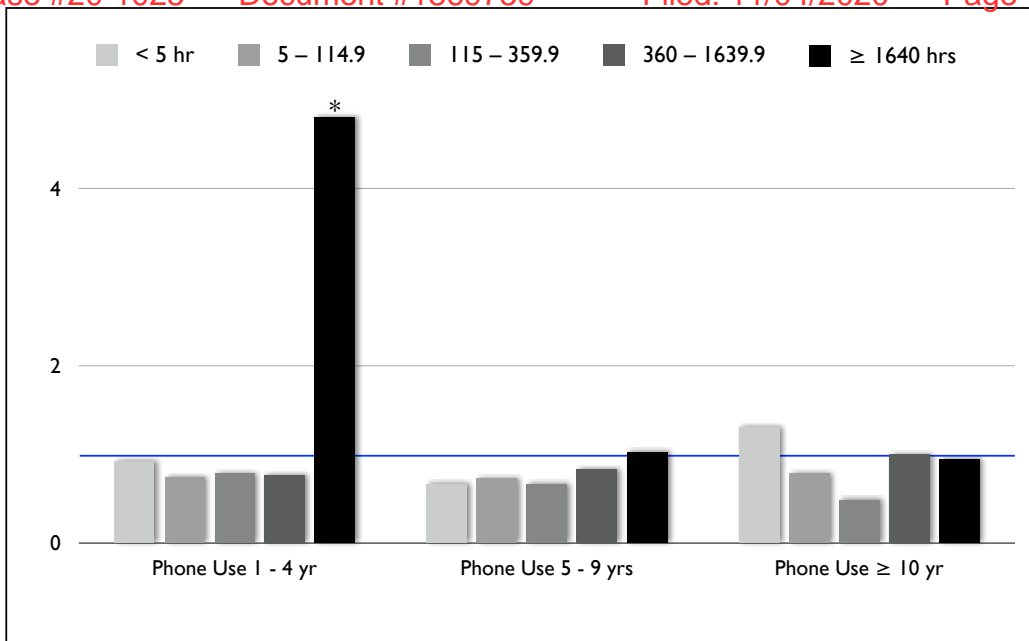
Half of the subjects in the study had less than 115 hours of lifetime exposure.

Note that a significantly higher risk for glioma was seen with more than 1640 hours of exposure.

OR for glioma = 1.40 [95% CI = (1.03–1.89)]

From Table 2: INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* (2010); 39(3):675-694.

Odds Ratio for Meningioma with Cell Phone Use



Charted data from the Interphone study for risk of meningioma.

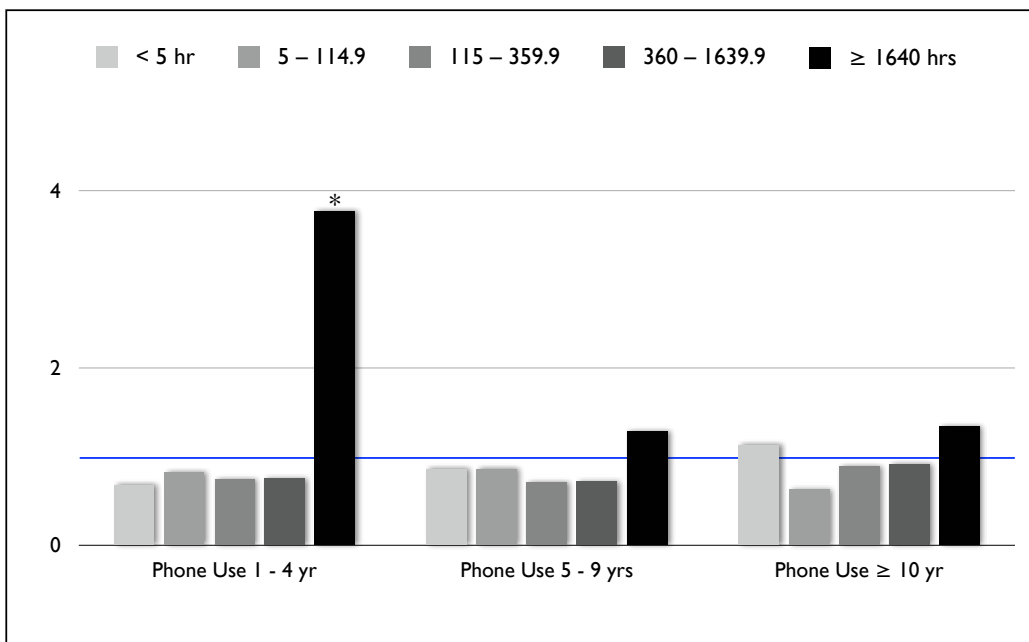
With ≥ 1640 hrs exposure in 1 - 4 years, OR = 4.80 [95% CI = (1.49-15.4)]

1640 hours in 4 years = 7.9 hrs/wk

(range in cohort was 8 - 30 hrs/wk, which the authors discounted as "implausible values of use" in their summary of results)

From Table 3: INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* (2010); 39(3):675-694.

Odds Ratio for Glioma with Cell Phone Use



Charted data from INTERPHONE study group, glioma risk.

Stratified by cumulative call time (without hands/free devices).

Also stratified by years of use.

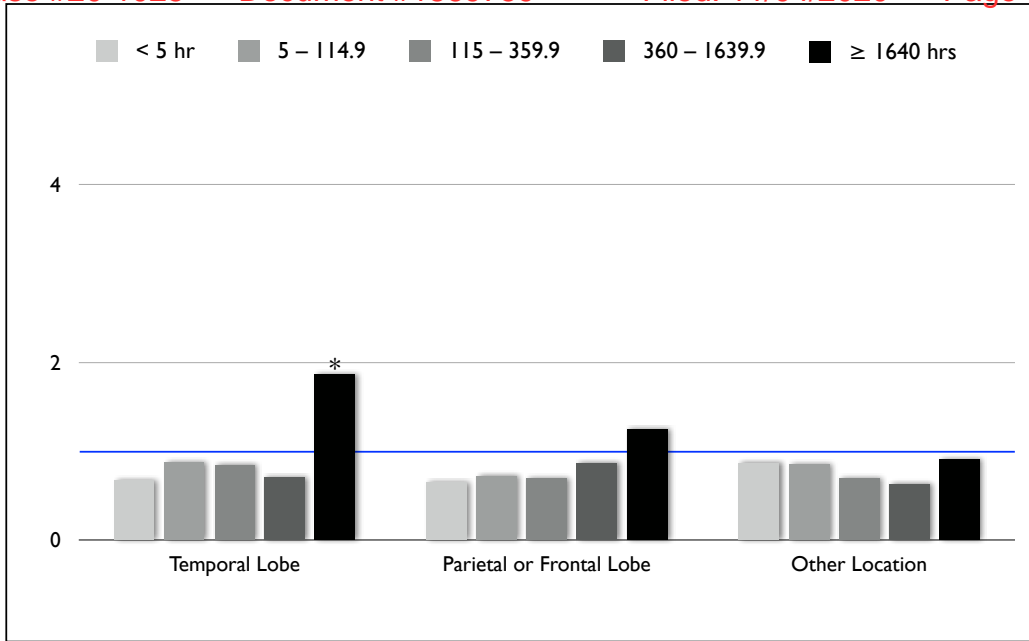
With ≥ 1640 hrs exposure in 1 - 4 years, OR for Glioma = 3.77 [95% CI = (1.25-11.4)]

1640 hours in 4 years = 7.9 hrs/wk (range in cohort was 8 - 30 hrs/wk)

The authors rejected their own findings on glioma, stating that this level of reported cell phone use was "implausible".

From Table 3: INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* (2010); 39(3):675-694.

Odds Ratio for Glioma with Cell Phone Use



Glioma risk by location in the brain.

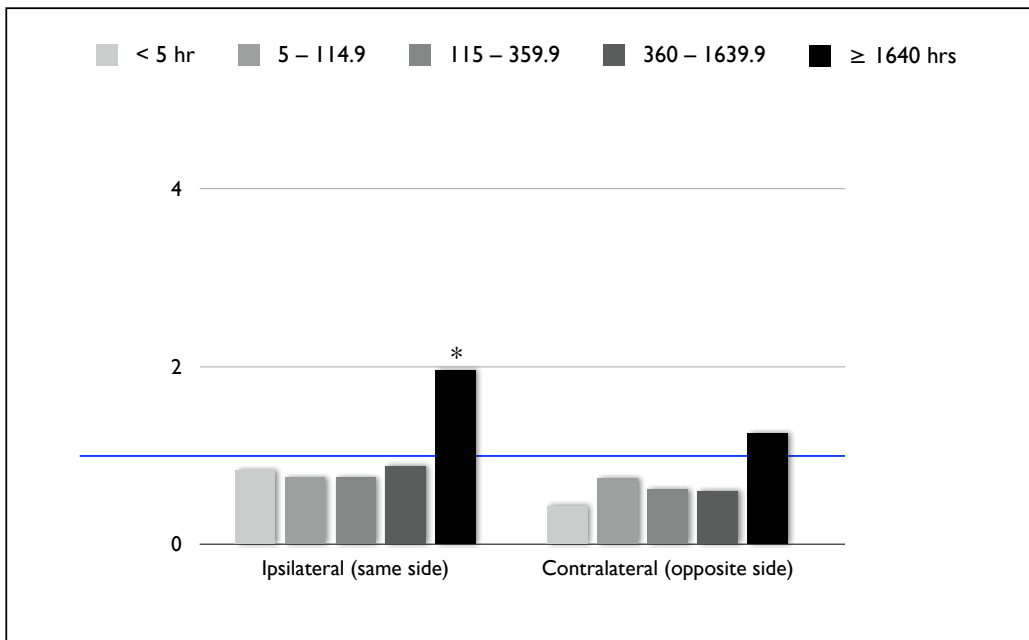
Also stratified by cumulative call time.

Temporal lobe (With ≥1640 hrs exposure, OR = 1.87 [95% CI = (1.09-3.22)])

From Table 4: INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* (2010); 39(3):675-694.

Interestingly, the study did report its statistics stratified by total time of reported use, and the top decile (greater than 1640 hours use over a ten year interval, averaging out as greater than 3 hours a week) had an increased risk of certain tumors. Individuals who accrued that greater than 1650 hours of use over a 1 to 4 year interval (ranging from 8 to over 30 hours a week) had a markedly higher odds ratio of meningioma (OR 4.80) or glioma (OR 3.27).

Odds Ratio for Glioma with Cell Phone Use



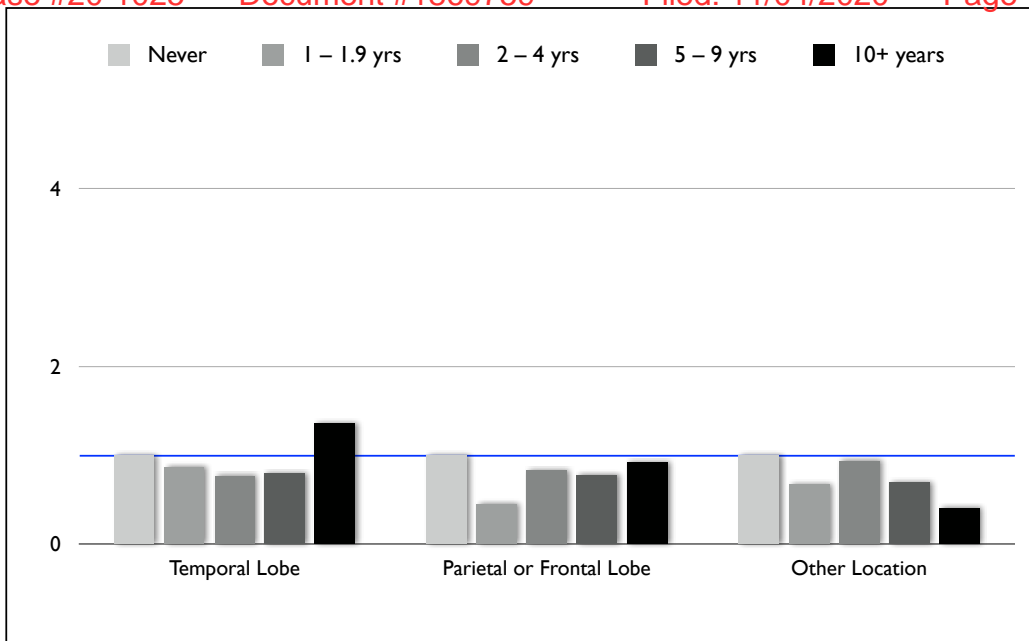
Glioma risk by side of head they habitually held the phone.

