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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

CTIA – THE WIRELESS ASSOCIATION®,

Plaintiff,

vs.

THE CITY AND COUNTY OF SAN FRANCISCO, CALIFORNIA,

Defendant.

Case No. C10-03224 WHA

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Hearing Date: October 20, 2011
Time: 8:00 a.m.
Place: Courtroom 9, 19th Floor

Date Action Filed: July 23, 2010
Trial Date: None set

Pursuant to Rule 201 of the Federal Rules of Evidence, Defendants hereby request that the Court take judicial notice of the following documents, each of which is taken from taken from San Francisco Board of Supervisors Legislative File No. 110656 (Ordinance No. 165-11):

Exhibit A: Letter from Melanie Nutter, Director of the San Francisco Department of the Environment, to the Clerk of the San Francisco Board of Supervisors, Dated June 9, 2011.

Exhibit B: Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, et al. 2009. Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. Fertil Steril: in press.

Exhibit C: Cardis E, Deltour I, Mann S, Moissonnier M, Taki M, Varsier N, et al. 2008. Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. Phys Med Biol 53(11): 2771-83.

Exhibit D: Conil E, Hadjem A, Lacroux F, Wong MF, Wiart J. 2008. Variability analysis of SAR from 20 MHz to 2.4 GHz for different adult and child models using finite-difference time-domain. Phys Med Biol 53(6): 1511-25.

Exhibit E: De Iuliis GN, Newey RJ, King BV, Aitken RJ. 2009. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. PLoS One 4(7): e6446.

Exhibit F: de Salles AA, Bulla G, Rodriguez CE. 2006. Electromagnetic absorption in the head of adults and children due to mobile phone operation close to the head. Electromagn Biol Med 25(4): 349-60.

Exhibit G: Divan HA, Kheifets L, Obel C, Olsen J. 2008. Prenatal and postnatal exposure to cell phone use and behavioral problems in children. Epidemiology 19(4): 523-9.

Exhibit H: Erogul O, Oztas E, Yildirim I, Kir T, Aydur E, Komesli G, et al. 2006. Effects of electromagnetic radiation from a cellular phone on human sperm motility: an in vitro study. Arch Med Res 37(7): 840-3.

Exhibit I: Fejes I, Zavaczki Z, Szollosi J, Koloszar S, Daru J, Kovacs L, et al. 2005. Is there a relationship between cell phone use and semen quality? Arch Androl 51(5): 385-93.

Exhibit J: Gandhi OP, Lazzi G, Furse CM. 1996. Electromagnetic absorption in the human head and neck for mobile telephones at 835 and 1900 MHz. IEEE Transactions on Microwave Theory and Techniques 44(10): 1884 - 97.

Exhibit K: Gandhi OP, Kang G. 2002. Some present problems and a proposed experimental phantom for SAR compliance testing of cellular telephones at 835 and 1900 MHz. Phys Med Biol 47(9): 1501-18.

Exhibit L: Hardell L, Carlberg M, Hansson Mild K. 2005. Use of cellular telephones and brain tumour risk in urban and rural areas. Occup Environ Med 62(6): 390-4.

Exhibit M: Hardell L, Carlberg M, Hansson Mild K. 2006a. Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997-2003. Int J Oncol 28(2): 509-18.

Exhibit N: Hardell L, Carlberg M, Hansson Mild K. 2006. 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 79(8): 630-9.

Exhibit O: Hardell L, Carlberg M, Hansson Mild K. 2009. Epidemiological evidence for an association between use of wireless phones and tumor diseases. Pathophysiology: in press.

Exhibit P: Hardell L, Mild KH, Carlberg M. 2003. Further aspects on cellular and cordless telephones and brain tumours. Int J Oncol 22(2): 399-407.

Exhibit Q: Hours M, Bernard M, Montestrucq L, Arslan M, Bergeret A, Deltour I, et al. 2007. [Cell Phones and Risk of brain and acoustic nerve tumours: the French INTERPHONE case-control study]. Rev Epidemiol Sante Publique 55(5): 321-32.

Exhibit R: INTERPHONE Study Group. 2010. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case–control study. International Journal of Epidemiology 2010; 1–20.

Exhibit S: Kheifets L, Repacholi M, Saunders R, van Deventer E. 2005. The sensitivity of children to electromagnetic fields. Pediatrics 116(2): e303-13.

Exhibit T: Kundi M. 2009. The Controversy about a Possible Relationship between Mobile Phone Use and Cancer. Environ Health Perspec 117(3): 316-24.

Exhibit U: Lahkola A, Auvinen A, Raitanen J, Schoemaker MJ, Christensen HC, Feychting M, et al. 2007. Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer 120(8): 1769-75.

Exhibit V: Lee KS, Choi JS, Hong SY, Son TH, Yu K. 2008. Mobile phone electromagnetic radiation activates MAPK signaling and regulates viability in Drosophila. Bioelectromagnetics 29(5): 371-9.

Exhibit W: Lonn S, Ahlbom A, Hall P, Feychting M. 2004. Mobile phone use and the risk of acoustic neuroma. Epidemiology 15(6): 653-9.

Exhibit X: Martinez-Burdalo M, Martin A, Anguiano M, Villar R. 2004. Comparison of FDTD-calculated specific absorption rate in adults and children when using a mobile phone at 900 and 1800 MHz. Phys Med Biol 49(2): 345-54.

Exhibit Y: Mild KH, Hardell L, Carlberg M. 2007. 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. Int J Occup Saf Ergon 13(1): 63-71.

Exhibit Z: NRC. 2008. National Research Council. Identification of Research Needs Relating to Potential Biological or Adverse Health Effects of Wireless Communication.

Exhibit AA: Sadetzki S, Chetrit A, Jarus-Hakak A, Cardis E, Deutch Y, Duvdevani S, et al. 2008. Cellular phone use and risk of benign and malignant parotid gland tumors--a nationwide case-control study. Am J Epidemiol 167(4): 457-67.

Exhibit BB: Salama N, Kishimoto T, Kanayama HO. 2009. Effects of exposure to a mobile phone on testicular function and structure in adult rabbit. Int J Androl: in press.

Exhibit CC: Sato Y, Akiba S, Kubo O, Yamaguchi N. 2011. A Case-Case Study of Mobile Phone Use and Acoustic Neuroma Risk in Japan. Bioelectromagnetics 32:85-93 (2011).

Exhibit DD: Saravi FD. 2011. Asymmetries in hip mineralization in mobile cellular phone users. J Craniofac Surg 22(2): 706-10.

Exhibit EE: Schoemaker MJ, Swerdlow AJ, Ahlbom A, Auvinen A, Blaasaas KG, Cardis E, et al. 2005. Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. Br J Cancer 93(7): 842-8.

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

Exhibit GG: Schuz J, Bohler E, Berg G, Schlehofer B, Hettinger I, Schlaefer K, et al. 2006. Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone Study Group, Germany). Am J Epidemiol 163(6): 512-20.

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

Exhibit II: Wang J, Fujiwara O. 2003. Comparison and Evaluation of Electromagnetic Absorption Characteristics in Realistic Human Head Models of Adult and Children for 900-MHz Mobile Telephones IEEE Transactions on Microwave Theory and Techniques 51(3): 966-70.

