Dose and Exposure in Mobile Phone Research

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ABSTRACT

One of the great difficulties in determining possible health risks associated with exposure to electromagnetic fields is our lack of knowledge of what constitutes “dose” in this context. The present analysis of research papers was undertaken to advance our understanding of a dose-related factor. We have analysed the effects after exposure to fields similar to the ones emanating from mobile phones, concentrating on the time aspect and the exposure levels in different experiments. The papers are divided into three separate areas, human, animal and cellular studies, to facilitate the comparison of the studies.

A number of papers have documented various biological effects in cellular systems exposed to mobile phone-like signals. Some of the studies report effects at low SAR levels, suggesting the possibility of nonthermal effects. However, no studies have looked for threshold levels where effects start to occur. Furthermore, the in vitro experiments indicate that effects can occur both after single short-term exposures and be due to cumulative effects. In some of the animal studies, the SAR dependency is showed, possibly indicating threshold levels. However, this has not been studied systematically. Effects on the human nervous system are also noted. Typically, exposures in those cases are poorly described, lacking information about SAR values and time dependency. Taken together, it is difficult, however, to see a pattern in terms of common exposure parameters that cause a specific effect.

Key words: RF exposure; Mobile phones; Specific Absorption Rate; Electromagnetic fields

SAMMANFATTNING

En av de största svårigheterna i bestämning av eventuella hälsorisker associerade med exponering för elektromagnetiska fält, är vår brist på kunskap om vad som utgör ”dos” i detta sammanhang. Den föreliggande analysen av vetenskapliga arbeten har gjorts för att förbättra vår kunskap om dos-relaterade faktorer. Arbetet är indelat i tre separata områden; studier på människa, djur, och celler, för att underlätta jämförelsen.

Flera arbeten har dokumenterat olika biologiska effekter i cellulära system exponerade för mobiltelefonliknande signaler. Några av dessa arbeten rapporterar effekter vid låga SAR nivåer, vilket antyder en möjlighet av icke-termiska effekter. Ingen av studierna har emellertid undersökt effekten av tröskelvärden där effekten börjar att bli detekterbar. Vidare har in vitro försök indikerat att effekter kan förekomma både efter enstaka korttidsexponering som vid långtidsexponering och kumulativa effekter. I några av djurstudierna så har man visat på ett SAR beroende, vilket indikerar möjliga tröskelnivåer. Detta är dock icke studerat systematiskt. Effekter på människans nervsystem har också detekterats. Typiskt är att exponering i dessa fall är dåligt beskriven, det saknas information om t ex SAR värden och tidsberoende. Tillhopataget är det svårt att se ett mönster i vanliga exponeringsparametrar som förorsakar en specifik effekt.

INTRODUCTION

A great difficulty in determining possible health risks associated with exposure to electromagnetic fields is our lack of knowledge of what constitutes “dose” in this context. Present exposure guidelines are focused on eliminating acute thermal effects from microwaves and neuroexcitation from low frequency fields. The radiofrequency exposure is described as “Specific Absorption Rate”, SAR (W/kg), which denotes how much energy per time and mass unit that is absorbed by the tissue, and SAR is proportional to the square of the electric field (E^2). For low frequency fields, induced current density (A/m^2) is used, which is directly proportional to the E-field in the tissue. Both these variables are exposure measures that give a real-time image of how the electric field is distributed within the tissue. However, any unit for dose has not been created in this area.

Present research has primarily focused on effects of exposure levels substantially below guidelines. The question regarding the connection between exposure and dose thus becomes obvious. The simplest model would be to directly integrate over time, which for the RF spectrum would yield totally absorbed energy, SA, with the unit J/kg. This is used in ionising radiation, where the SA unit is named Gray (Gy). In the low-frequency area, a dose corresponding to μT-hours has been discussed. Both these measures presuppose that the possible exposure related effect is cumulative, which may or may not be relevant.

To advance our understanding of a dose-related factor, we have analysed research papers regarding effects after exposure to fields similar to the ones emanating from mobile phones. There are furthermore several compilations of research reports available, including the COST-244 bis update (1999) of the McKinlay report from 1996. In addition, recent updates on EMF research performed by NIEHS (1999) and IARC (2001) are important and informative documents.

We have divided the papers into three separate areas, human, animal, and cellular and molecular studies, respectively. The rationale is that the papers in each category has the organisation level in common, which makes it easier to compare the studies. Our interpretation of certain of the studied papers is given, with comments and conclusions of the overall subject area at the end of the paper.

Experimental observations on biological molecules, and on in vitro preparations of isolated cells or tissue samples, could define mechanisms of any action of mobile phone exposure on living organisms. The results of work on simple molecular and cellular preparations are often easier to interpret, since the nature of any effects can be more precisely defined and the condition of the preparation can be more accurately assessed and controlled than in animals. However, even when robust effects are seen in vitro, it is often difficult to extrapolate them to a health risk for people.

Laboratory studies on animals play an essential role in evaluating if the exposure to RF fields can affect organisms, and the integrated reactions of various, intact systems of the body, particularly the nervous, endocrine (hormone) and immune systems. Of course, phenomena seen in experimental animals do not necessarily imply a health risk for people. An effect found in only one animal species may be specific to that type of animal and not relevant to

humans. Appropriate animal studies provide the opportunity to test whether long-time exposure to mobile phones causes cancer. Research on animals can also demonstrate influence of mobile phone exposure on susceptibility to cancer promotion and progression, as well as on various physiological functions, including behavioural performance in tasks involving learning, memory, etc.