Also stratified by cumulative call time.

(With ≥1640 hrs exposure, Ipsilateral OR = 1.96 [95% CI = (1.22-3.22)])

From Table 5: INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* (2010); 39(3):675-694.

Odds Ratio for Glioma (by Years of Use)



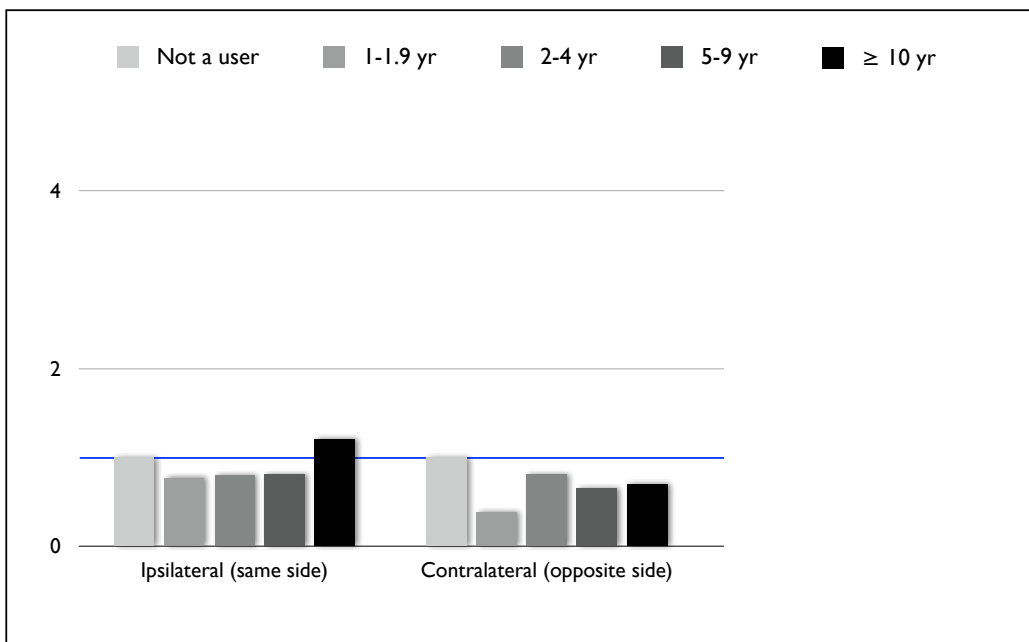
Stratified by years of exposure.

1640 hours in 10+ years ~ > 3 hrs/wk

1640 hours in 4 years = 7.9 hrs/wk (range in cohort was 8 - 30 hrs/wk)

INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* (2010); 39(3):675-694.

Odds Ratio for Glioma (by Years of Use)



Glioma risk by side of head they habitually held the phone.

Also stratified by cumulative call time.

1640 hours in 10+ years ~ > 3 hrs/wk

INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* (2010); 39(3):675-694.

INTERPHONE Study 2011

Acoustic neuroma risk in relation to mobile telephone use: Results of the INTERPHONE international case-control study

The INTERPHONE Study Group^{*,1}

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 Brain tumour
 Mobile phones
 Radiofrequency electromagnetic fields
 Epidemiology

ABSTRACT

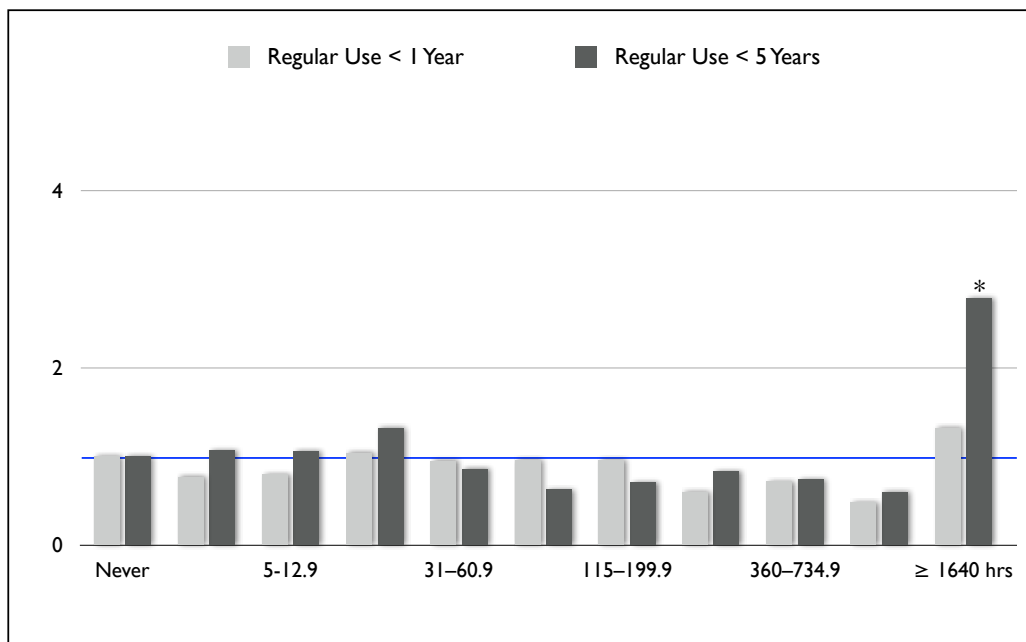
Background: The rapid increase in mobile telephone use has generated concern about possible health risks of radiofrequency electromagnetic fields from these devices. **Methods:** A case-control study of 1105 patients with newly diagnosed acoustic neuroma (vestibular schwannoma) and 2145 controls was conducted in 13 countries using a common protocol. Past mobile phone use was assessed by personal interview. In the primary analysis, exposure time was censored at one year before the reference date (date of diagnosis for cases and date of diagnosis of the matched case for controls); analyses censoring exposure at five years before the reference date were also done to allow for a possible longer latent period. **Results:** The odds ratio (OR) of acoustic neuroma with ever having been a regular mobile phone user was 0.85 (95% confidence interval 0.69–1.04). The OR for >10 years after first regular mobile phone use was 0.76 (0.52–1.11). There was no trend of increasing ORs with increasing cumulative call time or cumulative number of calls, with the lowest OR (0.48 (0.30–0.78)) observed in the 9th decile of cumulative call time. In the 10th decile (≥ 1640 h) of cumulative call time, the OR was 1.32 (0.88–1.97); there were, however, implausible values of reported use in those with ≥ 1640 h of accumulated mobile phone use. With censoring at 5 years before the reference date the OR for >10 years after first regular mobile phone use was 0.83 (0.58–1.19) and for ≥ 1640 h of cumulative call time it was 2.79 (1.51–5.16), but again with no trend in the lower nine deciles and with the lowest OR in the 9th decile. In general, ORs were not greater in subjects who reported usual phone use on the same side of the head as their tumour than in those who reported it on the opposite side, but it was greater in those in the 10th decile of cumulative hours of use. **Conclusions:** There was no increase in risk of acoustic neuroma with ever regular use of a mobile phone or for users who began regular use 10 years or more before the reference date. Elevated odds ratios observed at the highest level of cumulative call time could be due to chance, reporting bias or a causal effect. As acoustic neuroma is usually a slowly growing tumour, the interval between introduction of mobile phones and occurrence of the tumour might have been too short to observe an effect, if there is one.

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2011 INTERPHONE study of acoustic neuroma
 Funded in significant part by the telecommunications industry.

Cardis E, Schüz J. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol* (2011); 35(5):453-464.

Odds Ratio for Acoustic Neuroma with Cell Phone Use



From 2011 INTERPHONE study of acoustic neuroma, Table 2.

This study was also funded in major part by the telecommunications industry.

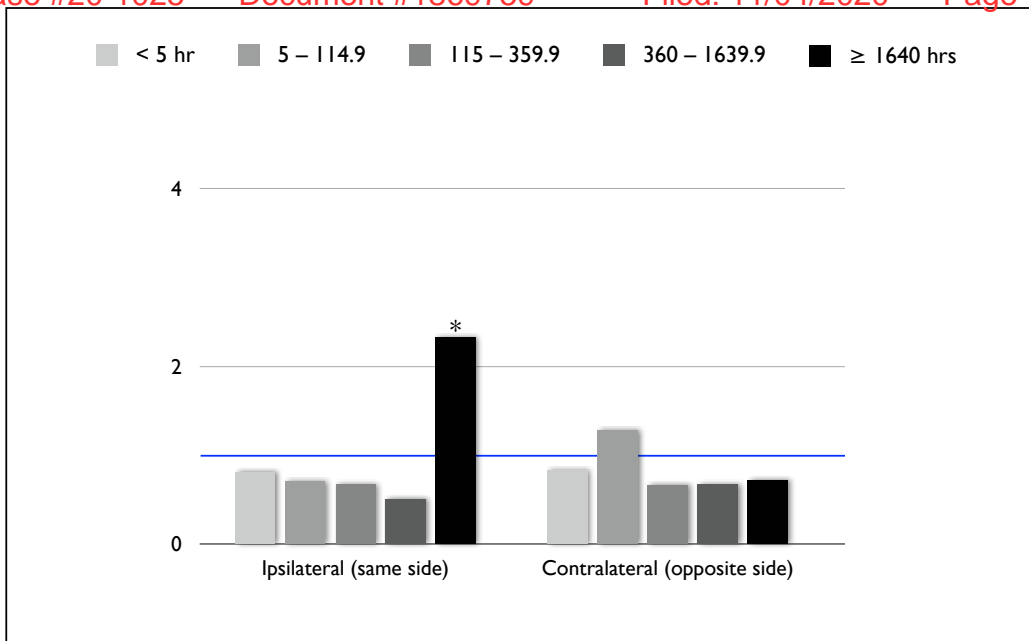
In their conclusion, the authors stated that this data showed “no trend of increasing risk with increasing cumulative call time”

They discounted their findings for the highest decile of exposure.

But with ≥ 1640 hrs exposure in 1 - 5 years of exposure, OR = 2.79 [95% CI = (1.51–5.16)]

From Table 2: Cardis E, Schüz J. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol* (2011); 35(5):453-464.

Acoustic Neuroma Risk (< 1 year of cell phone use)



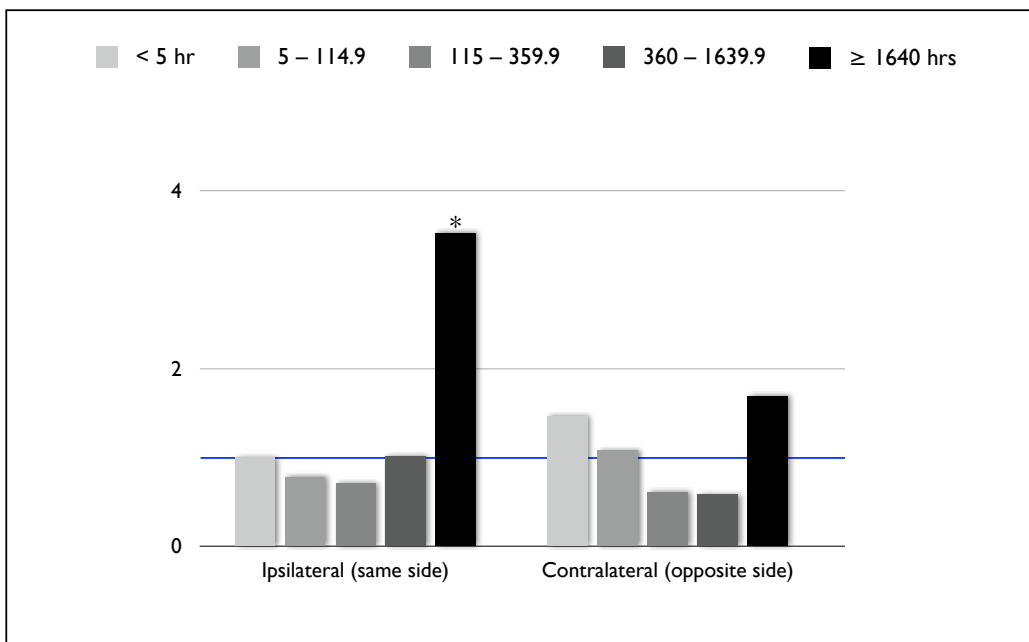
In the high use group, risk of acoustic neuroma was significantly higher on the side of the head where the subject habitually held the cell phone.