Exhibit JJ: Wiart J, Hadjem A, Wong MF, Bloch I. 2008. Analysis of RF exposure in the head tissues of children and adults. Phys Med Biol 53(13): 3681-95. Wiedemann PM, Schutz H, Clauberg M. 2008. Influence of information about specific absorption rate (SAR) upon customers' purchase decisions and safety evaluation of mobile phones. Bioelectromagnetics 29(2): 133-44.

Exhibit KK: Yan JG, Agresti M, Bruce T, Yan YH, Granlund A, Matloub HS. 2007. Effects of cellular phone emissions on sperm motility in rats. Fertil Steril 88(4): 957-64.

Dated: October 7, 2011

DENNIS J. HERRERA
City Attorney
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By: /s/ Vince Chhabria
VINCE CHHABRIA

Attorneys for Defendant
CITY AND COUNTY OF SAN FRANCISCO

EXHIBIT A

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

SF Environment
Our home. Our city. Our planet.
A Department of the City and County of San Francisco

EDWIN LEE
Mayor

MELANIE NUTTER
Director

June 9, 2011

Angela Calvillo
Clerk of the Board
1 Dr. Carlton B. Goodlett Place
City Hall, Room 244
San Francisco, Ca. 94102-4689

Regarding File No. 110656

I have enclosed for the Board's consideration copies of the following studies, which indicate a possible link between cell phone use and adverse health effects:

Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, et al. 2009. Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. Fertil Steril: in press.

BioInitiative. 2007. BioInitiative Report: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF). Available: http://www.bioinitiative.org/ report/index.htm [accessed January 27, 2009].

Cahill DF. 1983. A suggested limit for population exposure to radiofrequency radiation. Health Phys 45(1): 109-26.

Cardis E, Deltour I, Mann S, Moissonnier M, Taki M, Varsier N, et al. 2008. Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. Phys Med Biol 53(11): 2771-83.

Cardis, E, Sadetzi, S. 2011. Indications of possible brain-tumour risk in mobile-phone studies: should we be concerned? Occup. Environ. Med. 68(3): 169-71.

Conil E, Hadjem A, Lacroux F, Wong MF, Wiart J. 2008. Variability analysis of SAR from 20 MHz to 2.4 GHz for different adult and child models using finite-difference time-domain. Phys Med Biol 53(6): 1511-25.

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Fejes I, Zavaczki Z, Szollosi J, Koloszar S, Daru J, Kovacs L, et al. 2005. Is there a relationship between cell phone use and semen quality? Arch Androl 51(5): 385-93.

Gandhi OP, Lazzi G, Furse CM. 1996. Electromagnetic absorption in the human head and neck for mobile telephones at 835 and 1900 MHz. IEEE Transactions on Microwave Theory and Techniques 44(10): 1884 - 97.

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Russian National Committee on Nonionizing Radiation Protection. 2011 Electromagnetic Fields from Mobile Phones: Health Effect on Children and Teenagers

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Wang J, Fujiwara O. 2003. Comparison and Evaluation of Electromagnetic Absorption Characteristics in Realistic Human Head Models of Adult and Children for 900-MHz Mobile Telephones IEEE Transactions on Microwave Theory and Techniques 51(3): 966-70

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Wiedemann PM, Schutz H, Clauberg M. 2008. Influence of information about specific absorption rate (SAR) upon customers' purchase decisions and safety evaluation of mobile phones. Bioelectromagnetics 29(2): 133-44

Yan JG, Agresti M, Bruce T, Yan YH, Granlund A, Matloub HS. 2007. Effects of cellular phone emissions on sperm motility in rats. Fertil Steril 88(4): 957-64

With sincere thanks,

Melanie Nutter

Melanie Nutter
Director, San Francisco Department of Environment

EXHIBIT B

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study

Ashok Agarwal, Ph.D., Nisarg R. Desai, M.D., Kartikeya Makker, M.D., Alex Varghese, Ph.D., Rand Mouradi, M.S., Edmund Sabanegh, M.D., and Rakesh Sharma, Ph.D.

Center for Reproductive Medicine, Glickman Urological and Kidney Institute, Obstetrics and Gynecology, and Women's Health Institute, Cleveland Clinic, Cleveland, Ohio

Objective: To evaluate effects of cellular phone radiofrequency electromagnetic waves (RF-EMW) during talk mode on unprocessed (neat) ejaculated human semen.
Design: Prospective pilot study.
Setting: Center for reproductive medicine laboratory in tertiary hospital setting.
Samples: Neat semen samples from normal healthy donors (n = 23) and infertile patients (n = 9).
Intervention(s): After liquefaction, neat semen samples were divided into two aliquots. One aliquot (experimental) from each patient was exposed to cellular phone radiation (in talk mode) for 1 h, and the second aliquot (unexposed) served as the control sample under identical conditions.
Main Outcome Measure(s): Evaluation of sperm parameters (motility, viability), reactive oxygen species (ROS), total antioxidant capacity (TAC) of semen, ROS-TAC score, and sperm DNA damage.
Result(s): Samples exposed to RF-EMW showed a significant decrease in sperm motility and viability, increase in ROS level, and decrease in ROS-TAC score. Levels of TAC and DNA damage showed no significant differences from the unexposed group.
Conclusion(s): Radiofrequency electromagnetic waves emitted from cell phones may lead to oxidative stress in human semen. We speculate that keeping the cell phone in a trouser pocket in talk mode may negatively affect spermatozoa and impair male fertility. (Fertil Steril® 2008; ■: ■–■. ©2008 by American Society for Reproductive Medicine.)

Key Words: Cell phone radiation, radiofrequency electromagnetic waves, sperm, fertility, reactive oxygen species, oxidative stress, EMW

The tremendous development and use of mobile telecommunication services in the last decade has drastically increased the amount of radiofrequency electromagnetic wave (RF-EMW) exposure in our daily lives. As the use of cell phones has increased, so have concerns regarding the harmful effects of cell phone exposure on human health. As part of its charter to protect public health, the World Health Organization (WHO) established the International EMF Project in 1996 to assess the scientific evidence of possible health effects of electromagnetic frequencies in the range of 30 Hz to 300 GHz (1). Despite more than a decade of research in this field, the potential harmful effects of cell phone radiation remain controversial.

Recent epidemiologic (cross-sectional or prospective) studies have highlighted the role of cell phone exposure on sperm motility, morphology, and viability, suggesting a reduction in male fertilization potential (2–6). These studies examined the relationship of cell phone use and its effect on semen parameters and concluded that mobile phone use may cause a decrease in fertility (2–6). To conduct a scientifically robust epidemiologic study, a control group of people who are not using and have not used cell phones in the past is a necessity. However, enrolling a pool of such control subjects in today's culture is extremely difficult. An in vivo human exposure study to investigate the effects of cell phone radiation on semen parameters is not feasible, owing to ethical issues.

Various in vitro studies using animal models have consistently demonstrated oxidative stress in different tissues (kidney, endometrium, eye, testis, brain, myocardial tissue, and so on) in response to cell phone radiation (7–13). Studies have also shown potential beneficial effects of antioxidants, such as melatonin, vitamin C, and vitamin E, on oxidative stress status induced by RF-EMW in animals (7, 8, 12, 13). However, results of animal studies related to the effects of cell phone radiation on reproductive functions are conflicting (14–19). An animal model is not preferable for study purposes for several reasons, including the smaller dimensions of the testes, the nonpendulous scrotum, the free migration

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A.A. has nothing to disclose. N.D. has nothing to disclose. K.M. has nothing to disclose. A.V. has nothing to disclose. R.M. has nothing to disclose. E.S. has nothing to disclose. R.S. has nothing to disclose.
Supported by the Center for Reproductive Medicine, Cleveland Clinic.
Reprint requests: Ashok Agarwal, Ph.D., H.C.L.D., Professor and Director, Center for Reproductive Medicine, Cleveland Clinic, 9500 Euclid Avenue, Desk A19.1, Cleveland, OH 44195 (FAX: 216-636-3118, 216-445-6049; E-mail: Agarwaa@ccf.org).