Human studies can broadly be divided into two groups, acute studies on individual subjects or epidemiological studies on populations. In the present overview, we have focused on the former. The epidemiological studies naturally lack pertinent information on specific exposure details, which makes it difficult to advance our understanding of a dose concept from such papers. The largest problems concerning the chosen human studies are the absence of SAR and time depending observations. The authors have to a large extent only observed if there are any influences from the mobile phone on the humans.

In our study of the individual papers, we have been concentrating on the time aspect of the exposure in different experiments. Relevant questions have been:

- For how long did the exposure last, how often was it repeated, was there any dose-response relationship?

- Is there a connection between high and low exposure levels, respectively, and biological effects? Is there any monotonous increase in response to increasing exposure levels?

- What kind of data are there regarding short-term exposure and biological effects? What is the connection between long-lasting exposure and effects? Is there any data on intermittent exposure?

- Is it reasonable to expect a specific biological response after a certain exposure time?

- Is there any biological “reset time” among reported effects, how long time must pass before the investigated end-point is back to initial levels?

- Are there effects on nervous system functions and various signal transduction pathways?

Our aim has been to further our understanding of “dose” and exposure time, and thus be able to construct a relevant dose-measure for electromagnetic fields. This has been accomplished by studying more recent literature. The concept of “dose” has to be better characterised before the epidemiological research within the area can progress significantly. Our work has primarily focused on papers relevant for questions regarding the use of mobile phone. During the screening process, a substantial number of additional papers were studied, although the majority was omitted due to lack of information relevant for this particular review.

CELLULAR AND MOLECULAR STUDIES

In a series of papers it has been shown that exposure to mobile phone signals has an influence on cell proliferation (Kwee at al 1998, Velizarov et al. 1999, French 1997), cell morphology (Donnellan et al 1997, French at al 1997) and heat-shock protein level in the exposed cells (Kwee at al 2001).

Kwee and Raskmark (1998) investigated the effect of a GSM signal (960 MHz) on cell proliferation. The experiments were performed on cell cultures of transformed human epithelial amnion cells (AMA). The cells were exposed to three different power levels (corresponding to SAR values of 0.021, 0.21 and 2.1 mW/kg) and three different exposure times (20, 30 and 40 min), respectively. After exposure, cells were incubated for 24 h in a field-free incubator. The cell growth in the exposed cells differed from that in the control and sham exposed cells. A decrease in cell growth was seen at all three SAR values, and the effect was more dependent on exposure time than on SAR. This is not what one would expect, taking into account the relatively short exposure times as compared to the entire cell cycle.

Velizarov et al (1999) found that a temporary change in temperature did not affect cell proliferation, whereas exposure to an RF electromagnetic field resulted in a significant change in cell proliferation. The changes were almost on the same magnitude at both temperatures used in these experiments as in their previous experiments (Kwee and Raskmark 1998). The AMA cell cultures were exposed to a GSM type signal with a power level resulting in a SAR value of 2.1 mW/kg and an exposure time of 30 min at two different temperatures (35^0C and 39^0C). The cells were incubated for 24 h immediately after exposure. Decrease in cell proliferation was interpreted as a result of GSM exposure and not due to heat generation. Importantly, this paper confirms findings in the earlier paper of the same group.

In an additional study, Kwee et al (2001) exposed AMA cells to a GSM signal of 960 MHz at a SAR value of 2.1 mW/kg for 20 min at 35, 37 and 40^0C. The presence of heat-shock proteins in the cells was determined immediately after exposure, and after 1, 1.5 and 24 h of post exposure incubation. At both 35 and 37^0C, higher amounts of hsp-70 were found in the field-exposed than in the sham-exposed cells. At 40 ^{0}C, the amounts of hsp-70 were considerably lower after exposure, which could be caused by a partial denaturation of the cells. The highest hsp level was detected immediately and 30 min after exposure. There was no difference between the exposed and sham-exposed cultures 24 h after exposure and no hsp-70 was present. These findings showed that exposure to RF fields can result in biological changes at field strengths far below the accepted standard for mobile phone and a time dependent effect is possible. However, such a rapid response on the protein level is not expected, rather a change in protein expression would normally take several hours.

French et al (1997) and Donnellan et al (1997) reported that 835 MHz electromagnetic exposures at high SAR value (7 W/kg (personal communication)) could alter the cell morphology and inhibit cell proliferation. They irradiated the human astrocytoma cell line U-87 MG and mast cells RBL-2H3 three times per day, for 20 min at a time, at four-hourly intervals during seven days, at a power density of 8.1 or 40 mW/cm^2 (U-87 cells) and 8.1 mW/cm^2 (RBL-2H3 cells). This particular exposure schedule is actually a form of intermittent exposure. The rationale behind this is unclear. The authors found that the cells exposed to