1640 hours in 1 year = 4.5 hours a day = 31.5 hours/week

With ≥1640 hrs exposure, ipsilateral tumor Odds Ratio = 2.33 [95% CI = (1.23-4.40)]

From Table 3: Cardis E, Schüz J. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol* (2011); 35(5):453-464.

Acoustic Neuroma Risk (< 5 years of cell phone use)



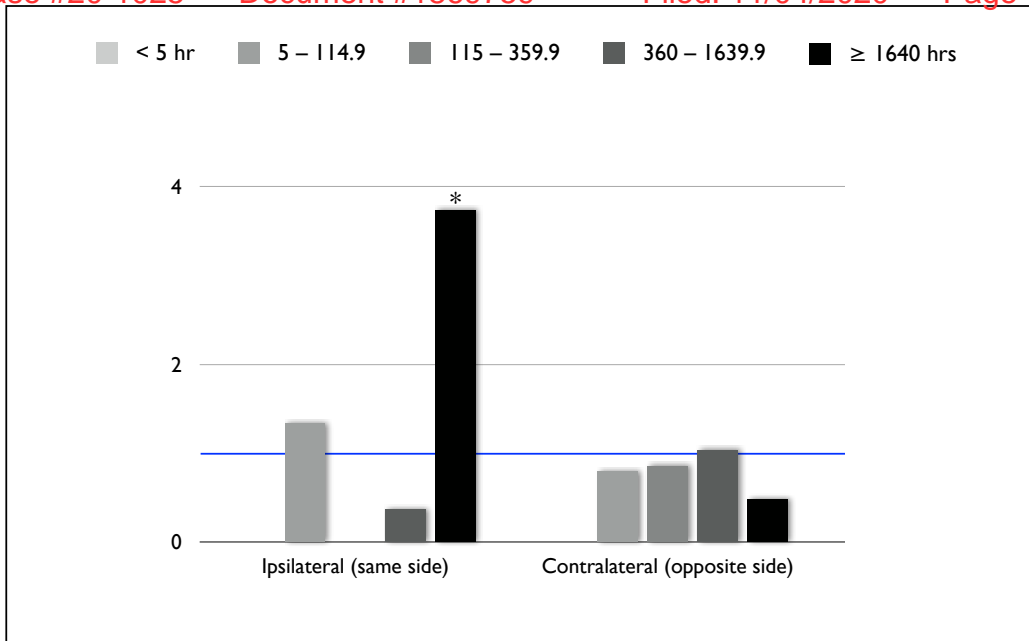
Risk increased with increased years of exposure.

1640 hours in 5 years = 0.9 hours a day = 6.3 hours/week

With ≥1640 hrs exposure, ipsilateral tumor Odds Ratio = 3.53 [95% CI = (1.59-7.82)]

From Table 3: Cardis E, Schüz J. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol* (2011); 35(5):453-464.

Acoustic Neuroma Risk (> 10 years of cell phone use)



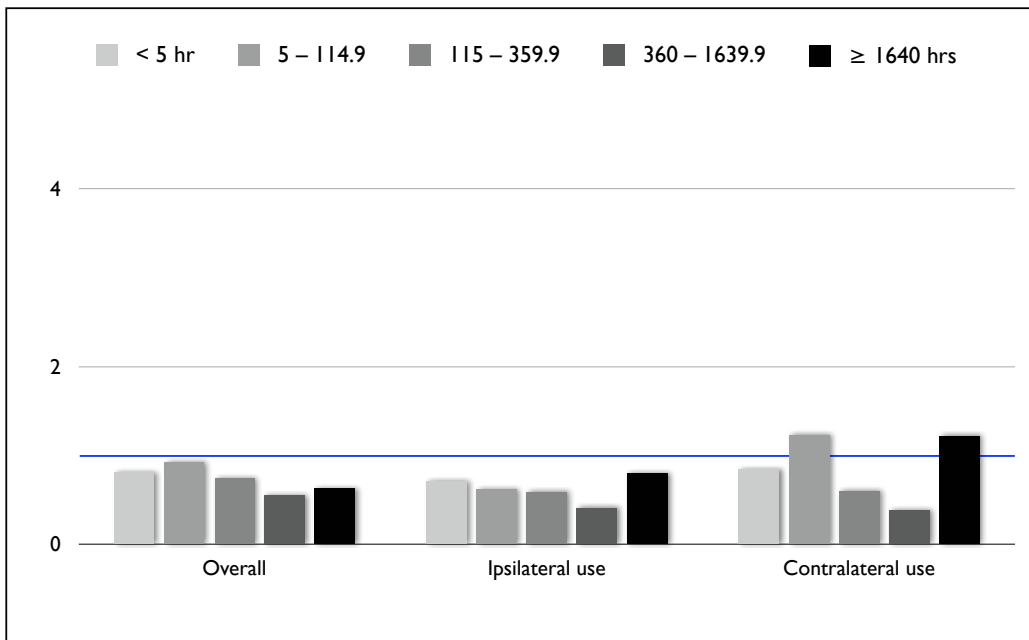
Higher risk with ten or more years of exposure.

1640 hours in 10 years = less than half an hour a day. = 3.2 hours/week = 0.45 hours a day

With ≥1640 hrs exposure, ipsilateral tumor Odds Ratio = 3.74 [95% CI = (1.58-8.83)]

From Table 4: Cardis E, Schüz J. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol* (2011); 35(5):453-464.

Acoustic Neuroma Risk with 1 to 4 Years of Cell Phone Use

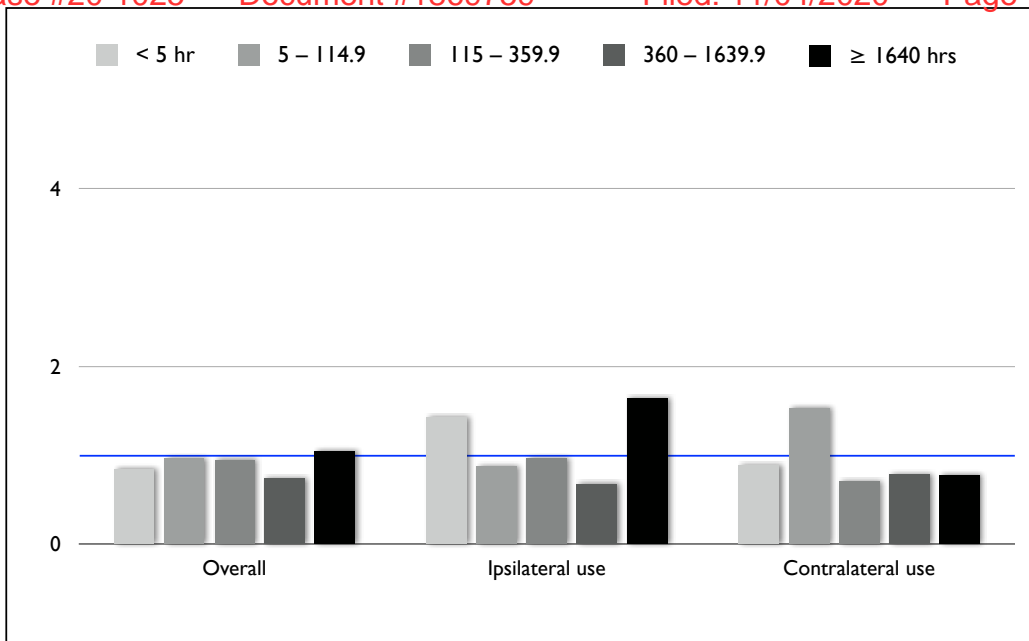


2011 INTERPHONE study of acoustic neuroma

From Table 4: Short, medium, long-term accumulation of >1640 hours.

Cardis E, Schüz J. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol* (2011); 35(5):453-464.

Acoustic Neuroma Risk with 5 to 9 Years of Cell Phone Use

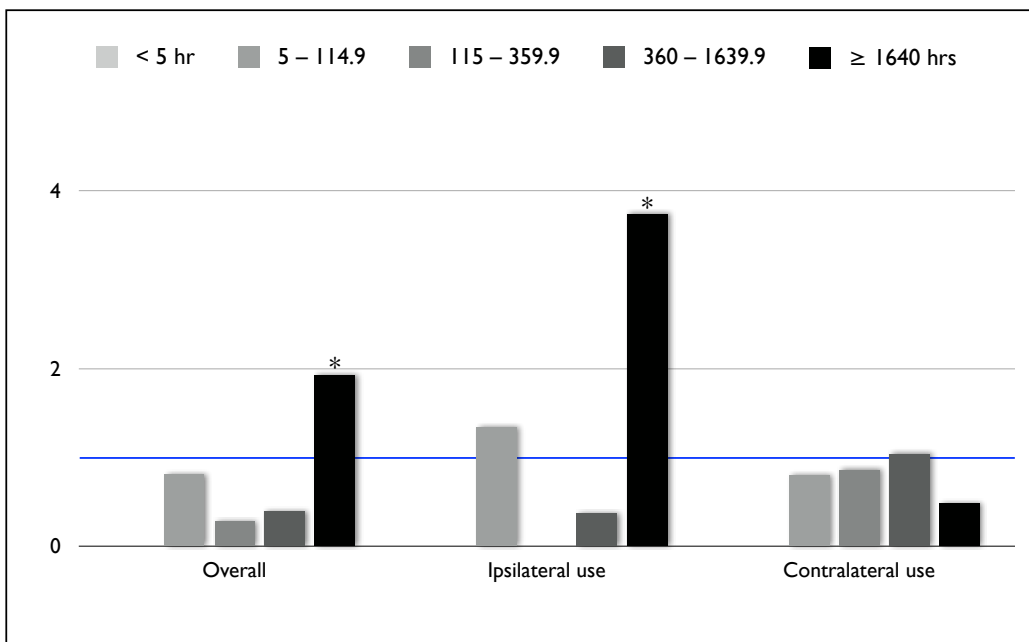


2011 INTERPHONE study of acoustic neuroma

From Table 4: Short, medium, long-term accumulation of >1640 hours.

Cardis E, Schüz J. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol* (2011); 35(5):453-464.

Acoustic Neuroma Risk with 10 + Years of Cell Phone Use



2011 INTERPHONE study of acoustic neuroma

From Table 4: Short, medium, long-term accumulation of ≥1640 hours.

Cardis E, Schüz J. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol* (2011); 35(5):453-464.

INTERPHONE Study 2011



Risk of brain tumours in relation to estimated RF dose from mobile phones: results from five Interphone countries

E Cardis,¹ B K Armstrong,² J D Bowman,³ G G Giles,^{4,5} M Hours,⁶ D Krewski,⁷ M McBride,⁸ M E Parent,⁹ S Sadetzki,^{10,11} A Woodward,¹² J Brown,² A Chetrit,¹⁰ J Figuerola,¹ C Hoffmann,^{11,13} A Jarus-Hakak,¹⁰ L Montestrucq,⁶ L Nadon,⁹ L Richardson,¹⁴ R Villegas,¹ M Vrijheid¹

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ABSTRACT

Objectives The objective of this study was to examine the associations of brain tumours with radio frequency (RF) fields from mobile phones.

Methods Patients with brain tumour from the Australian, Canadian, French, Israeli and New Zealand components of the Interphone Study, whose tumours were localised by neuroradiologists, were analysed. Controls were matched on age, sex and region and allocated the 'tumour location' of their matched case. Analyses included 553 glioma and 676 meningioma cases and 1762 and 1911 controls, respectively. RF dose was estimated as total cumulative specific energy (TCSE; J/kg) absorbed at the tumour's estimated centre taking into account multiple RF exposure determinants.