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of the testes through the inguinal canal between the abdomen and the scrotum and the unavoidable exposure of the animal's entire body to RF-EMW at the time of the experiment (7, 20). Therefore, an in vitro model would be the most scientific way to assess the effects of cell phone exposure, allowing us to obtain reproducible results that can be replicated by in vivo studies. The World Health Organization's recent research agenda (2006) for studies on RF suggests that in vitro studies play a supporting role in health risk assessments and are critical to the optimal design of animal and epidemiology studies (21).

There are reports of exposure of human semen samples to cell phone radiation under in vitro conditions resulting in a decrease in sperm motility (neat semen) after 5 min (22). Other investigators found no effect of RF-EMW on mitochondrial membrane potential of spermatozoa and motility at a specific absorbance rate (SAR) of 2 W/kg. However, they showed a decrease in straight-line velocity and beat-cross frequency at an SAR of 5.7 W/kg (23).

We hypothesized that cell phone radiation (talk mode) disturbs free radical metabolism in human semen by increasing free radical formation, by decreasing antioxidants, or by both mechanisms. In the present pilot study, our objective was to validate the results of several recent epidemiologic studies by establishing a cause-and-effect relationship between RF radiation emitted from a cell phone in talk mode and changes in semen parameters. We tested our hypothesis by examining the effects of RF-EMW on ROS levels, total antioxidant capacity, and DNA integrity of spermatozoa in unprocessed ejaculated human semen.

MATERIALS AND METHOD

The study was approved by the Cleveland Clinic Institutional Review Board.

Subjects (Data Collection)

Semen samples were collected from 23 healthy donors and 9 patients presenting to the infertility clinic and referred to our lab. All specimens were collected by masturbation after an abstinence period of 48–72 h and allowed to liquefy completely for 15–30 min at 37 C. Following liquefaction, each sample was divided into two aliquots: control group (sample not exposed, i.e. no exposure to cell phone) and exposed group (sample exposed to cell phone radiation).

Exposure of Semen Samples to Electromagnetic Waves

One aliquot of each divided semen sample was exposed to EMW emitted from a commercially available cellular telephone in talk mode (Sony Ericsson w300i; service provider AT&T; GSM-Global System for Mobile communications network; 850 MHz frequency; maximum power <1 W; SAR 1.46 W/kg). This phone model had a loop-shape, omnidirectional antenna placed on the top back of its handset. The distance between the phone antenna and each specimen was kept at 2.5 cm. In the United States the most common frequency is 850–900. Therefore, we decided to use this frequency in this pilot study. The duration of exposure was 60 min. Unexposed (control) aliquots were kept under identical conditions but without RF-EMW exposure (6,7).

Power Density ($\mu W/cm^2$)

According to the International Commission for Non-Ionizing Radiation Protection (ICNIRP) and the Federal Communications Commission (FCC), the reference level for exposure of RF-EMW is peak power density. It is a commonly used term for characterizing an RF electromagnetic field (24, 25).

Power density was monitored during basal condition (no cell phone radiation) and experimental condition (cell phone in talk mode) in the laboratory throughout the experiment. Power density in the control condition was 0.01–0.1 $\mu W/cm^2$. Power density in the experimental condition (during cell phone in talk mode and at 2.5 cm from cell phone antenna) was 1–40 $\mu W/cm^2$.

Frequency and Temperature

The frequency emitted by the cell phone was confirmed with the help of a RF spectrum analyzer (Tektronix, Beaverton, OR). Both specimens (aliquots) were kept at room temperature to avoid the effect of temperature on ROS formation and semen parameters.

Semen Analysis

Immediately after exposure to cell phone radiation, both aliquots (control and exposed) were analyzed for sperm concentration, motility, and viability according to WHO guidelines (26).

ROS Measurement

Measurement of ROS in the exposed and unexposed aliquots was performed after 1 h by chemiluminescence assay using luminol (5-amino-2,3-dihydro-1,4-phthalazinedione; Sigma Chemical Co., St Louis, MO). A 100-mmol/L stock solution of luminol was prepared in dimethyl sulfoxide. For the analysis, 10 μL of the working solution (5 mmol/L) was added to 400 μL of neat sperm sample. Chemiluminescence was measured for 15 min using a Berthold luminometer (Autolumat LB 953; Berthold, Bad-Wildbad, Germany). Results were expressed as $\times 10^6$ counted photons per minute (cpm)/20 $\times 10^6$ sperm and as log (ROS + 0.001) (27), with the 0.001 constant chosen to achieve approximate normality for the ROS scale.

Total Antioxidant Assay (TAC) Measurement

The technique for total antioxidant (TAC) assay used in this study has been described previously (28).

This assay measures the combined antioxidant activities of all constituents, including vitamins, proteins, lipids, glutathione, uric acid, and so on. All samples were centrifuged at

1,000*g* for 10 min at 4°C. Clear seminal plasma was aliquoted and frozen at −70°C until the time of TAC assay. Seminal plasma total antioxidant measurements were performed using the antioxidant assay kit (Cat. no. 709001; Cayman Chemical, Ann Arbor, MI).

The principle of the assay is the ability of aqueous and lipid antioxidants in the seminal plasma specimens to inhibit the oxidation of 2,2′-azino-di-[3-ethylbenzthiazoline sulphonate] (ABTS) to $ABTS^{+}$. Under the reaction conditions used, the antioxidants in the seminal plasma cause suppression of the absorbance at 750 nm proportional to their concentration. The capacity of the antioxidants present in the sample to prevent ABTS oxidation was compared with that of standard Trolox, a water-soluble tocopherol analogue. Results were reported as μmoles of Trolox equivalent.

ROS-TAC Score

The ROS-TAC score was calculated as described in our earlier study (29), although ROS in the present study was measured on a different scale, requiring the use of updated values for the mean and SD of ROS in the principal component standardization. The updated equation for standardized ROS is as follows:

$$\text{Standardized ROS} = [\log(\text{ROS} + 0.001) - (-2.0238)]/0.5151$$

For TAC, we used the earlier standardization:

$$\text{Standardized TAC} = (\text{TAC} - 1650.93)\ 532.22$$

With ROS and TAC negatively correlated, as in the earlier analysis, the original linear combination derived by the first principal component of standardized variables is once again the first principal component, even with original ROS measurements on a different scale. This first principal component, which accounts for the most variability among correlated variables, is as follows:

$$\text{Principal component} = (-0.707 \times \text{standardized ROS}) + (0.707 \times \text{standardized TAC})$$

As in earlier analyses, transformation of the ROS-TAC scores was done to ensure that the distribution of ROS-TAC scores had a mean of 50 and SD of 10.

$$\text{ROS-TAC score} = 50 + (\text{principal component} \times 10.629).$$

DNA damage

Sperm DNA fragmentation was evaluated using the terminal deoxynucleotidyl transferase–mediated fluorescein-dUTP nick-end labeling (TUNEL) assay kit (Apo-Direct; BD Biosciences Pharmingen, San Diego, CA) as described previously (30–32). Briefly, 1×10^6 spermatozoa were washed in phosphate-buffered saline (PBS), resuspended in 1% paraformaldehyde, and placed on ice for 30–60 min. Subsequently, spermatozoa were washed again and resuspended in 70% ice-cold ethanol.