8.1 mW/ cm^2 did not start to proliferate until day four, and thereafter continued to proliferate at a significantly lower rate than the unexposed cells. The proliferation of U-87 MG cells irradiated at 40 mW/cm^2 was no different from the control cells. However, after 7 days, the cell exposed at both power densities showed a marked alteration in cell shape. At the same time, the U-87 MG cells exposed at 8.1 mW/ cm^2 lost the actin-containing cell surface projections observed in the control cells. The cells exposed at 40 mW/cm^2 showed similar results with the difference that the cells exposed to 40 mW/cm^2 exhibited actin aggregates localised at specific sites on the cell membrane. No inhibition of RBL-2H3 cell proliferation occurred in exposed cultures, whereas the cells in the control cultures decreased in number after 4-5 days. From 0 to 5 days of exposure, the height of the exposed cells was average on 11.4 µm, compared to 11.3 µm for the control cells. After 6 days the exposed cells decreased in cell height. At day 7 the average height was 8.6 µm. Morphological changes persisted following subculture for at least 7 days in the absence of further exposure. From day 4 onwards with a maximum after 7 days of exposure a significant increase in beta-hexosaminidase was observed in response to an added calcium ionophore. These noted effects may indicate that the exposure gives rise to cumulative effects, effects that are reasonable considering the time frame. Since the SAR values are high, noted effects might be thermal, and are of little interest when discussing possible health effects of mobile phones.

Harvey and French (1999) have also reported that exposure of the human mast cell line HMC-1 to an electromagnetic field with a frequency of 864.3 MHz at SAR of 7.3 W/kg caused an increase in the amount of protein kinase C in the membrane with a concomitant decrease in the cytosolic fraction. The cells were exposed for 20 minutes, three times per day, at four-hourly intervals for seven days. These cells responded differently than the previously mentioned U-87 MG cells and RBL-2H3 cells. No consistent significant morphological difference between exposed and unexposed cell was observed at any time point in the exposure period. Furthermore in two separate experiments, changes in gene expression between the exposed and the control cells were seen in three genes of a total of 558 genes screened. This indicates that such exposure did not result in a broad effect on gene expression.

de Pomerai et al (2000) showed that prolonged exposure to low-intensity microwave fields could induce heat-shock responses in a genetically modified soil nematode *Caenorhabditis elegans*. They exposed the worms overnight to CW microwave radiation at 750 MHz at SAR of 0.1 mW/kg. The authors noted that such SAR values are insufficient to cause measurable tissue heating and the induction of heat-shock proteins could involve non-thermal mechanisms. This experimental approach is very promising and can definitely be a useful tool for studies of mechanisms underlying non-thermal responses.

In some other studies, the authors showed that RF exposure could have an influence on the DNA molecule (Ivaschuk et al 1997, Phillips et al 1998). Transient changes in the transcript levels of c-jun were reported, in response to 836.55 MHz modulated time-domain multiple-access radio frequency exposures (Ivaschuk et al 1997). Rat PC 12 cells were treated with nerve growth factor and then exposed to the RF field. Exposure times 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. The power densities used were 0.09, 0.9 and 9 mW/cm^2 with corresponding SAR values of 0.26, 2.6 and 26 mW/kg. Transcript levels for c-jun were altered (average 38% decrease) only after 20 min exposure to 9 mW/cm^2 at the SAR of 26 mW/kg, and then returned to control levels after 60 min exposure. This suggests an

adaptation to the exposure. Importantly, there was no detectable rise in temperature at any power density used in these experiments.

Phillips et al (1998) detected a SAR and exposure time depending increase, respectively a decrease of DNA damage in the Molt-4 T lymphoblastoid cells exposed to pulsed signals at cellular telephone frequencies of 813.5625 MHz (iDEN signal), a special pulse signal (every 9 s one training pulse is emitted with 10 times the slot average power) or 836.55 MHz (TDMA signal). The cells were RF exposed (20 min on/20 min off) and the total incubation times were 2, 3 and 21 h, respectively. The SAR values were 2.4 and 24 mW/kg for iDEN signal and 2.6 and 26 mW/kg for TDMA signal. Both signals at SARs of 2.4 and 2.6 mW/kg induced a statistically significant decrease in DNA damage after exposure for 2 and 21 h total incubation time but exposure to the iDEN signal at SAR of 24 mW/kg produced a significant increase in DNA damage after 2 h and 21 h total incubation times. In contrast, after 2 h total incubation time, the TDMA signal at SAR of 26 mW/kg induced a statistically significant decrease in DNA damage compared to control cells. The noted effects are probably not directly associated to DNA itself, but rather an effect on DNA repair mechanisms.

Schirmacher et al (2000) investigated in vitro a model of BBB (blood-brain-barrier) sucrose permeability in rat astrocytes and porcine brain capillary endothelial cells (BCEC) exposed to a 1 800 MHz GSM signal. The samples were exposed for 4 days and the overall average SAR was 0.3 W/kg. The permeability of the samples was monitored over four days and compared with the control unexposed samples. The permeability of the exposed samples increased faster during the observation time. Within four days, the sucrose permeability increased by a factor of three, whereas control values rose only slightly.

Litovitz et al (1997a) showed that exposure of L929 murine fibroblast cells to a modulated (AM at 16 or 60 Hz) 835 MHz field, at SAR of 2.5 W/kg, could transiently alter ornithine decarboxylase. The ODC activity reached a peak at 8 h of exposure (biologically plausible) and returned to control levels after 24 h of exposure. Other types of modulated signals (speech, analog phone, 60 Hz frequency modulated) did not elicit any change in ODC activity. Under almost equal conditions, Litovitz et al (1997b) found that a superimposed ELF field (30-100 Hz, 2-10 µT) inhibits the ODC response to microwave signals. Apparently, the nature of the signal is of importance. Furthermore, due to the transient effect, the biological system seems to adapt to the external factor.