Results ORs with ever having been a regular mobile phone user were 0.93 (95% CI 0.73 to 1.18) for glioma and 0.80 (95% CI 0.66 to 0.96) for meningioma. ORs for glioma were below 1 in the first four quintiles of TCSE

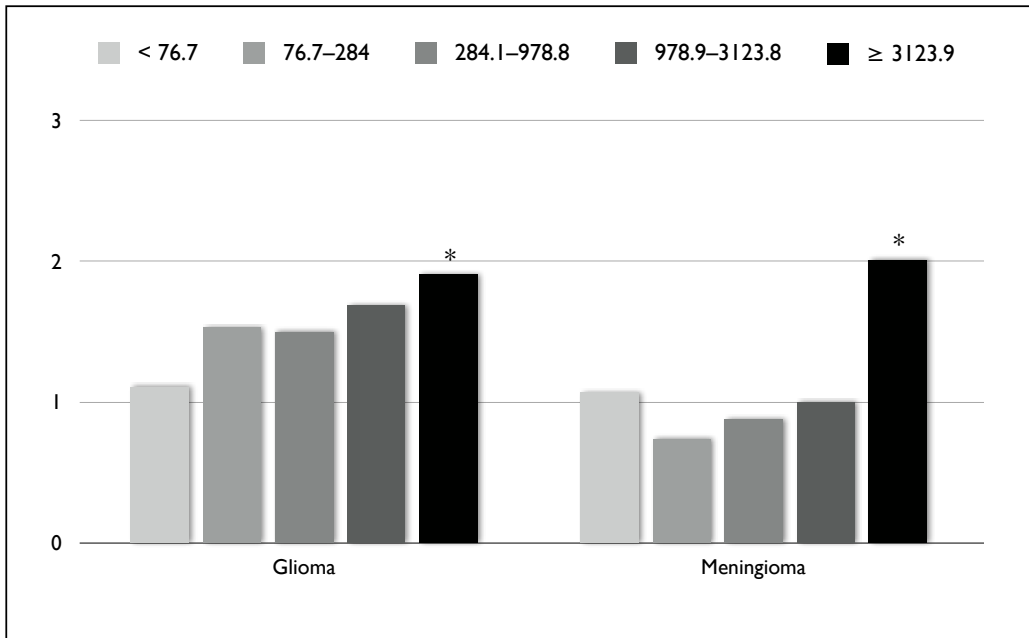
What this paper adds

- ▶ Previous epidemiological studies of mobile phone use and brain cancer risk have used information on mobile phone use as a proxy measure of exposure to radio frequency fields from mobile phones.
- ▶ Most studies have not observed increased ORs in relation to ever having been a mobile phone user. There were suggestions, however, of an increased risk of glioma in long-term and heavy users, though biases and errors prevent a causal interpretation.
- ▶ The relationship between radio frequency energy absorbed at the tumour location and mobile phone use history is complex. In addition to amount of use, it depends on phone type, network properties, conditions of use and

Interphone latest study 2011

Cardis E, Armstrong BK, Bowman JD et al. Risk of brain tumours in relation to estimated RF dose from mobile phones: results from five Interphone countries. *Occup Environ Med* (2011); 68(9):631-640.

Odds Ratio for Brain Tumor (7+ years of cell phone use)



Stratified by Total Cumulative Energy Exposure (joules/kilogram)

From Table 3: Cardis E, Armstrong BK, Bowman JD et al. Risk of brain tumours in relation to estimated RF dose from mobile phones: results from five Interphone countries. *Occup Environ Med* (2011); 68(9):631-640.

Our results suggest that there may be an increase in risk of glioma in the most exposed area of the brain among long-term and heavy users of mobile phones. These results are uncertain (in light of the uncertainties associated with tumour centre localisation, radio frequency dose estimation and sample size) and require replication before they can be taken to indicate a cause effect relationship.

From the conclusions of the 2001 INTERPHONE study (industry-financed).

Study authors finally admitted that their data showed increase risk of glioma, but said that this finding required replication before being taken as a cause and effect relationship.

This despite the fact that this finding was already a replication of their previously published data, and had also been confirmed several times in the published data of the Hardell group in Sweden.

BBC NEWS**HEALTH**

20 October 2011 Last updated at 21:11 ET

Mobile phone brain cancer link rejected**By Nick Triggle**

Health correspondent, BBC News

Further research has been published suggesting there is no link between mobile phones and brain cancer.

The risk mobiles present has been much debated over the past 20 years as use of the phones has soared.

Danish study: Proclaimed as evidence that cell phones are safe.

420,095 subscribers in the cohort — who had subscriptions by 1994/95.

Exposure is judged by presence of a cell phone contract, no record of actual usage.

200,507 corporate users excluded — **and placed in the control group.**

2550 juveniles excluded — **and placed in the control group.**

Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schuz J. Use of mobile phones and risk of brain tumours: update of Danish cohort study. *BMJ* (2011); 343(d6387).

Danish Study 2011**Danish study: Proclaimed as evidence that cell phones are safe.**

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200,507 corporate users excluded — and placed in the control group.

2550 juveniles excluded — and placed in the control group.

Half the subjects in the 2009 Johansen et al study had less than two years of cell phone use.

Second publication: Schuz 2006

Only 61% of subscribers reported making or receiving at least 1 call a week in prior six months

All users who began subscription after 1995 were put in the “unexposed” reference population.

Third publication Schuz et al 2011

Same study group

Control group 2.9 million Danes

Fourth publication: Frei et al 2011 *BMJ*

~ 42% of initial cohort excluded (and placed in control group).

Also in the control group — the 85% of Danes that got a cell phone contract between 1995 and 2004.

“Number of subscription years” is used as a surrogate for actual hours of usage.

18–29 year old excluded

Cohort established by grants from Danish telecom companies. Sources of funding of the International Epidemiology Institute (Rockville, MD, USA) have never been declared.

In this study, the control group was contaminated with so many cell phone users that the results of the study were essentially meaningless. Two reviews stating this fact were published in the same issue of *BMJ*, along with the Friestudy.

Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schuz J. Use of mobile phones and risk of brain tumours: update of Danish cohort study. *BMJ* (2011); 343(d6387).

Philips A, Lamburn G. Updated study contains poor science and should be disregarded. *BMJ* (2011); 343(d7899); author reply d7912).

Soderqvist F, Carlberg M, Hardell L. Review of four publications on the Danish cohort study on mobile phone subscribers and risk of brain tumors. *Rev Environ Health* (2012); 27(1):51-58.

Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects

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Abstract. We studied the association between use of mobile and cordless phones and malignant brain tumours. Pooled analysis was performed of two case-control studies on patients with malignant brain tumours diagnosed during 1997-2003 and matched controls alive at the time of study inclusion and one case-control study on deceased patients and controls diagnosed during the same time period. Cases and controls or relatives to deceased subjects were interviewed using a structured questionnaire. Replies were obtained for 1,251 (85%) cases and 2,438 (84%) controls. The risk increased with

emissions from wireless devices such as mobile phone base stations, broadcast transmission towers, pagers and personal digital assistants, wireless networks and other sources of RF radiation (1).

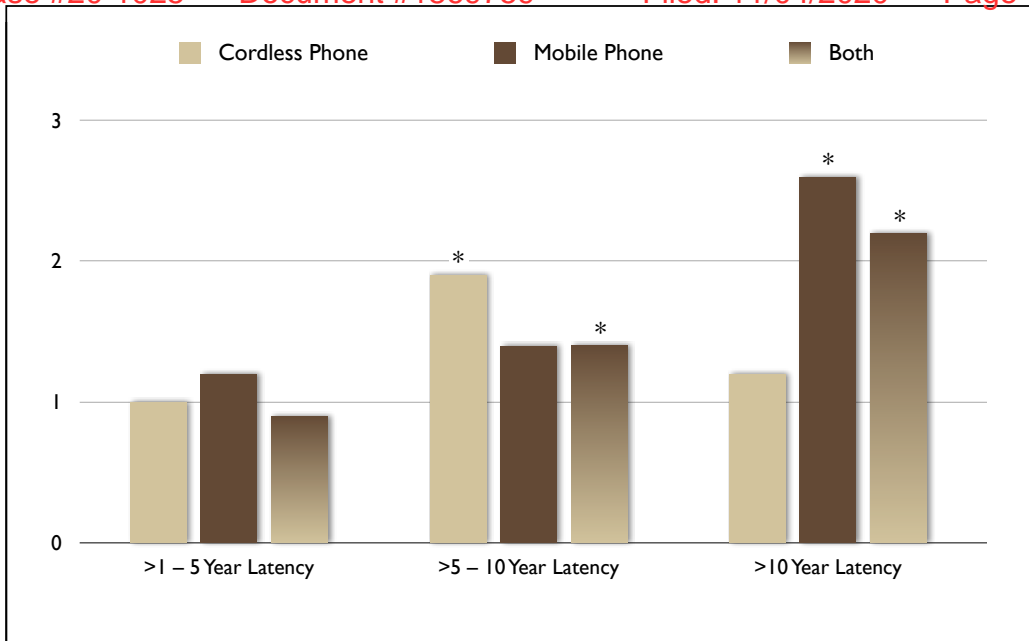
The brain is the target organ of the body with highest near field exposure to microwaves during use of a handheld wireless phone. Thus, fear of an increased risk for brain tumours from RF fields emitted from mobile phones has dominated the debate the last decade. Of equal importance is use of the desktop cordless phones.

The most reliable research on the tumor risks of cell phones has been performed by the Hardell group in Sweden. This group does not receive funding from the cell phone industry.

This is the only group that has controlled for use of in-home cordless phones as well as cell phones [which makes their data more reliable].

Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

Tumor Risk by Years of Use – Glioma

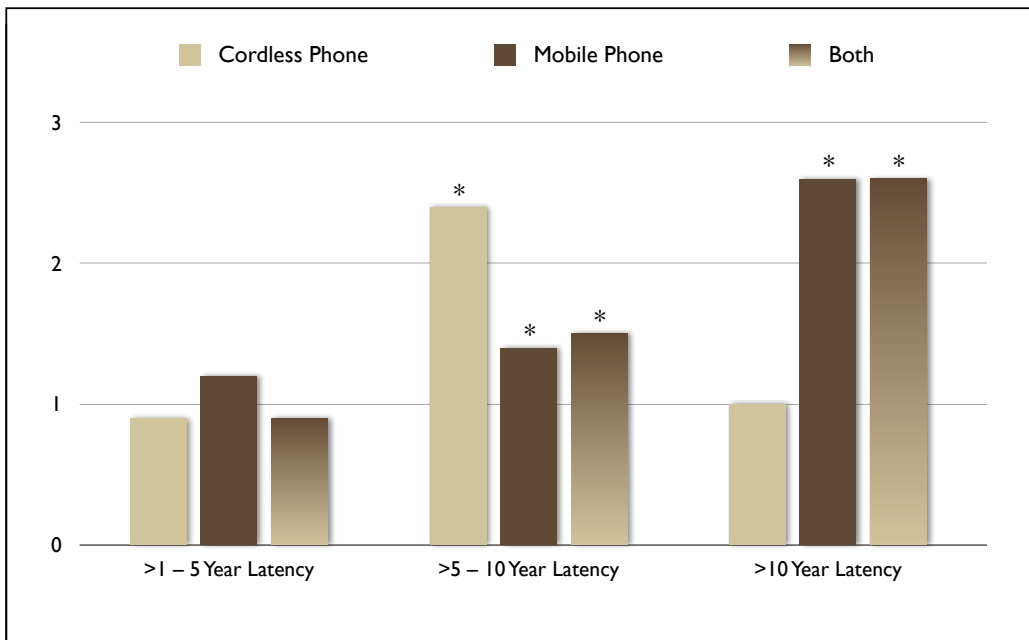


Orient to the bar graph.