Following a second wash in PBS to remove the ethanol, sperm pellet samples as well as the positive and negative control samples provided with the assay kit were resuspended in 50 μL of the staining solution for 60 min at 37°C. The staining solution contained terminal deoxytransferase (TdT) enzyme, TdT reaction buffer, fluorescein-tagged deoxyuridine triphosphate nucleotides (FITC-dUTP), and distilled water. All cells were further washed in rinse buffer, resuspended in 0.5 mL propidium iodide/RNase solution, and incubated for 30 min in the dark at room temperature followed by flow cytometric analysis. Results of the TUNEL test were expressed as percentage DNA fragmentation (%DFI).

Statistical Analysis

Comparison of all parameters between the exposed and unexposed groups was done by using the Wilcoxon rank sum test. Analyses were performed using R version 2.3.1; *P* values of $<.05$ were considered to be significant. Statistical analysis was also performed separately in patient samples and donor samples. Summaries of analysis included mean and SD. Results of ROS values included median (25th and 75th percentiles), because SD was larger than the mean of ROS values.

RESULTS

Sperm Parameters

No significant difference was seen in sperm concentration between exposed and unexposed samples (58.87 ± 34.34 million/mL vs. 58.84 ± 35.20 million/mL).

Sperm motility was significantly lower in exposed samples compared with unexposed samples. Mean motility for exposed and unexposed samples was 48.62 ± 17.36% and 52.11 ± 18.34%, respectively ($P=.003$). A significant difference was observed within donors ($P=.01$) but not in patient samples.

Sperm viability was significantly lower in exposed samples than in unexposed samples ($P<.001$). Mean viability for exposed and unexposed samples was 52.33 ± 13.21% and 58.97 ± 14.81%, respectively. A significant difference was observed in donor samples ($P<.001$) but not in patient samples (Table 1).

Reactive Oxygen Species (ROS)

The ROS levels were significantly higher in exposed samples than in unexposed samples in all three groups, (overall: $P=.002$; donors: $P=.04$; patients: $P=.014$) (Table 1). Log (ROS + 0.001) values were significantly higher in the exposed group (overall: $P=.001$; donors: $P=.017$) and in patients ($P=.014$) (Table 1). The increase in both ROS value ($\times 10^6$ cpm/20 $\times 10^6$ sperm) and log (ROS + 0.001) was

TABLE 1

Comparison of ROS, TAC, ROS-TAC score, sperm parameters, and DFI between exposed and unexposed samples from various groups.

	ROS ($\times 10^6$ cpm/20 million sperm)		Log (ROS + 0.001)		TAC(mol Trolox)	
Group	Exp	NE	Exp	NE	Exp	NE
Overall	0.11 ± 0.21; 0.013 (0.0047, 0.1258)	0.06 ± 0.11; 0.0075 (0.0017, 0.0387)	−1.72 ± 0.86	−1.97 ± 0.85	1.55 ± 0.38	1.66 ± 0.48
P value	.002		.001		.24	
n	32		32		24	
Donors	0.06 ± 0.12; 0.01 (0.0035, 0.022)	0.05 ± 0.10; 0.007 (0.002, 0.0305)	−1.85 ± 0.78	−1.94 ± 0.80	1.53 ± 0.38	1.72 ± 0.52
P value	0.048		0.017		.08	
n	23		23		16	
Patients	0.22 ± 0.33; 0.02 (0.012, 0.293)	0.07 ± 0.15; 0.008 (0, 0.062)	−1.37 ± 1.00	−2.03 ± 1.03	1.59 ± 0.41	1.52 ± 0.41
P value	.014		.014		.74	
n	9		9		8	

Note: ROS values are expressed as mean ± SD; median (25th, 75th percentiles). DFI = DNA fragmentation index; Exp = exposed; NE = not exposed; RF-EMW = radiofrequency electromagnetic waves; ROS = reactive oxygen species; TAC = total antioxidant capacity; TUNEL = terminal deoxynucleotidyl transferase–mediated fluorescein-dUTP nick-end labeling assay.

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significantly higher in infertile patients compared with the increase in these values in donors (Table 2). These values were counted by deducting the mean ± SD value of exposed samples from the mean ± SD value of unexposed samples (of patients and donor samples) (Table 1).

Total Antioxidant Capacity (TAC) and ROS-TAC Score

No significant difference was observed in TAC between exposed and unexposed samples. Overall, a significant decrease in ROS-TAC score was seen in exposed versus unexposed samples ($P=.032$) (Table 1). Exposed samples had a score of 46.29 ± 11.20 compared with 51.54 ± 13.37 for unexposed samples. However, the difference between ROS-TAC scores was not significant when comparing exposed and unexposed samples from donors and patients.

DNA Integrity

No significant differences in DNA integrity (%DFI) were seen between the exposed and unexposed groups (7.80 ± 6.62% vs. 8.44 ± 5.77%) (Table 1).

DISCUSSION

In the present study, we analyzed the cause-and-effect relationship between cell phone radiation (in talk mode) and decreases in semen parameters. Our results showed a significant increase in ROS production in exposed samples and a decrease in sperm motility, viability, and ROS-TAC score in exposed samples. No significant difference in DNA integrity and TAC levels between exposed and unexposed samples was found.

The most remarkable finding of the present study was an increase in ROS levels in RF-EMW–exposed semen samples. A plausible explanation for the ROS production is that it is due to stimulation of the spermatozoa's plasma membrane redox system by RF-EMW or the effect of EMW on leukocytes present in the neat semen.

Recently, Friedman et al. (33) showed that RF-EMW stimulate plasma membrane NADH oxidase in mammalian cells and cause production of ROS. This may be attributed to an increase in the activity of spermatozoal NADH oxidase after RF-EMW exposure. Aitken et al. (34–36) demonstrated that human spermatozoa possess a multiple plasma membrane redox system that shares similarities with transmembrane NADH oxidase. Activation of plasma membrane NADH oxidase may cause production of ROS (33) . This can be detected by luminol-based chemiluminescence because luminol measures both intra- and extracellular ROS (27, 37).

Development of oxidative stress or disturbance in free radical metabolism by cell phone radiation has been demonstrated in a few animal studies. Chronic exposure to RF-EMW can decrease the activity of catalase, superoxidae dismutase (SOD), and glutathione peroxidase, and thus decrease total antioxidant capacity, but experimental studies designed to measure malonaldehyde level and SOD activity show conflicting results (7, 8, 13, 16–18, 38, 39).

Reactive oxygen species are produced continuously by spermatozoa, and they are neutralized by antioxidants present in the semen (29, 40). However, when ROS production exceeds the capacity of antioxidants, a state of oxidative stress is created. Previously, we demonstrated that ROS-

TABLE 1

Continued.