Table I. Cellular studies

Reference	**Research object**	**Exposure time and "Dose"**	Effect of exposure
Donnellan et al. 1997	Mast cells (RBL-2H3)	**20 min, 3 times per day for 7 days**. 835 MHz. **7 W/kg*.**	Significant alteration of cell morphology. **Dependent on exposure time**. *Personal communication
French et al. 1997	Astrocytoma cells (U-87 MG)	**20 min, 3 times per day for 7 days.** 835 MHz. **7 W/kg*.**	Altering the cell morphology and inhibiting cell proliferation. **Dependent on exposure time.** *Personal communication
Harvey et al. 1999	Human mast cells (HMC-1)	**20 min, 3 times per day for 7 days**. 864.3 MHz. **Average SAR 7.3 W/kg.**	No significant morphological effect. An increase in the amount of protein kinase C in the membrane fraction and a concomitant decrease in the cytosolic fraction. No general effect on gene expression.
Ivaschuk et al. 1997	Rat PC12 pheochromocytoma cells	**20, 40 and 60 min (20 min on/20 min off). Average SAR 2.6 mW/kg.**	No changes in c-fos mRNA levels. Significant change in c-jun transcript level after 20 min exposure to 9 mW/cm^2. No apparent SAR effect.
Kwee et al. 1998	AMA (transformed human epithelial cells) cells	**20, 30 or 40 min**. 960 MHz GSM. **SAR 0.021, 0.21 and 2.1 mW/kg**	EMF can affect cell proliferation at very low SAR values. Cell growth decreased at all three SAR values. Strongest effect 30 min after exposure.
Kwee et al. 2001	AMA (transformed human epithelial cells) cells	**20 min**. 960 MHz (GSM). **SAR 2.1 mW/kg**	Can affect Hsp70 (not significant), stronger effect on actively growing cells. The effect is most pronounced immediately after exposure and decreases with time

Reference	**Research object**	**Exposure time and ”Dose”**	Effect of exposure
Litovitz et al. 1997a	L929 murine fibroblast cells	**Between 2 and 24 h**. Modulated 835 MHz. **SAR 2.5 W/kg.**	A statistically significant effect on ODC (ornithine decarboxylase) activity after 6 h of exposure and with an activity peak after 8 h of exposure. Transient effect.
Litovitz et al. 1997b	L929 Murine fibroblast cells	**8 h**. 835 MHz respective 840 MHz. **SAR 2.5 W/kg.**	A superimposed random EMF inhibits the ODC response to the RF exposure.
Phillips et al. 1998	Molt-4 T-lymphoblastoid cells	**1, 1.67 and 10.67 h. (20 min on/20 min off)**. **Average SAR 2.4 and 24 mW/kg for iDEN 2.6 and 26 mW/kg for TDMA.**	The iDNA and TDMA RF produced similar decreases in DNA damage at SAR of 2.4 and 2.6 mW/kg. The exposure to iDEN at SAR of 24 mW/kg producd a significant increase in DNA damage **(dependent on SAR and exposure time)**. The TDMA at SAR 26 mW/kg for 2 h decrease the DNA damage.
de Pomerai et al 2000	Caenorhabditis elegans	**18 h 750 MHz CW 0.1 mW/kg**	An increase in hsp response to exposure.
Schirmacher et al. 2000	Rat astrocytes and porcine brain capillary endothelial cells (BCEC)	**4 days.** GSM 1800 MHz. **SAR 0.3 W/kg.**	A significant increase in BBB permeability **(depending on the exposure time)**.
Velizarov et al. 1999	AMA (transformed human epithelial cells)	**30 min**. 960 MHz (GSM). **SAR 2.1 mW/kg**	EMF affects the cell proliferation without heat generation.

ANIMAL STUDIES

Fritze et al (1997a) have investigated if a GSM signal has an effect on gene expression in the rat brain. Male Wistar rats were exposed for 4 hours at SAR values of 0.3 W/kg (GSM signal), 1.5 W/kg (GSM signal) or 7.5 W/kg (900 MHz continuous signal). Immediately after exposure, they found a transient and modest induction of hsp70 mRNA and c-fos mRNA after 7.5 W/kg exposure, but not at the lower exposures. Thus, the SAR value seems to have to be above a threshold level to affect the animals.

In another study, Fritze et al (1997b) found that field exposure affected the blood-brain barrier permeability for serum albumin in rats irradiated for 4 h at the highest (7.5 W/kg) SAR value. They exposed the male Wistar rats to a GSM signal or continuous microwave radiation of 900 MHz, respectively. The SAR values were 0.3 and 1.5 W/kg for the GSM signal and 7.5 W/kg for the continuous wave, respectively. At the highest SAR, a significant increase of serum albumin extravasations was detected. The barrier lesions could only be detected at the end of the microwave exposure (thus depending on the time and SAR) and were no longer visible when the animals were investigated 7 days later (a reversible effect).

A study on transgenic mice overexpressing the Eμ-Pim1 oncogene (Repacholi et al., 1997) revealed that long-term (up to 18 months) exposure to a 900 MHz signal (217 Hz repetition frequency, SAR average 0.008-4.2 W/kg) enhanced lymphoma development. The exposure regimen included two 30-minute exposures per day and can thus be considered as intermittent. Furthermore, the study is performed on a specifically senistive animal, since the Eμ-Pim1 gene expression causes lymphoma-prone individuals. It thus raises the question if there is especially sensitive individuals within a population.