Hardell group -- current summary

From Table IV: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

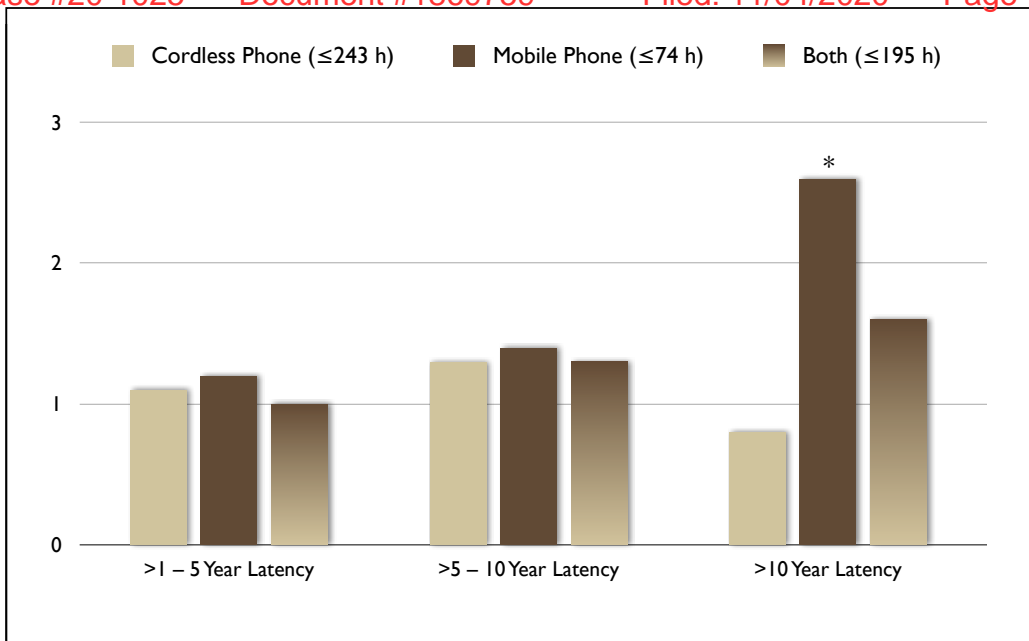
Tumor Risk by Years of Use – Astrocytoma



Hardell group -- current summary

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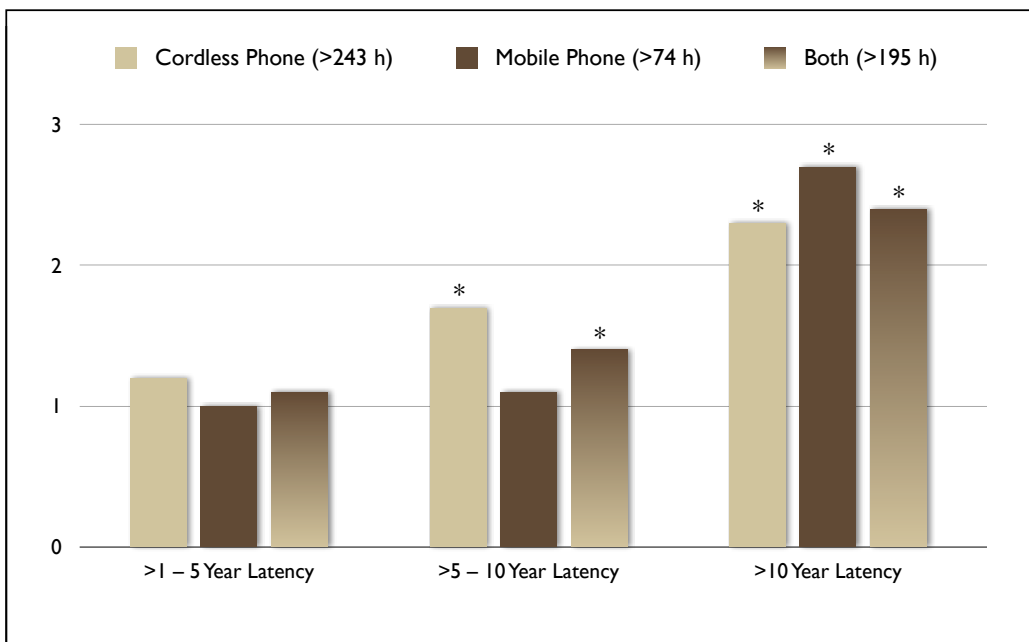
Risk of All Brain Tumors (Usage Below Median)



Hardell group -- current summary

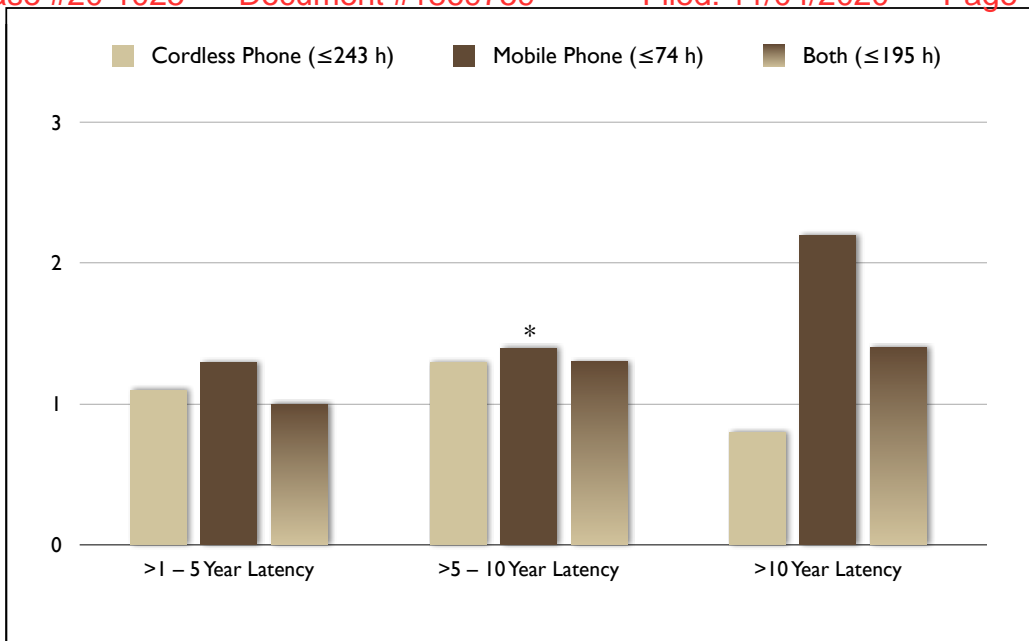
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Risk of All Brain Tumors (Usage Above Median)



Hardell group -- current summary

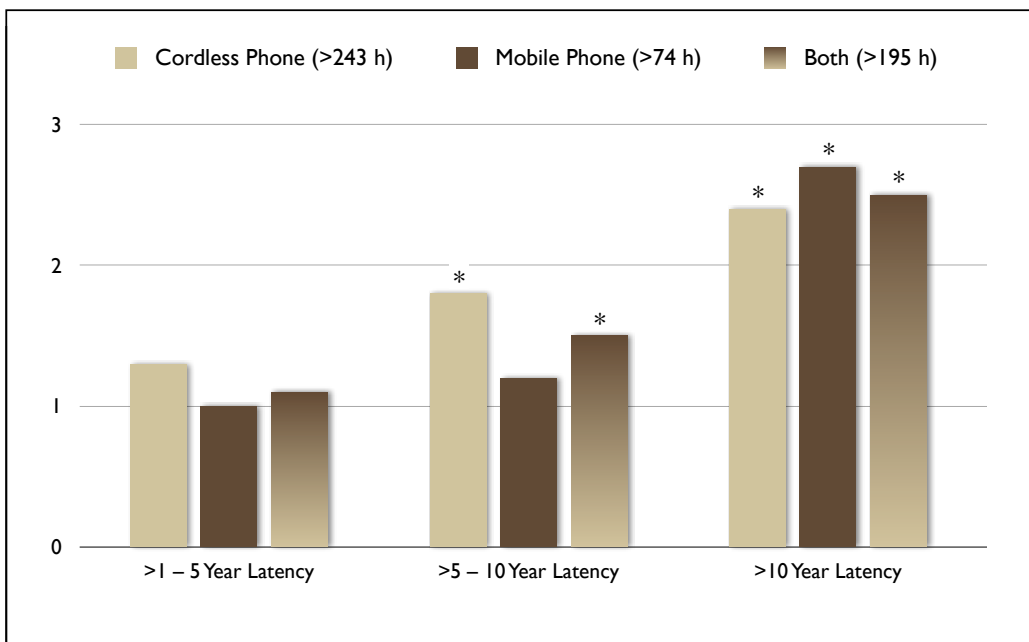
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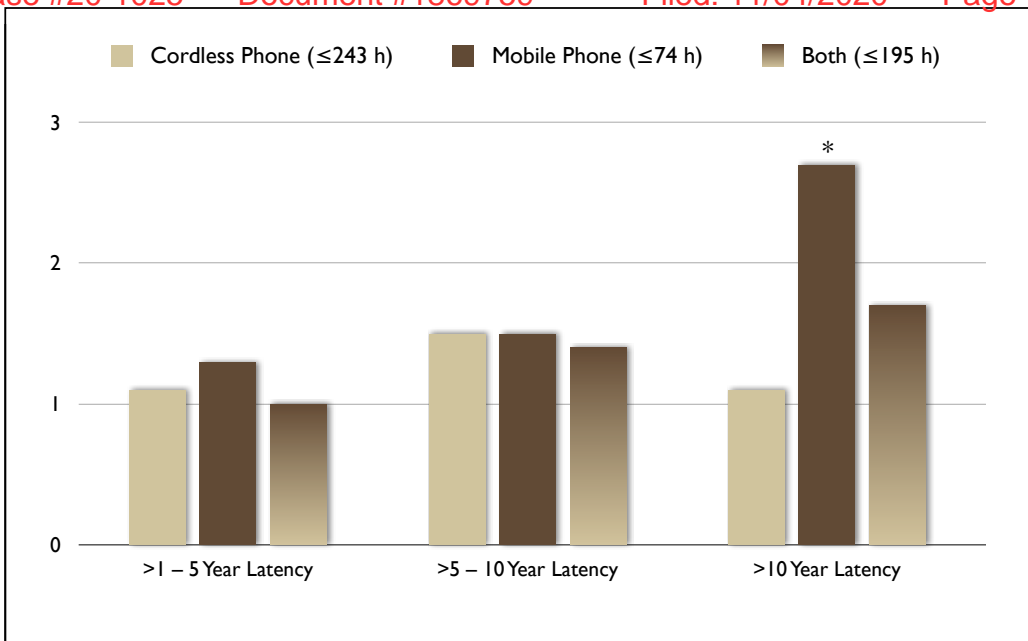
Risk of Glioma (Usage Above Median)



Hardell group -- current summary

From Table IV: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

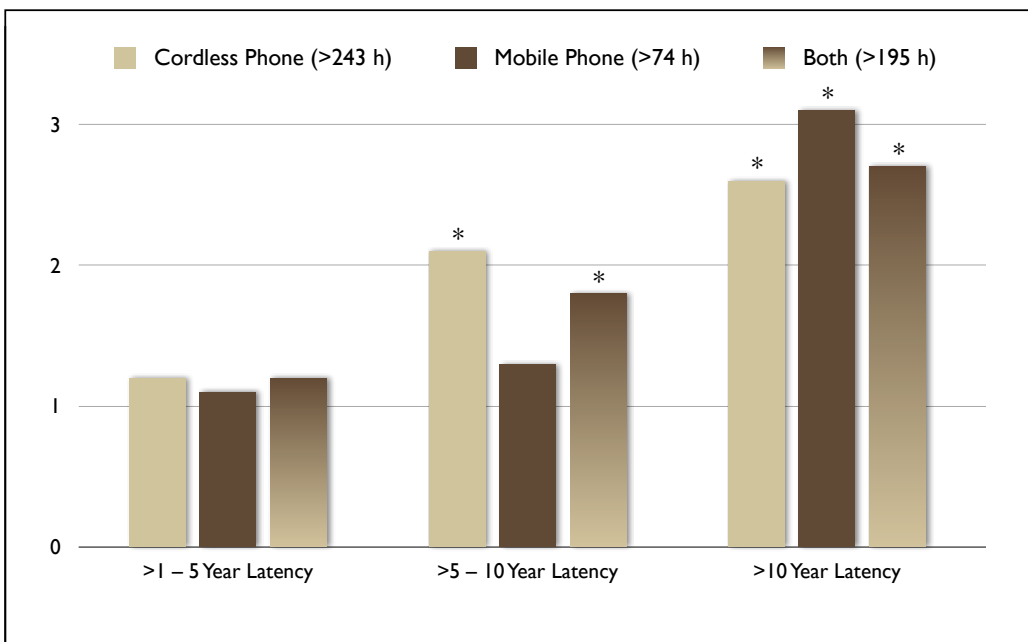
Risk of Astrocytoma (Usage Below Median)