ROS-TAC score		Viability (%)		Motility (%)		TUNEL DFI (%)	
Exp	NE	Exp	NE	Exp	NE	Exp	NE
46.29 ± 11.20	51.54 ± 13.37	52.33 ± 13.21	58.97 ± 14.81	48.62 ± 17.36	52.11 ± 18.34	7.80 ± 6.62	8.44 ± 5.77
.032		<.001		.003		.62	
23		32		30		20	
48.63 ± 11.53	51.71 ± 13.75	53.52 ± 13.05	61.00 ± 13.71	50.60 ± 17.49	54.80 ± 17.61	8.21 ± 7.24	8.66 ± 6.45
.14		<.001		.01		.78	
15		23		23		16	
41.91 ± 9.74	51.23 ± 13.54	48.43 ± 13.99	52.29 ± 17.41	43.56 ± 16.94	45.25 ± 19.42	6.16 ± 3.38	7.56 ± 1.24
.15		.14		.38		.88	
8		9		7		4	

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TAC score is a more accurate measure of oxidative stress than ROS or TAC alone (29). The decrease in ROS-TAC seen in the present study suggests an increase in oxidative stress due to cell phone exposure. A decrease in sperm motility and viability is linked to concentration of superoxide anion in semen. When superoxide is produced extracellularly, it can oxidize membrane phospholipids and cause a decrease in viability (41). Short-term in vitro exposure to RF-EMW should not cause a decline in sperm concentration; however, chronic oxidative stress (in vivo examples: smoking, varicocele) may lead to a decrease in sperm count (40, 42).

Due to methodologic variations, interpretations of studies regarding DNA damage are complicated. Aitken et al. (15) demonstrated that exposure of mice to RF-EMW, 900 MHz, 12 h/day for 7 days led to damage to the mitochondrial genome and nuclear beta-globin locus of epididymal spermatozoa. In contrast, Stronati et al. (43) demonstrated no significant DNA damage in human lymphocytes exposed to RF-EMW at SAR of 1 and 2 W/kg for 24 h. Results of other studies are equally conflicting (44–52). Recent data suggest that RF-EMW may not have enough energy to cause DNA damage (46, 49, 51, 52). However, it may induce gene expression of proteins, including heat shock proteins (51, 53–55). In the present study, the sperm DNA integrity did not change in the EMW-exposed group compared with the unexposed control samples. The lack of any DNA damage may be explained by short-term exposure to cell phone radiation or the scavenging of free radicals by antioxidants in seminal plasma (29, 41, 56).

To assess the effect of EMW on sperm function, we used neat semen samples, which contain both mature and immature spermatozoa, unlike a recent study by Falzone et al. (23) who studied only mature sperm from the Percoll fraction. It has been suggested that free radical generating capacity may be higher in spermatozoa in the low-density region of

TABLE 2

Comparison of increase in ROS value between donor and patient groups.

	Donors (n = 23)	Patients (n = 9)	*P* value
Increase in ROS value ($\times 10^6$ cpm/20 million sperm)	0.01 ± 0.03	0.15 ± 0.24	.022
Increase in log (ROS + 0.001) value	0.09 ± −0.21	0.66 ± 0.90	.019

Note: Increase in ROS value [or log (ROS + 0.001)] = mean ± SD value of exposed minus mean ± SD value of unexposed samples of patients as well as of donors. ROS = reactive oxygen species.

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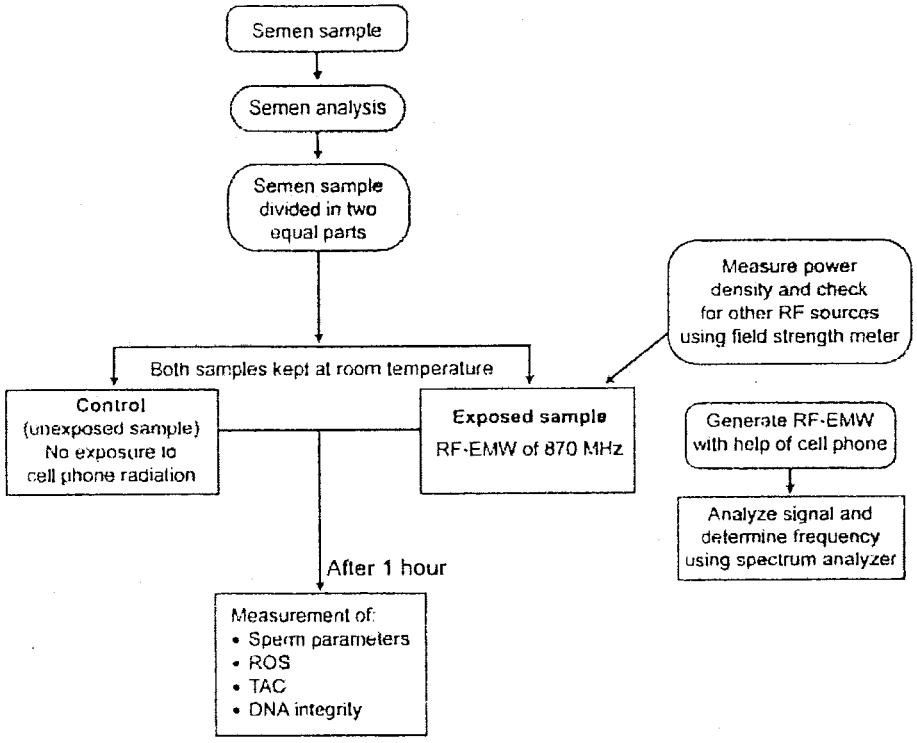
FIGURE 1

Study design and set-up for the exposure of semen sample to RF-EMW. RF-EMW = radiofrequency electromagnetic waves; ROS = reactive oxygen species; TAC = total antioxidant capacity.



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the Percoll gradient (immature spermatozoa) compared with the capacity of sperm from the higher-density fraction (mature spermatozoa) (36). The present results show that the increase in seminal ROS values in donors and patients and the increase in ROS levels in exposed samples from patients were significantly higher than the increase in ROS levels in donor samples. We therefore propose that immature and abnormal spermatozoa may be more susceptible to cell phone radiation. This may be explained by the fact that these patients already present with poor quality sperm in terms of both poor motility and abnormal morphology and presence of leukocytes. Poor sperm quality has been shown to generate higher levels of ROS. Therefore, excessive exposure to cell phone–emitted RF-EMW would be more likely to further deteriorate the sperm quality, even after this short exposure, in both mature as well as immature sperm to a larger extent, thereby increasing the likelihood of these patients being infertile.

This is a pilot study, and we acknowledge its limitations. One of them was that we did not measure seminal leukocyte counts. Semen volume also was a limiting factor in the number of samples that were available for measuring sperm parameters, ROS, TAC, and DNA damage.

The possibility that the higher ROS production in neat semen of the exposed group is due to the specific effects of RF-EMW on leukocytes is a concern. Studies on immune-relevant cell lines regarding the effect of RF-EMW on free radical formation are equally conflicting. Various researchers have shown that RF-EMW has no effect on free radical release from immune-relevant cells (57–60). Many earlier studies have shown that a 50-Hz magnetic field at 1 mT induces free radical formation in phagocytes or monocytes (61, 62). In the present pilot study, we did not measure the magnetic field emitted by the cell phone battery.