Adey et al (1999) exposed (included fetal exposure) Fischer rats to 836 MHz modulated microwaves (TDMA) for 22 months, 2 hrs/day, 4 days per week, at SAR between 1.0-1.6 W/kg. No evidence of tumorigenic effects in the central nervous system (CNS) was found due to exposure. The result was the same in a second study (Adey et al 2000), where they investigated if a frequency-modulated microwave field of 836.55 MHz has an effect on spontaneous tumorigenicity of CNS tumors in the offspring of pregnant rats exposed for 2 years, 24 hrs/day, 4 days per week, at the SARs of 1.0 (female) and 1.2 W/kg (male).

Persson et al (1997) demonstrated that microwave exposure produced a distinct effect on the BBB in rats. In their investigation, male and female Fischer 344 rats were exposed to microwaves of 915 MHz (CW and PW) at different SAR values from 2 to 960 min. The frequency of pathological rats was significantly different from the control, and the number of pathological rats after exposure to PW was significantly less than after exposure to CW. The SAR values used in this investigation were from 0.1 mW/kg to 8.3 W/kg. The most interesting finding was the BBB-permeability for albumin in rats exposed at SAR values between 0.4-8 mW/kg. Although the SAR values are very low, this group includes the highest fraction of pathological findings recorded in the entire investigation. Grouping the animals according to the level of specific absorbed energy (J/kg), normally referred to as “Specific Absorption” (SA), gave a significant difference at all levels of absorbed energy above 1.5 J/kg, compared to control.

Tattersall et al (2001) showed that acute exposure (5 to 15 min) to 700 MHz electromagnetic fields (CW) could produce significant changes in evoked and spontaneous electrical activity in hippocampal slices although there was no detectable increases in temperature. They found that at low intensities, the predominant effect was a potentiation of the amplitude of the evoked population spike by up to 20%, but higher intensity fields could produce either increases or decreases of up to 80% in the amplitude of the population spike. The maximum field intensity used in their experiment was calculated to produce a SAR of 1.6-4.4 mW/kg, thus well below levels that would produce thermal heating. The effect is discussed in connection with the effects seen in human volunteer studies on brain function and electrical activity.

Table II. Animal studies

Reference	Research object	Exposure time and ”Dose”	Effect of exposure
Adey et al. 1999	Pregnant Fischer 344 rats.	2 hrs/day, 4 days per week for 22 months. 836.55 MHz. **SAR between 1.0 and 1.6 W/kg.**	No tumorigenic effects in the CNS.
Adey et al. 2000	Fischer 344 rats.	2hrs/day, 4days/week for 2 years. 836.55 MHz. **SAR 1.0 W/kg (females) or 2.2 W/kg (males)**.	No tumorigenic effects in the CNS.
Fritze et al. 1997a	Male Wistar rats.	**4 h.** **SAR 0.3, 1.5 W/kg (GSM) and 7.5 W/kg (continuous exposure).**	No significant effect on gene expression in the rat brain.
Fritze et al. 1997b	Male Wistar rats	**4 h.** GSM. **SAR 0.3, 1.5 W/kg (GSM) and 7.5 W/kg (continuous exposure).**	**Effects dependent on SAR.** The BBB permeability is significantly affected only at a SAR of 7.5 W/kg. A reversible effect.
Imaida et al. 1998	Male F344 rats.	**90 min/day, 5 days per week for 6 weeks.** 929.2 MHz. **SAR 1.7-2.0 W/kg.**	No effect on rat lever carcinogenesis. **No time related effect.**

Reference	Research object	Exposure time and ”Dose”	Effect of exposure
Persson et al 1997	Fischer 344 rats.	**From 2 to 960 min.** 915 MHz pulsed and continuous exposure. **SAR 0.4-8 mW/kg, 20-100mW/kg, 110-950 mW/kg, 1.7-8.3 W/kg**	Significant increase in BBB permeability. The frequency of pathological rats is significant in all levels of absorbed energy above 1.5 J/kg **SAR dependent effects.**
Repacholi et al 1997	Transgenic mice	**GSM 900 SAR 0.008-4.2 W/kg 30 min two times per day 18 months**	Lymphoma risk significantly higher in exposed group OR=2.4, 95%CI:1.3-4.5
Tattersall et al 2001	Male porton strain wistar rats	**5-15 min 700 MHz CW RF SAR 1.6-4.4 mW/kg**	Modulation of the excitability of hippocampal tissue in vitro.

HUMAN STUDIES

The literature contains few studies on human subjects investigated in a laboratory setting. The papers include work on neurological and behavioural parameters, as well as on endocrine end-points. Unfortunately, most do not report the SAR values and time dependent observations in the studies.

Koivisto et al (2000a,b) and Krause et al (2000 a,b) have in their studies used a 902 MHz GSM signal on a number of healthy subjects. They have studied reaction time (Koivisto et al. 2000a), working memory (Krause et al., 2000a), auditory memory (Koivisto et al 2000b), and brain oscillatory activity (Krause et al 2000b).

In the first paper (Koivisto et al, 2000a) they observed that exposure to EMF emitted by cellular phones have a facilitating effect on brain function, especially in tasks requiring attention and manipulation of information in working memory. The results showed that exposure speeded up response time in simple reaction time and vigilance tasks, and that the cognitive time needed in a mental arithmetic's task was decreased. Similar results have been reported by Preece et al (1999).