Hardell group -- current summary

From Table IV: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

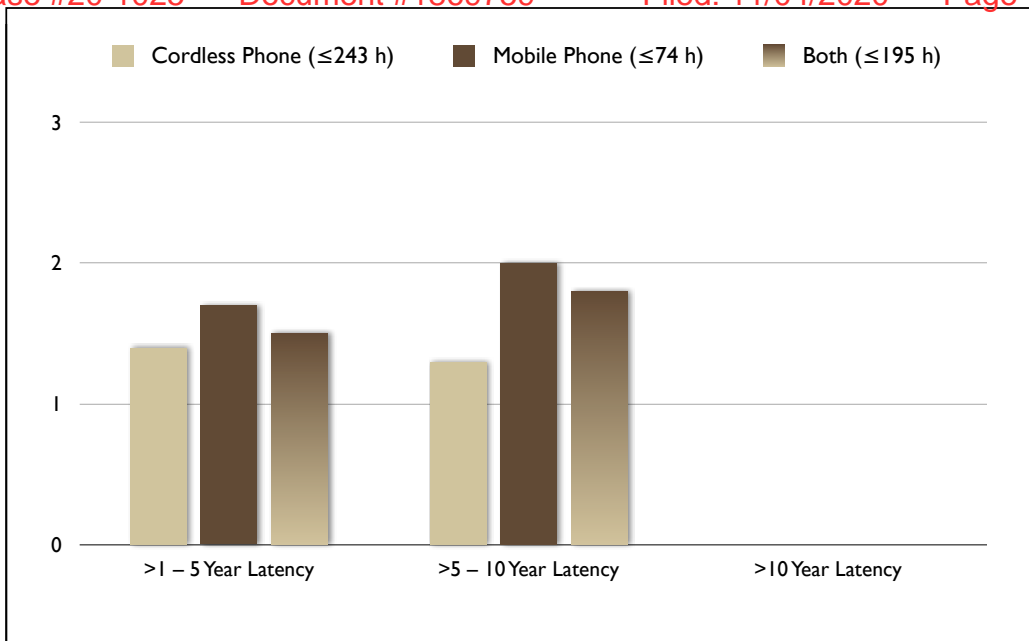
Risk of Astrocytoma (Usage Above Median)



Hardell group -- current summary

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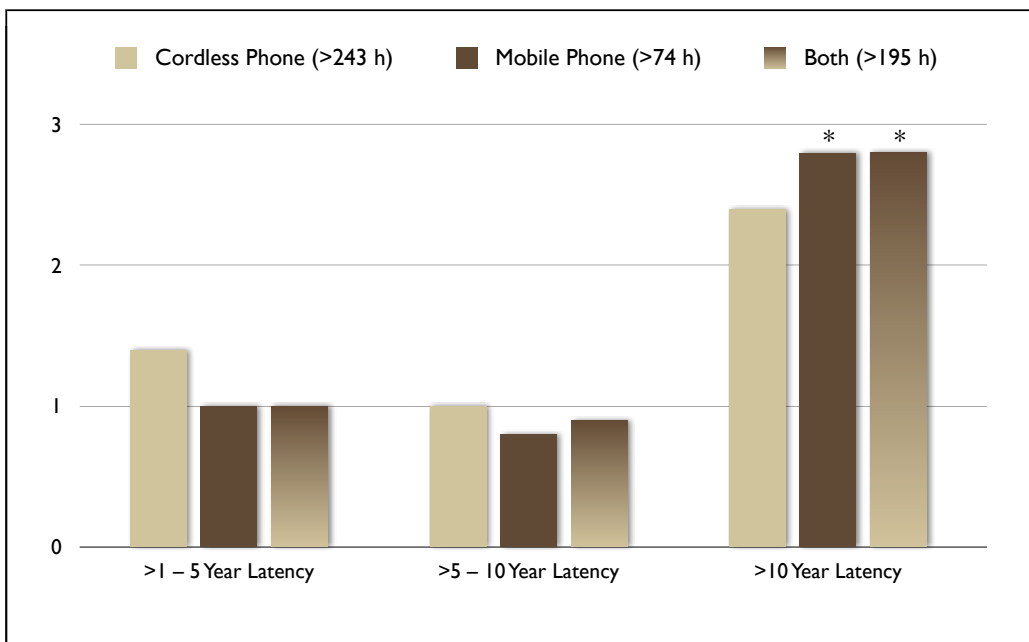
Risk of Oligodendroglioma (Usage Below Median)



Hardell group -- current summary

From Table IV: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

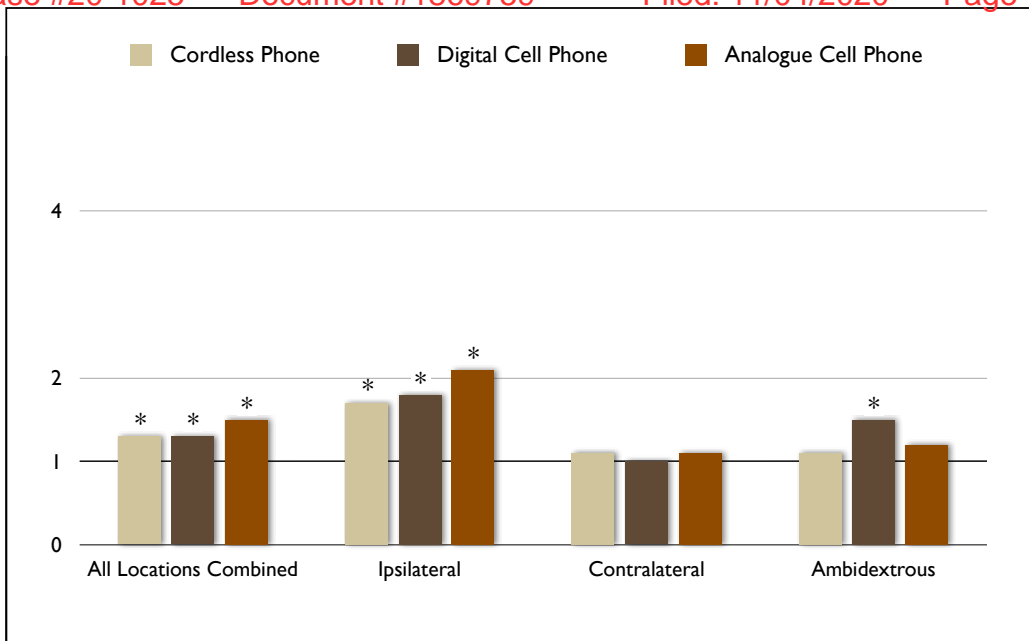
Risk of Oligodendroglioma (Usage Above Median)



Hardell group -- current summary

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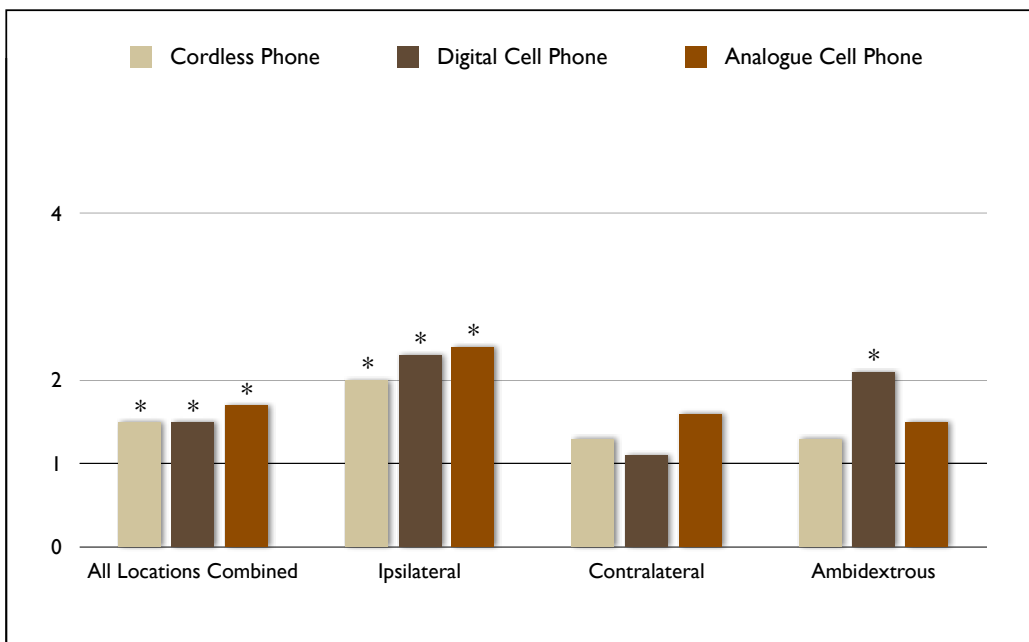
Risk of Tumor by Location – All Tumor Types



Hardell group -- current summary

From Table 3: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997-2003. *Int Arch Occup Environ Health* (2006b); 79(8):630-639.

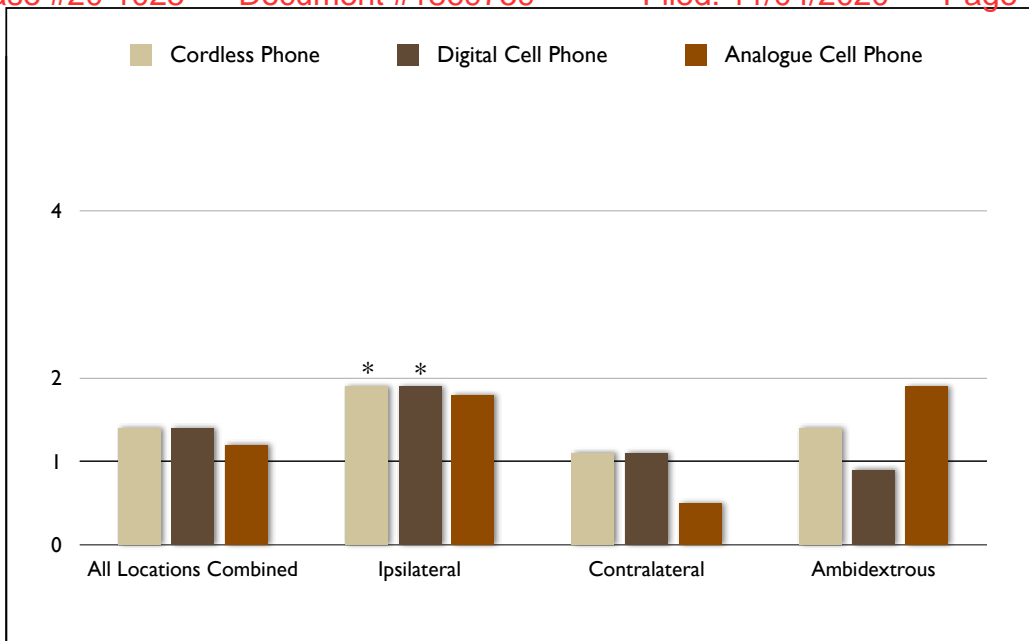
Risk of Tumor by Location – High Grade Astrocytoma



Hardell group -- current summary

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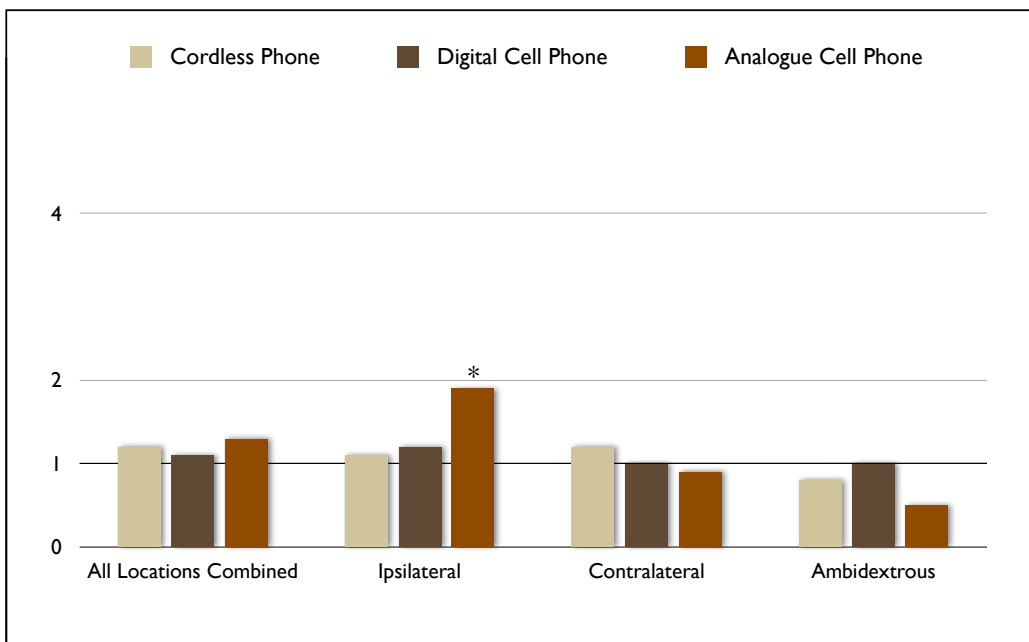
Risk of Tumor by Location – Low Grade Astrocytoma



Hardell group -- current summary

From Table 3: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997-2003. *Int Arch Occup Environ Health* (2006b); 79(8):630-639.