The duration of RF-EMW exposure and experimental temperature during this pilot study were selected according to guidelines of EMW exposure in an in vitro experiment. Talk time on a cell phone differs from individual to individual, so deciding the duration for the experimental condition was a complicated matter. Recent in vitro studies on human sperm and human endothelial cell lines have used 1 h of in vitro exposure (55). A decline in ROS levels in semen with time at 37°C has been demonstrated (27). In a study by Esfandiari et al. (63), ROS levels were significantly higher in semen samples stored at a lower temperature (25°C vs. 37°C). According to the available guidelines, sensitivity of the experiment should be at the highest level to maximize the possibility of detecting any significant effect(s) of RF-EMW. To maximize the likelihood of observing the deleterious effects in the present pilot study, we chose

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an exposure time of 60 min at room temperature (1, 21, 64). The distance of 2.5 cm was selected to mimic the close proximity of the testis to a cell phone in a trouser pocket (on talk mode), e.g., while the man is talking on Bluetooth. Although we monitored the room temperature, we did not measure the temperature of semen samples after exposure; recent studies have shown that RF-EMW has no thermal effects at SAR <2 W/kg RF (19, 65, 66).

In conclusion, in this pilot study we have demonstrated that cell phone radiation causes oxidative stress in neat semen and leads to decreases in spermatozoa motility and viability. The fact that many men carry their cell phones in a trouser pocket (or clipped to their belts at the waist) while using Bluetooth is important. This technology exposes the testes to high-power-density cell phone radiation compared with the cell phone in standby mode. Based on our in vitro results, we can speculate that carrying a cell phone in a pocket may cause deterioration of sperm quality through oxidative stress. However, the phone and the male reproductive organs are separated by multiple tissue layers, so to extrapolate the effects seen under in vitro conditions to real-life conditions requires further studies, which currently are under way in our laboratory.

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Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study

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Exposure to cell phone radiation for 1 h leads to oxidative stress. Radiofrequancy electromagnetic waves cause a decrease in sperm motility and viability due to increased production of reactive oxygen species.

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EXHIBIT C

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Distribution of RF energy emitted by mobile phones in anatomical structures of the brain

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Distribution of RF energy emitted by mobile phones in anatomical structures of the brain

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Abstract

The rapid worldwide increase in mobile phone use in the last decade has generated considerable interest in possible carcinogenic effects of radio frequency (RF). Because exposure to RF from phones is localized, if a risk exists it is likely to be greatest for tumours in regions with greatest energy absorption. The objective of the current paper was to characterize the spatial distribution of RF energy in the brain, using results of measurements made in two laboratories on 110 phones used in Europe or Japan. Most (97–99% depending on frequency) appears to be absorbed in the brain hemisphere on the side where the phone is used, mainly (50–60%) in the temporal lobe. The average relative SAR[8] is highest in the temporal lobe (6–15%, depending on frequency, of the spatial peak SAR in the most exposed region of the brain) and the cerebellum (2–10%) and decreases very rapidly with increasing depth, particularly at higher frequencies. The SAR distribution appears to be fairly similar across phone models, between older and newer phones and between phones with different antenna types and positions. Analyses of risk by location of tumour are therefore important for the interpretation of results of studies of brain tumours in relation to mobile phone use.

(Some figures in this article are in colour only in the electronic version)

[8] SAR is the specific energy absorption rate i.e. energy absorption rate per unit mass (measured in W kg^{-1}).

1. Introduction

The very rapid worldwide increase in mobile phone use in the last decade, with more than 2 billion users to date (http://www.mobiletracker.net/archives/2005/05/18/mobile-subcribers-worldwide), has generated considerable interest in the possible health effects of exposure to radio frequency (RF) electromagnetic fields.

A multinational case-control study, INTERPHONE, was set up to investigate whether mobile phone use increases the risk of cancer and, more specifically, whether exposure to the RF fields emitted by mobile phones is carcinogenic. The study focused on tumours arising in some of the tissues expected to be most exposed to RF fields from mobile phones: glioma, meningioma, acoustic neurinoma and parotid gland tumours (Cardis *et al* 2007).

Because exposure to RF fields from mobile phones is very localized (Dimbylow and Mann 1994, Rothman *et al* 1996, Watanabe *et al* 1996, Wiart *et al* 1998), it was judged essential to identify as accurately as possible the location of the origin of brain tumours so that the RF 'exposure' at that location could be evaluated. A generic cartography of a human head, the Gridmaster Computer Program (2007), has been produced in three planes (sagittal, coronal, axial), whose various cuts are similar to the acquisition planes (see figure 1) used in MRI. A protocol was developed and tested for neuro-radiologists to identify the likely anatomical origin of the brain tumour from MRIs and CT scans using this cartography. It has been used in all INTERPHONE participating countries, and estimates of the amount of RF energy absorbed at the locations of the tumours are being derived for all of the glioma and meningioma cases in the study for whom images could be retrieved and localization achieved (Cardis *et al* 2007).

The spatial distribution of the specific absorption rate (SAR) of energy in the head depends on many different parameters, including the frequency band, the phone model and the position of the phone in relation to the head (Kainz *et al* 2005, Wiart *et al* 1998). Overall, several hundred different phone models have been used at one time or another by subjects in the INTERPHONE study. Ideally, therefore, the study would require, for each brain tumour case, the estimation of the SAR at the probable location of the origin of the tumour for each phone used by that subject (and similarly the estimation of the SAR at the same location for the matched control). An essential aspect of the RF exposure assessment within INTERPHONE was to determine whether phones could be categorized into a discrete number of classes based on the SAR distribution they produce. Detailed analyses of data on the spatial distribution of SAR in the head were conducted, based on results of measurements conducted with over 100 different phone models from different countries and time periods. The frequency band appeared to be the main general characteristic of the phones that resulted in significantly different spatial distributions during normal phone use (unpublished results).

Because information about precise localization was not available for all cases in the INTERPHONE study and is not available at all in the majority of other mobile telephone studies, the objective of the current paper was to characterize the spatial distribution of SAR, by phone class, within specific anatomical structures. Results of these analyses are presented here as analyses of risk in different anatomical structures are important in the interpretation of results of studies of brain tumours in relation to mobile telephone use.

2. Materials and methods

2.1. SAR measurement data available

SAR distributions of 129 different phone models measured either at the France Telecom RD laboratory in France or at the TELEC laboratory (Telecom Engineering Center) in Japan were