Krause et al (2000a) also investigated the effects of a mobile phone signal (no SAR value given) on the performance of 48 subjects in an n-back working memory task. In line with the previous study, this study suggests that RF fields may have measurable influences on human brain function and cognition. The results from the n-back task showed that response time to target letters were speeded up (only in the 3-back condition) when the RF exposure was on. No effects on the accuracy of performance were observed.

In another study, Koivisto et al (2000b) found that GSM phones caused an increase in brain electric oscillations during cognitive processing. The effects were studied in 16 normal subjects who performed an auditory memory task both with and without exposure to a digital 902 MHz EMF in counterbalanced order. The exposure time was 30 min and no SAR value was calculated. In a similar study, Krause et al (2000b), reported that exposure to a GSM signal at SAR of <2 W/kg for ~60 min, have significant effects on human brain oscillatory activity (~8 Hz), especially during mental processes requiring attention.

Ullsperger et al (1998) demonstrated that PEMF might alter the brains electrical response to acoustic stimuli, Kellenyi et al (1999) reported a significant effect of the GSM on the V latency on the exposed side, and Huber et al (1999) observed that GSM signal at SAR <1 W/kg significantly reduced the duration of waking after sleep onset and affected the EEG in non-REM sleep. Lebedeva et al (1999) found that the GSM signal affects the sleep structure and reduce slow-wave and REM-stage sleep percentage.

Other studies have shown that RF could slightly affect secretion of the antepituitary hormones in humans (Radon et al 2001), slightly alter the waking after sleep onset, sleep latency and sleep quality (Borbely et al 2000), alter (not significantly) the conventional sleep parameters and EEG (Röschke et al 1999).

Grigoriev et al (1999) studied the effect of three different type of phones - NMT 450, GSM 900 and GSM 1800 – on the bioelectric activity of the brain of human volunteers. Both the NMT 450 and the GSM 900 gave significantly increased activity in the alpha region, wheras GSM 1800 did not elict any response. The first observation was done after five minutes of exposure and the effect did not increase with time (10 or 30 min of exposure) and the effect persisted 15-20 min after completion of the exposure. No SAR values are given.

Table III. Human studies

Reference	Research object	Exposure time and "Dose"	Effect of exposure
Borbely et al. 2000	16 healthy males.	**30 min.** GSM 900 MHz. **SAR 0.14 W/kg.**	No significant effects on the waking after sleep onset, sleep latency, or sleep quality. Effects are transitory and restricted to the initial part of sleep.
Eulitz et al. 1998	13 healthy male volunteers.	Exposure during an auditory discrimination task. GSM. **No SAR value.**	Alteration of specific aspects of the brain electrical response to task-relevant stimuli.
Grigoriev et al. 1999	10 healthy men.	**20 min** **NMT 450, GSM 900 GSM 1800**	Significant changes in EEG spectra, mainly alpha region. Effect seen after 5 min exposure, persisted 20 min after exposure.
Huber et al. 1999	24 healthy males.	**15 min on/off during night (23^{00}-07^{00} h).** GSM 900 MHz. **Max SAR 1 W/kg.**	Reduces significantly the duration of waking after sleep onset. Affect the EEG in non-REM sleep.
Kellenyi et at. 1999	10 healthy volunteers (7 men and 3 women)	15 min. GSM. **No SAR value.**	Affects significantly the V latency on the exposed side.
Koivisto et al. 2000 a	48 healthy volunteers (24 men and 24 women).	**1 h**. GSM 902 MHz. **No SAR value.**	A facilitating effect on cognitive processing, especially in tasks that require attention or cognitive manipulation in working memory.
Koivisto et al. 2000 b	48 healthy volunteers (24 men and 24 women)	**30 min**. GSM 902 MHz. No SAR value.	The response time shortened during the RF exposure. No effects on the accuracy of performance.
Krause et al. 2000 a	16 healthy volunteers (8 men and 8 women).	**30 min**. GSM 902 MHz. **No SAR value.**	Significant effects on brain electric oscillation in the 8-10 Hz frequency band.
Krause et al. 2000 b	24 healthy volunteers (12 men and 12 women).	**~60 min**. GSM 902 MHz. **SAR <2 W/kg**	EMF seems to have significant effects on brain oscillatory activity at ~8 Hz, specifically during cognitive processes.

Reference	Research object	Exposure time and ”Dose”	Effect of exposure
Preece et al. 1999	36 healthy volunteers (18 men and 18 women)	Exposure during a series of cognitive function tests lasting ~25-30 min. 915 MHz. **No SAR value.**	Effect on cognitive function. A trend for faster simple reaction times.
Radon et al. 2001	Eight 20 to 30-year-old healthy male students.	GSM 900 MHz. **Twenty 4 h sessions. Maximum local SAR in the head 0.025 W/kg.**	No significant effects on the salivary concentrations of melatonin, cortisol, neopterin and sIgA.
Röschke et al. 1997	34 healthy male volunteers.	3.5 min. GSM **No SAR value.**	No effects on the awake human EEG.
de Seze et al. 1998	Twenty healthy male volunteers aged from 19 to 40 years.	**2 h per day, 5 days per week for 4 weeks.** GSM. **No SAR value.**	No effects on the secretion of the antepituitary hormones.
Wagner et al. 2000	20 healthy men.	**During one night.** 900 MHz. **SAR<2 W/kg.**	No significant effects on the conventional sleep parameters and EEG.