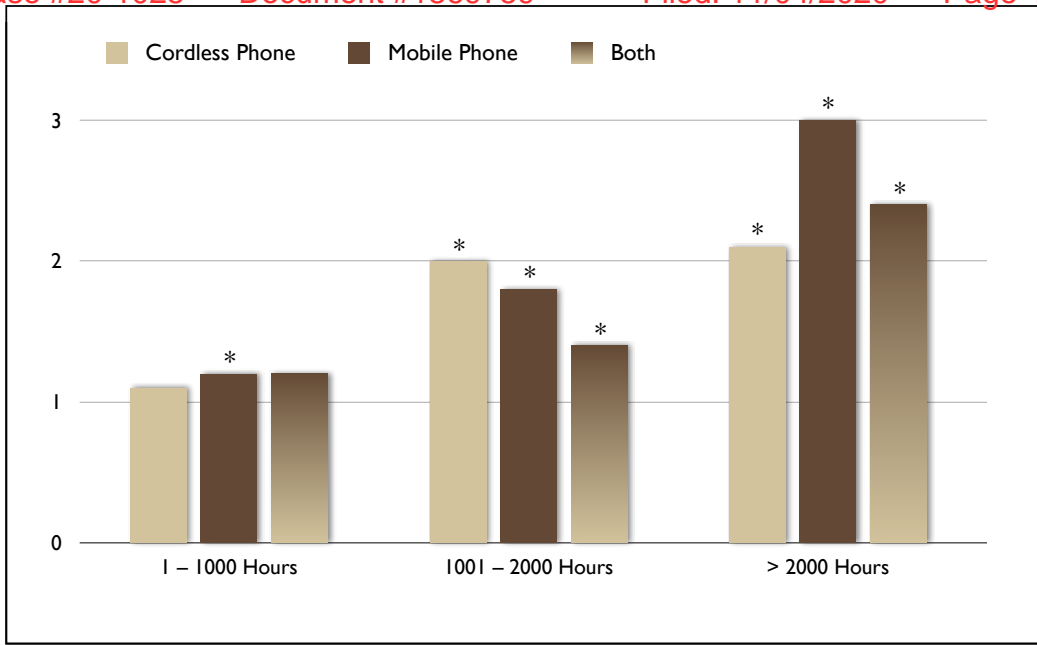
Risk of Tumor by Location – Other Malignant Tumors



Hardell group -- current summary

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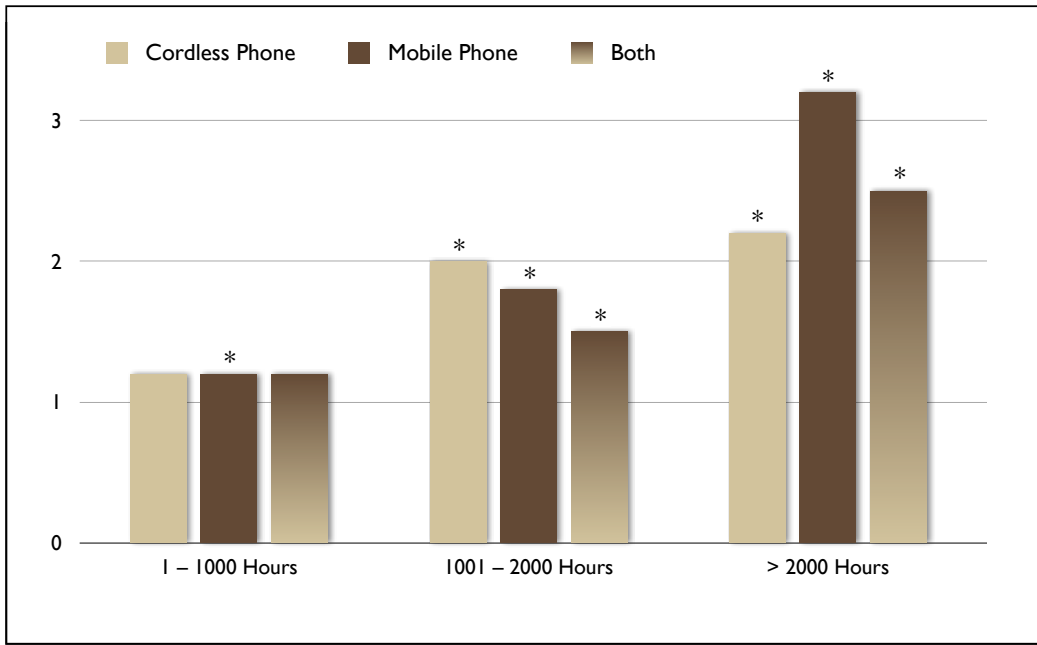
Tumor Risk by Cumulative Hours of Use – Any Brain Cancer



Hardell group -- current summary

From Table III: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

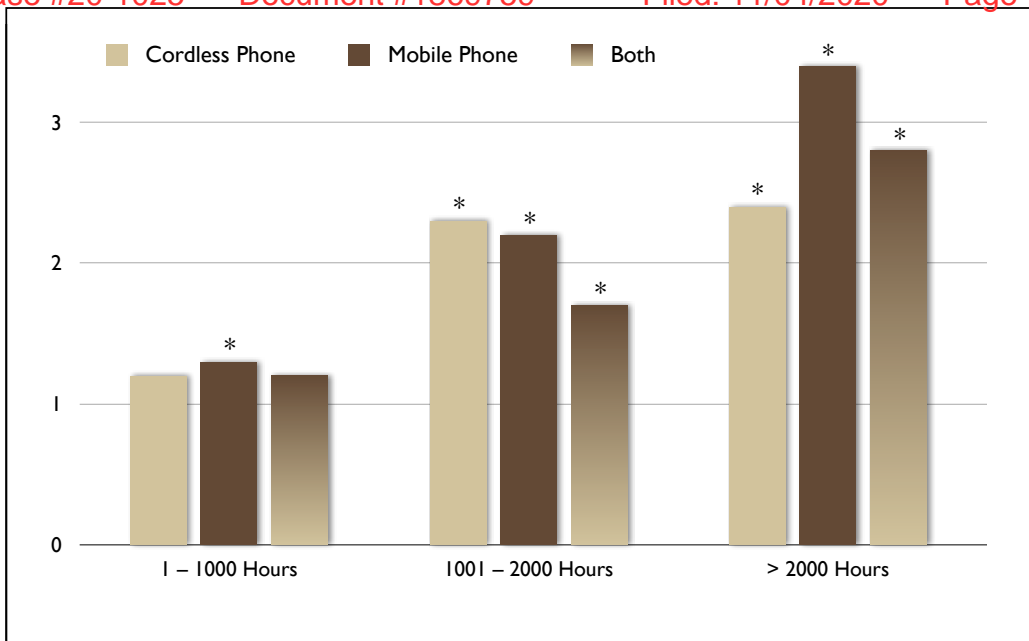
Tumor Risk by Cumulative Hours of Use – Glioma



Hardell group -- current summary

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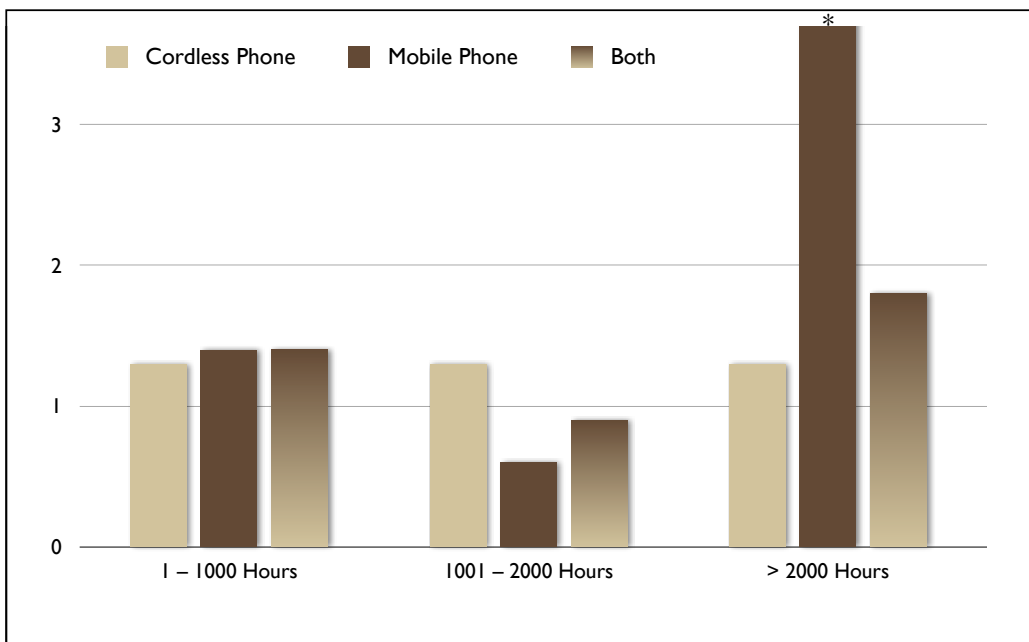
Tumor Risk by Cumulative Hours of Use – Astrocytoma



Hardell group -- current summary

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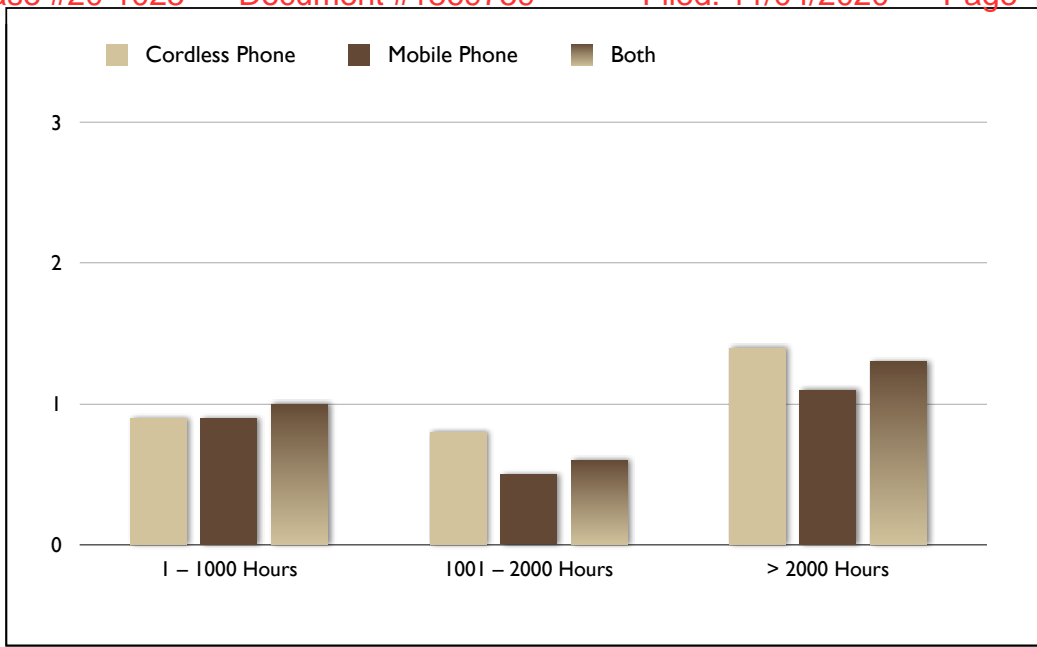
Tumor Risk by Cumulative Hours of Use – Oligodendroglioma