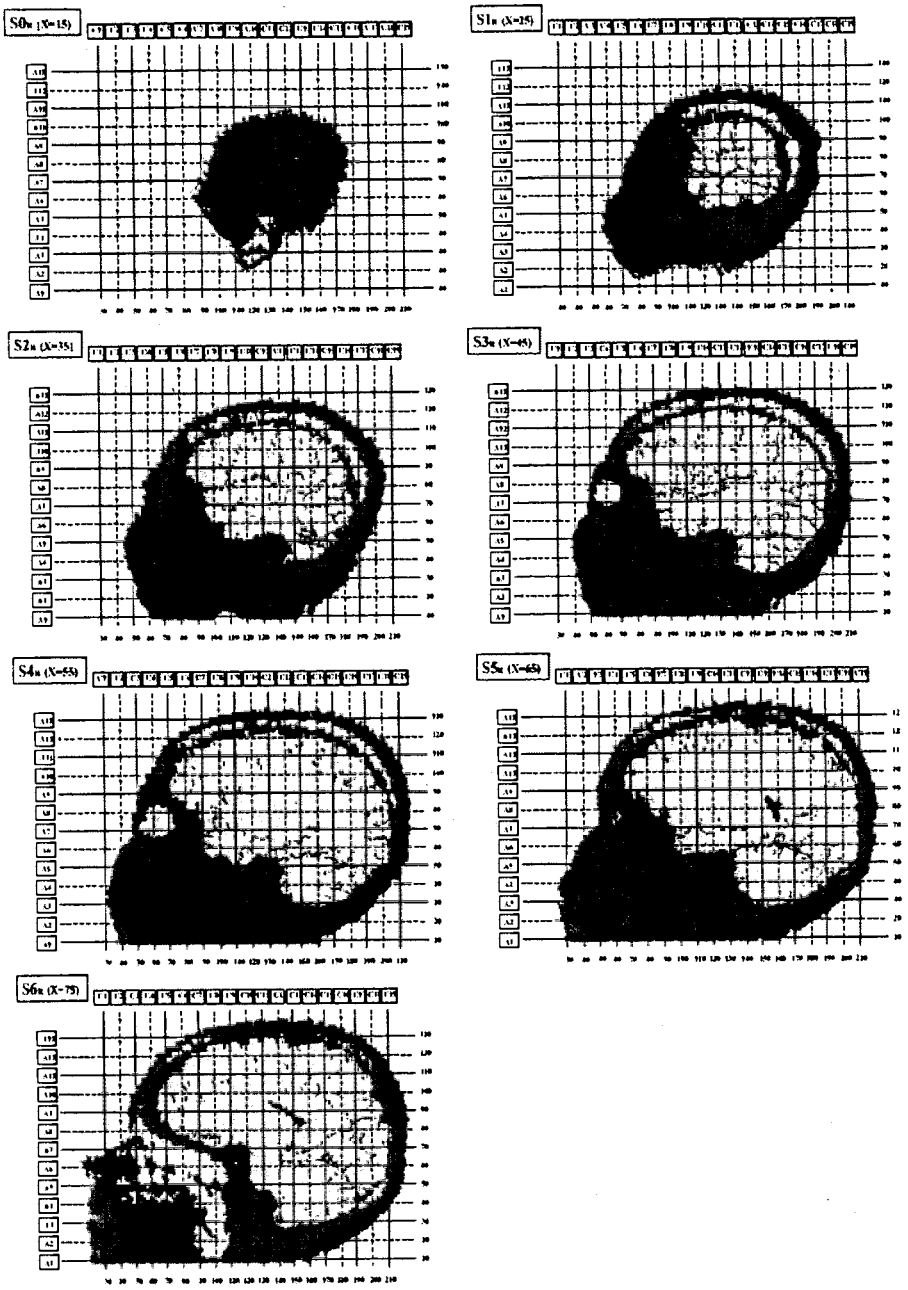

Figure 1. Example of three sagittal acquisitions taken at different points: 15, 25, 35, 45, 55, 65 and 75 mm from the side of the head. (Note: arbitrary colours were used to show the different tissues in the head.)

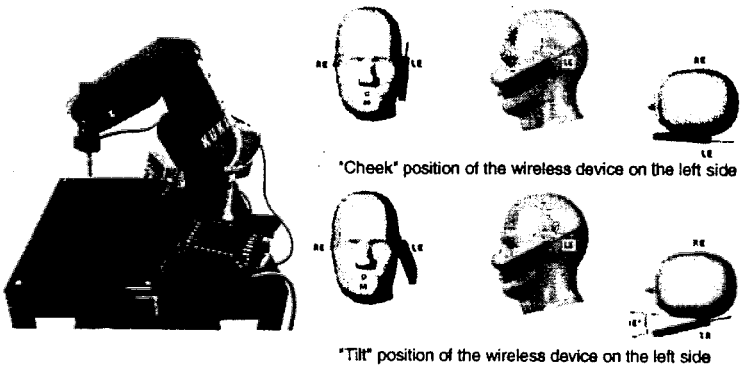

Figure 2. Left : measurement equipment. Right: test position.

available for analysis, including a total of 1051 measurements of SAR spatial distributions. In France, measurements were made on popular phone models used between 1996 and 2002. In Japan, they were made on all available models on the market in 2001. The measurement system, composed of a phantom, a SAR measurement probe, a scanning system and a mobile phone holder (figure 2), allowed measurement of the internal electric field in the phantom while the mobile phone emitted at maximum power. The phantom, representing a human head, was filled with a homogeneous liquid with dielectric properties designed to overestimate the maximum SAR averaged over 1 and 10 gm cubes in a real head (IEC 2005). The measurements were performed in 'cheek' and 'tilt' positions (figure 2), on the left and right side of the phantom, and, in France, at different frequencies (lowest, middle and highest) in the frequency band in which the handset is able to operate. Phones with retractable antennas were measured both with the antenna extracted and retracted. The measurement equipment (figure 2), phantom, liquid and test positions were in accordance with standards for compliance testing: IEC 62209-1 (IEC 2005), IEEE 1528 (IEEE 2003), CENELEC (CENELEC 2001).

Measurements of 76 phones operating in the 800–900 [9] MHz frequency band (using either the Personal Digital Cellular (PDC) or cdmaOne Japanese systems) or the 1500 MHz (PDC) frequency bands in Japan and of 34 Global System for Mobile (GSM) phones operating in the 900 and 1800 MHz bands in France were made using the TWIN phantom (CENELEC 1997).

A further 17 GSM and 2 Nordic Mobile Telephony (NMT) phones operating at 900 MHz were measured on the SAM phantom (CENELEC 2001) in France. The measurements on SAM were not considered in the main analyses presented here, as the data used to derive the spatial distribution of SAR throughout the head were based on measurements made in a very restricted volume, resulting in large uncertainties in extrapolating energy absorption outside of this volume. Sensitivity analyses were performed, however, using the measurements made on the SAM phantom.

[9] The Japanese 800 MHz PDC and CDMA system uses 900 MHz frequencies (in the range 938–958 and 887–925 MHz respectively) for uplink connection and 800 MHz (respectively 810–885 and 832–870 MHz) for downlink. Thus the frequency emitted by the Japanese 800 MHz phones is similar to that of the European 900 MHz GSM phones (890–915 MHz for uplink and 935–960 MHz for downlink).

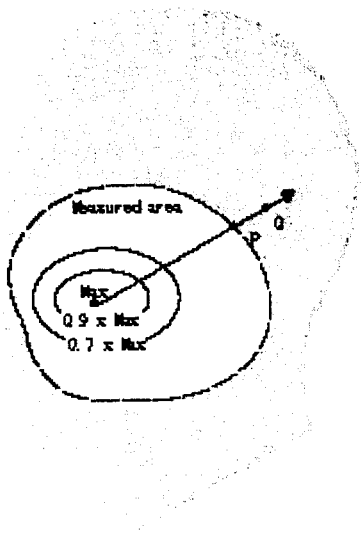

Figure 3. Illustration of extrapolation process: SAR at an arbitrary position Q outside of the measured area is estimated by extrapolation assuming exponential decay from the value at P on the boundary of the measured area.