DISCUSSION

A number of papers have documented various biological effects in cellular systems due to RF exposure, including exposure to mobile phone-like signals. It is difficult, however, to see a pattern in terms of common exposure parameters that cause a specific effect. Thus, Kwee and co-workers have consistently employed a GSM signal (960 MHz) at low SAR values. They report proliferation related effects already at 0.021 W/kg, and higher, after very short exposure times. The specific absorption (SA) would thus be very low. In contrast, papers from French and co-workers use very high SAR levels (several W/kg), and repeated exposures over long time, summing up to high SA values. Irrespective of experimental end-point, the approach in these two cases is very dissimilar, one arguing for effective low-level one-time exposures, whereas the other argues for a cumulative effect of exposure.

Other experimentalists have also seen responses at low SAR-levels. A case in point is the innovative studies by de Pomerai (2000) who used a genetically modified nematode with a hsp promoter-coupled reporter gene. This paper suggests that low SAR values impose a stress on the organism, leading to increased expression of heat shock proteins. The idea is compelling, and definitively worthwhile exploring further. Also Kwee et al. (2001) claimed effects along that line.

The importance of modulation and also a transient effect of exposure is shown in the papers by Litovitz et al (1997a,b). Only the amplitude modulated 835 MHz signal was effective. Furthermore, these studies suggest a cumulative effect up to a point. In summary, the in vitro studies suggest the possibility of biological responses at low SAR-values, although no study systematically has looked for thresholds where effects start to occur.

In certain of the animal studies, the SAR dependency is illustrated. Thus, Fritze et al. (1997a,b) indicate a threshold level during a 4 hr exposure to a GSM or continuous 900 MHz signal. Their results suggest that gene expression changes and effects on blood-brain-barrier permeability occur above 1.5 W/kg. However, the latter phenomenon has been shown to occur at lower SAR values (mW/kg range) according to Persson et al (1997). Furthermore, the paper discusses SA as dose, and indicates at threshold for effects to occur. However, there is no apparent classical dose response in their study.

The above mentioned studies include responses that demand processes on an hour scale, whereas Tattersall et al (2001) at low SAR values (mW/kg) demonstrated acute (minutes) effects on brain parameters. These findings are also in line with certain human studies, where acute effects on brain function at probably low SAR values are reported. These papers are typically employing a GSM signal for 30-60 minutes, mostly without disclosing any SAR values. There are furthermore no studies of the time dependency in these works. The most important finding is that a common GSM signal can affect the activities of the brain. Nothing is known of the possible reversibility of the effects. In general, the papers on human effects have to be considered to encourage additional research, with the dose question in focus.

When going through a substantial number of papers relevant for our questions regarding dose in the context of RF exposure, it becomes apparent that few papers have addressed this concept. Mainly, the literature contains examples of biological effects, that in several cases have to occur at non-thermal levels of exposure. Some of the papers indicate a SAR dependency, and a possible threshold level, but even this very basic question remains to be studied systematically. The other obvious aspect of dose, the time in connection with SAR, is neither studied with that in mind. The occasional finding suggests that SA might be appropriate, but additional studies are needed to clear this up.

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REFERENCES

Adey WR, Byus CV, Cain CD, Higgins RJ, Jones RA, Kean CJ, Kuster N, MacMurray A, Stagg RB, Zimmerman G, Phillips JL, Haggren W. Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats chronically exposed to 836 MHz modulated microwaves. *Radiation Research 152:293-302 (1999)*

Adey WR, Byus CV, Cain CD, Higgins RJ, Jones RA, Kean CJ, Kuster N, MacMurray A, Stagg RB, Zimmerman G. Spontaneous and nitrosourea-induced primary tumors of the CNS in Fischer 344 rats exposed to frequency-modulated microwave fields. *Cancer Research 60: 1857-1863 (2000)*

Borbely AA, Huber R, Graf T, Cote KA., Wittmann L, Gallmann E, Matter D, Schuderer J, Kuster N, Achermann P. Exposure to pulsed high-frequency EMF during waking affects human sleep EEG. *NeuroReport, 11:3321-3325 (2000)*

Donnellan M, McKenzie DR, French PW. Effects of exposure to electromagnetic radiation at 835 MHz on growth, morphology and secretory characteristics of a mast cell analogue, RBL-2H3. *Cell Biology International, 21:427-439 (1997)*

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

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

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 81:627-639 (1997a)*

Fritze K, Sommer C, Schmitz B, Mies G, Hossmann KA, Kiessling M, Wiessner C. Effect of global system for mobile communication (GSM) microwave exposure on BBB permeability in rat. Acta *Neuropathologica 94:465-470 (1997b)*

Grigoriev YG,Lukyanova SN, Rynskov VV, Grigoriev OA, Makarov VP, Polyntev YV. Human response to the electromagnetic radiation from cellular telephones. *In Proceedings of the International Meeting "Electromagnetic Fields: Biological Effects and Gygienic Standardization". Moscow 18-22 May 1998. Eds MH Repacholi, NB Rubtsova, AM Muc, WHO Geneva, 1999, pp 501-512.*

Harvey C, French PW. Effects on protein kinase C and gene expression in a human mast cell line, HMC-1, following microwave exposure. *Cell Biology International, 23:739-748 (1999)*

Huber R, Borbely AA, Graf T, Fuchs B, Gallmann E, Achermann P. Pulsed high-frequency EMF affects human sleep and sleep EEG. *Neuroscience Letters, 275:207-210 (1999)*