Hardell group -- current summary

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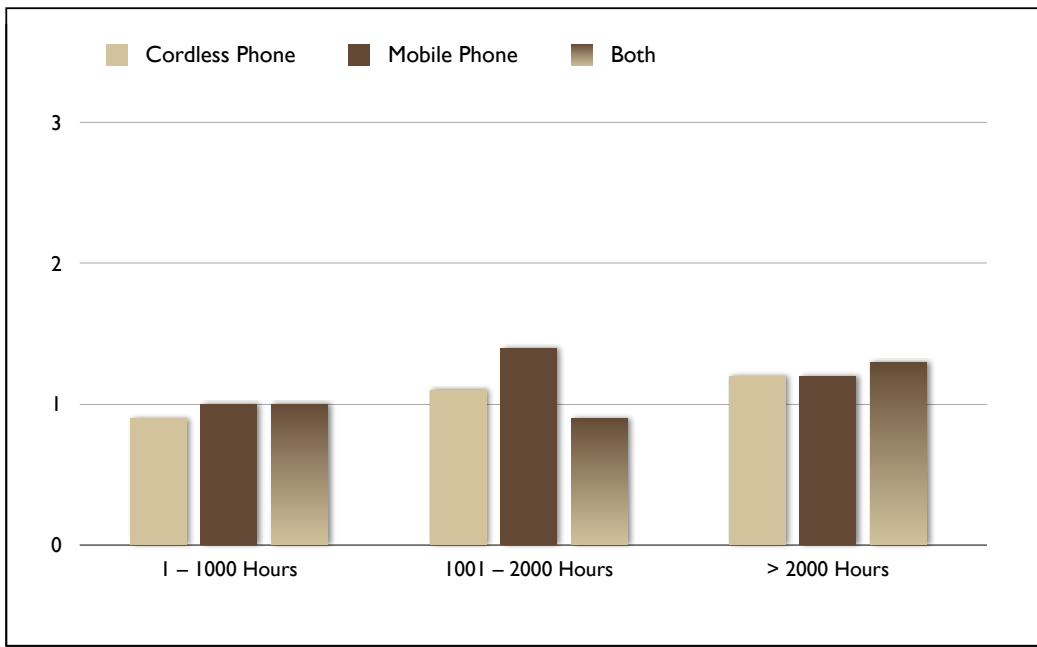
Tumor Risk by Cumulative Hours of Use – Other/Mixed Glioma



Hardell group -- current summary

From Table III: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

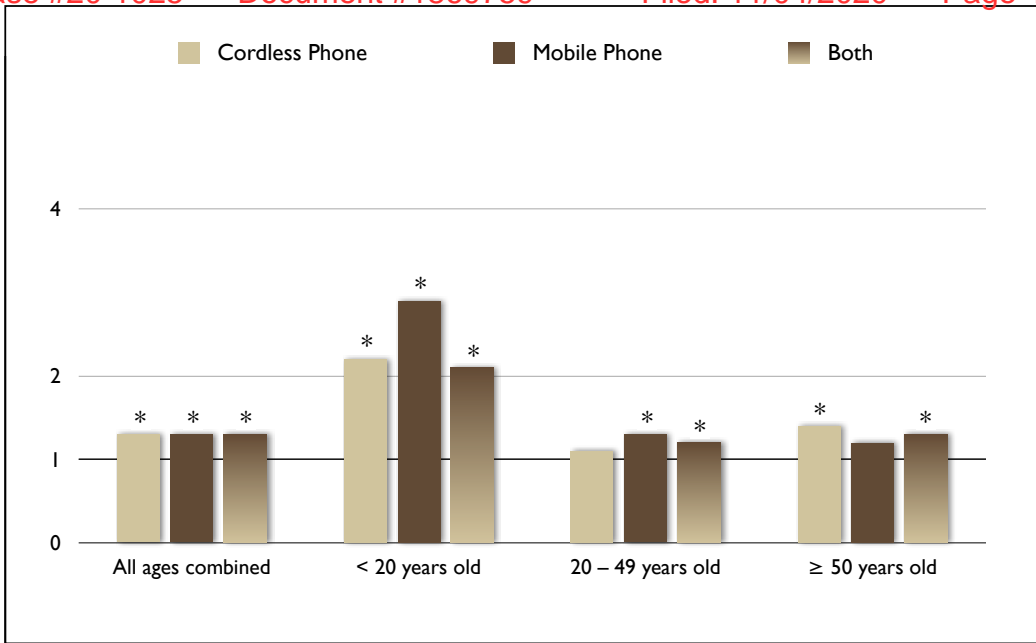
Tumor Risk by Cumulative Hours of Use – Other Brain Malignancy



Hardell group -- current summary

From Table III: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

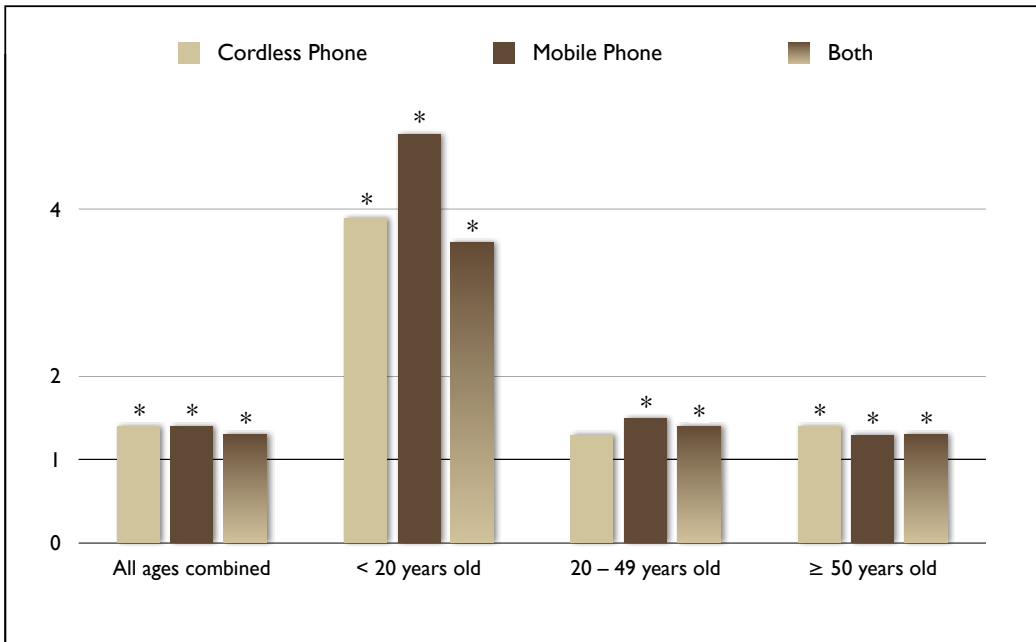
Tumor Risk by Age of First Use – Any Brain Cancer



Hardell group -- current summary

From Table V: Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* (2011b); 38(5):1465-1474.

Tumor Risk by Age of First Use – Astrocytoma



Hardell group -- current summary

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Jullian Gehman Esq. Comments, Jan. 31, 2019

**Before the
Federal Communications Commission
Washington, DC 20554**

In the Matter of)	
)	
Reassessment of the Federal Communications Commission Radiofrequency Exposure Limits And Policies)	ET Docket No. 13-84
)	
Proposed Changes in the Commission's Rules Regarding Human Exposure to Radiofrequency Electromagnetic Fields)	ET Docket No. 03-137
)	

COMMENTS OF JULIAN GEHMAN URGING USE OF SAR ABOVE 6 GHz

Julian Gehman, a telecommunications lawyer, hereby submits these Comments in response to the Commission's Notice of Inquiry (NOI)¹. The NOI solicits research on the adequacy of the Commission's current radiofrequency (RF) exposure limits for human health and safety.

Attached hereto as Exhibit A is a research paper (the "Nasim & Kim paper") on the effect of human exposure to 5G downlink transmissions.² This paper projects that a typical 5G installation configured according to 3GPP Release 15 could result in a specific absorption rate (SAR) of four to 300 watts per kilogram on the 5G downlink.³ Such an exposure would far exceed the Commission's SAR limit for frequencies under 6 GHz.⁴ The Commission should place the Nasim & Kim paper on public notice and solicit comments by interested parties, so that the authors' assumptions and calculations can be confirmed.⁵

¹ *In the Matter of Reassessment of the Federal Communications Commission Radiofrequency Exposure Limits And Policies; Proposed Changes in the Commission's Rules Regarding Human Exposure to Radiofrequency Electromagnetic Fields*, First Report and Order, Further Notice of Proposed Rulemaking, and Notice of Inquiry, ET Docket Nos. 13-184, 03-137, para. 205 (Mar 29, 2013).

² Intiaz Nasim and Seungmo Kim, *Mitigation of Human EMF Exposure in 5G Downlink*, Oct 24, 2018, <https://arxiv.org/pdf/1807.09094.pdf> (viewed Jan 31, 2019). It should be noted that the Nasim & Kim paper is limited to an 8X8 antennae array for 5G and does not study a 16X16 array, where presumably the effect could be more pronounced.

³ *Id.*

⁴ The FCC's SAR limits for general population/uncontrolled exposure are 0.08 W/kg, as averaged over the whole body, and a peak spatial-average SAR of 1.6 W/kg, averaged over any 1 gram of tissue (defined as a volume in the shape of a cube), subject to certain exceptions. 47 C.F.R. 1.1310(c).

⁵ Many previous RF investigations examined the health effects of a mobile device used near the human body. These could be characterized as examining the uplink or near-field. Nasim and Kim calculate the RF effects of a 5G downlink or far-field, from the transmitter array to humans.

If the Nasim & Kim paper is born out, the Commission's assumptions regarding how to measure RF from 5G systems may need to be re-examined. As the Commission is well aware, 5G is different in a number of respects: small cell sites covering a radius of 100 meters each, these cell sites are located closer to and interspersed within the population, each cell site will have a large number of antennae (distributed antenna systems, multiple input multiple output, etc.) and will perform beam forming to shape more sharply pointed RF emissions. Finally, the millimeter wave antennae will operate on higher frequencies and utilize much more bandwidth. Because of beam forming, greater bandwidth and closer proximity, 5G systems are projected to deliver signal strength and data transmission capacity that far exceeds that of 4G systems. These enhanced capabilities have implications for RF safety, as measured by the SAR.

SAR is a "measure of the rate at which energy is absorbed by the human body when exposed to a radio frequency electromagnetic field. . . . It is defined as the power absorbed per mass of tissue and has units of watts per kilogram."⁶ SAR measures thermal heat, *i.e.*, the capacity to burn skin and other human tissue. The FCC uses SAR to evaluate the impact of human exposure to RF radiation for frequencies below 6 GHz.⁷ For frequencies above 6 GHz, the Commission states that it relies on power density (PD) instead of SAR because "energy deposition would occur primarily on the surface of the skin, so an SAR-average over a one centimeter depth of tissue (corresponding to a 1 gram cube) would not be appropriate."⁸ Nasim and Kim respond to this by noting that "recent studies found that PD is not as useful as SAR or temperature exposure in assessment since SAR can display the level of EMF energy that is actually 'absorbed' in the body [] while PD cannot."⁹ This argues for the FCC establishing a limit on SAR in addition to its existing limit on PD.

Put simplistically, a burn is a burn. Prolonged human exposure to the SAR of four to 300 w/kg, that is projected by Nasim & Kim, would result in serious injury and possibly death. It does not matter to the victim whether the EMF energy comes from frequencies below or above 6 GHz.

⁶ https://en.wikipedia.org/wiki/Specific_absorption_rate (visited Jan 30, 2019).

⁷ 47 C.F.R. 1.1310(a).

⁸ *Supra*, n1, para 24, n48.

⁹ Nasim & Kim, *supra* n2 at 2 (citing studies).

WHEREFORE, it is respectfully requested that (1) the Nasim & Kim paper be placed on public notice and comments solicited so that their assumptions and calculations can be confirmed, and (2) the Commission establish an SAR standard for frequencies above 6 GHz.

Respectfully submitted,

JULIAN GEHMAN

/s/ Julian Gehman

Julian Gehman

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Dated January 31, 2019

Attachment:

Exhibit A Imtiaz Nasim and Seungmo Kim, Mitigation of Human EMF Exposure in 5G Downlink, Oct 24, 2018, <https://arxiv.org/pdf/1807.09094.pdf> (viewed Jan 31, 2019).