Imaida K, Taki M, Yamaguchi T, Ito T, Watanabe S-i, Wake K, Aimoto A, Kamimura Y, Ito N, Shirai T. Lack of promoting effects on the electromagnetic near field used for cellular phones (929.2 MHz) on rat liver carcinogenesis in a medium-term liver bioassay. *Carcinogenesis, 19:311-314 (1998)*

Ivaschuk OI, Jones RA, Ishida-Jones T, Haggren W, Adey RW, Phillips JL. Exposure of nerve growth factor-treated PC12 rat pheochromocytoma cells to a modulated radio frequency field at 836.55 MHz: Effect on c-jun and c-fos expression. *Bioelectromagnetics, 18:223-229 (1997)*

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

Koivisto M, Revonsuo A, Krause C, Haarala C, Sillanmäki L, Laine M, Hämäläinen H. Effects of 902 MHz EMF emitted by cellular telephones on response time in human. *NeuroReport, 11:413-415 (2000a)*

Koivisto M, Krause C, Revonsuo A, Laine M, Hämäläinen H. The effect of electromagnetic field emitted by GSM phones on working memory. *NeuroReport, 11:1641-1643 (2000b)*

Krause C, Koivisto M, Sillanmäki L, Häggqvist A, Saarela C, Revonsuo A, Laine M, Hämäläinen H. Effects of EMF emitted by cellular phones on the EEG during a memory task. *NeuroReport,11:761-764 (2000a)*

Krause CM, Koivisto M, Sillanmäki L, Häggqvist A, Saarela C, Revonsuo A, Laine M, Hämäläinen H. Effect of EMF emitted by cellular phones on the EEG during a visual working memory task. Int J *Radiat.Biol. 76:1659-1667 (2000b).*

Kwee S, Raskmark P. Changes in cell proliferation due to environmental non-ionising radiation 2. Microwave radiation. *Bioelectrochemistry and Bioenergetics, 48:251-255 (1998)*

Kwee S, Raskmark P, Velizarov S. Changes in cellular proteins due to environmental non-ionising radiation HS proteins. *Electro and magnetobiology, 20:141-152 (2001)*

Lebedeva NN, Sulimov AV, Sulimova OP, Korotkovskaya TI, Galius T. Investigation of brain potentials in sleeping humans exposed to the EMF of mobile phones. *Critical Reviews™ in Biomedical Engineering, 125-133 (2001)*

Lee TMC, Ho SMY, Tsang YH, Yang SYC, Li LSW, Chan CCH. Effect on human attention of exposure to the EMF emitted by mobile phones. *NeuroReport, 12:729-731 (2001)*

Litovitz T, Penafiel LM, Krause D, Desta A, Mullins JM. Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929 cells. *Bioelectromagnetics, 18:132-141 (1997a)*

Litovitz T, Penafiel M, Farell JM, Krause D, Meister R, Mullins JM. Bioeffects induced by exposure to microwaves are mitigated by superposition of ELF noise. *Bioelectromagnetics, 18:422-430 (1997b)*

Persson BRR, Salford LG, Brun A. BBB permeability in rats exposed to EMF used in wireless communication. *Wireless Networks, 3:455-461 (1997)*

Phillips JL, Ivaschuk OI, Jones RA, Ishida-Jones T, Haggren W. DNA damage in Molt-4 T-lymphoblastoid cells exposed to cellular telephone radio frequency fields in vitro. *Bioelectrochemistry and Bioenergetics, 45:103-110 (1998)*

de Pomerai D, Daniells C, David H, Allan J, Duce I, Mutwakil M, Thomas D, Jones D, Tattersall J, Sewell P, Candido P. Non-thermal heat-shock response to microwave**.** *Nature, 405:417-418 (2000)*

Preece AW, Iwi G, Davies-Smith A, Wesnes K, Butler S, Lim E, Varey A. Effect of a 915-MHz simulated mobile phone signal on cognitive function in man. *International Journal of Radiation Biology, 75:447-456 (1999)*

Radon K, Parera D, Rose DM, Jung D, Vollrath L. No effects of pulsed radio frequency EMF on melatonin, cortisol and selected markers of the immune system in man. *Bioelectromagnetics, 22: 280-287 (2001)*

Repacholi MH, Basten A, Gebski V, Noonan D, Finnie J, Harris AW. Lymphomas in Eμ-Pim1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields. *Radiation Research 147: 631-640 (1997*

Röschke J, Mann K. No short-term effects on digital mobile radiophone on the awake human electroencephalogram. *Bioelectromagnetics, 18:172-176 (1997)*

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

de Seze R, Fabbro-Peray P, Luis M. GSM radio cellular telephones do not disturb the secretion of antepituitary hormones in humans. *Bioelectromagnetics, 19:271-278 (1998)*

Tattersall J, Scott I, Wood S, Nettell J, Bevir M, Wang Z, Somasiri N, Chen X. Effects of low intensity radiofrquency electromagnetic fields on electrical activity in rat hippocampal slices. *Brain Research 904:43-53 (2001)*

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

Wagner P, Röschke J, Mann K, Fell J, Hiller W, Frank C, Grözinger M. Human sleep EEG under the influence of pulsed radio-frequency electromagnetic fields**.** Results from polysomnographies using submaximal high power flux densities. *Neuoropsychobiology 42:207-212 (2000)*