2.2. *Estimating average SAR in each 1 cm³ of the Gridmaster from the measurement data*

In order to make a link between a particular location in the brain and the energy absorbed at that location, a method was developed to estimate the average SAR in each cube of the 1 cm³ grid of the Gridmaster, using the SAR measurement data described above. The method is described in detail elsewhere (Wake 2005). Briefly, it involved establishing a link between the coordinate grids of the phantoms and those of the Gridmaster, after localization of the ear-to-mouth axis on the Gridmaster, and, *for each phone measured*:

- interpolating the measurements made near the surface of the phantom to obtain estimates on a 1 mm³ grid, extrapolating outside the measured region; identifying the 0.9∗max and 0.7∗max contours and determining the lateral decay factor as the distance between these contours (figure 3);
- projecting the extrapolated data onto the conformal plane on the Gridmaster;
- estimating the penetration decay factor k of the exponential decay from the data in the first three layers of the cube data and projecting the SAR values into the head using the exponential decay factor;
- and averaging the SAR in each 1 cm³ cube of the Gridmaster.

2.3. *Estimating the SAR distribution in a class of phones*

Because repeated measures were available for some phones, the following steps were taken for each phone:

- when phones were measured both with antenna extracted and retracted, the SARs estimated in each cube were averaged;

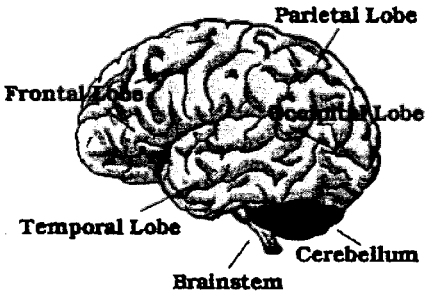

Figure 4. Anatomical structures of the brain (from http://www.waiting.com/brainanatomy.html).

- within a frequency band, the SARs in a given cube for a given phone were averaged over the specific frequencies at which they had been measured (French phones only—the Japanese phones were measured only near the centre of the frequency band);
- a weighted mean of the estimated SAR in each cube in each phone position was derived: $\frac{3}{4}$ tilt + $\frac{1}{4}$ cheek as this was judged by the Exposure Assessment committee of INTERPHONE to approximate typical exposure conditions;
- finally, the SAR estimated in each cube was taken to be the average of the SAR estimated in that cube and of the SAR estimated in the mirror image cube on the other side of the head when the phone was measured on both sides of the head. This is justified by the fact that the side of the external antenna (left or right mounting position on the top surface of the phone) varies across phones and the distribution of antenna side among phones used in the measurements may not be representative of the actual distribution of antenna side among all phones used by study subjects.

In this way, we calculated three quantities for each phone, in each frequency band, and in each of the cubes of the head in the Gridmaster: (1) the absolute average SAR value (in W kg^{-1}) and, because this varied with phone and the average SAR distribution might have been unduly influenced by a few phones with higher values, (2) the relative average SAR value, computed as the percentage of the average absolute SAR in a cube relative to the SAR in the cube of the brain which had the highest absolute SAR (the latter tended to be located near the ear, in the outer layer of the brain), and (3) the proportion of total energy absorbed, i.e. the proportion of the total energy in the brain which was absorbed in the cube.

In order to evaluate the distribution of SAR in different anatomical locations in the brain, the cubes in the Gridmaster were grouped according to major anatomical structures: frontal, temporal, occipital and parietal lobes, cerebellum and brain stem (figure 4). If a cube included tissue from two or more different structures, it was assigned to the structure with the largest proportion of tissue in the cube. The absolute and relative average SAR values in these structures and the proportion of total energy absorbed were obtained by averaging over all the cubes in the structure. The relative average SAR was normalized again so that the relative SAR in the cube with the highest value was 1. As the brain is not entirely symmetrical, the boundaries of the different anatomical structures differ on the left and right sides of the head. Separate analyses were conducted in the right and left halves of the brain, for a phone held on the right and left side respectively. For simplicity, results in this paper are shown for the right hemisphere of the brain, for a phone held on the same side. Results for the left half of the brain for a phone held on the left were similar.

We then calculated the distributions of absolute and relative SAR, and of the proportion of total energy absorbed, for different classes of phones (defined by frequency band—separating the 800–900 phones from Japan and Europe, because of their very different shape and size—and, for some additional analyses, by marketing year, type of antenna—patch, helix, extractable—and measurement position—tilt and cheek) by averaging these quantities in each anatomical location over all the measurements in the class.

3. Results

Table 1 shows the distribution of the average relative SAR and of the proportion of total energy absorbed in the brain, by anatomical location in the right hemisphere of the brain, for phones held on the right side of the head. Most (97–99%, depending on the frequency band) of the RF energy appears to be absorbed in the hemisphere of the brain located on the side of the head where the phone is used.

The average relative SAR was highest in the temporal lobe, whatever the frequency band. It ranged from 5% of the SAR in the cube with the highest absolute SAR value in GSM 1800 MHz phones to 15.5% in GSM 900 MHz phones. Analyses of average absolute SAR give similar results (not shown). The cerebellum appears to be the brain structure with the second highest average SAR. For GSM 900 and 1800 MHz phones, the average relative SAR was slightly higher in the frontal lobe and parietal lobes than in the occipital lobe and in the brain stem. For PDC and cdmaOne 800–900 and PDC 1500 MHz phones, the average SAR in the occipital lobe appears to be higher than in the frontal or parietal lobes.

The proportion of energy absorbed was also highest in the temporal lobe, whatever the frequency band: between 50 and 60% of the total RF energy in the brain was absorbed in the temporal lobe in the hemisphere of the brain located on the side of the head where the phone is used. For PDC and cdmaOne 800–900 and PDC 1500 MHz phones, the cerebellum had the second highest proportion of energy absorbed (22 and 25%, respectively), while for GSM 900 and 1800 phones, despite the fact that the average relative SAR was higher in the cerebellum, a higher proportion of energy was absorbed in the much larger frontal lobe (19% in frontal versus 12% in cerebellum at 900 MHz; 14 versus 13% at 1800 MHz).

Analyses by marketing year and by type of antenna show similar patterns of distributions across anatomical structures (table 2), as do analyses restricted to measurements in the tilt and the cheek position, except for Japanese phones in the tilt position where the average relative SAR in the cerebellum is similar to that in the temporal lobe (table 3). Sensitivity analyses using data on the phones measured on the SAM phantom show higher SAR at 900 MHz in the cerebellum and the occipital lobe than with the TWIN phantom (not shown).

While the average relative SAR in different anatomical structures varied between phones, as indicated in table 1, the relative ranks of the different anatomical structures were fairly constant. The cube with the highest average SAR was in the temporal lobe for all but two of the phones measured. The temporal lobe was the structure with the highest average SAR for all but 4 of the 800–900 PDC and cdmaOne phones, 1 of the GSM 900 phones, 17 of the PDC 1500 MHz phones and 5 of the GSM 1800 MHz phones. For the remaining phones, the average SAR was highest in the cerebellum, except for 2 phones at 1800 MHz. For these, the highest average SAR was seen in the frontal lobe, but the SAR levels in frontal and temporal lobes were very close.

Table 4 shows the distribution of average relative SAR by lobe and the frequency band in the saggital slices of the Gridmaster on the right-hand side of the head ($S0_R$-, $S1_R$-, $S2_R$-, $S3_R$-, $S4_R$-, $S5_R$-, $S6_R$-, -$S6_L$), for a phone held on the right-hand side of the head. The slices correspond to layers that are, respectively, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84

Table 1. Distribution of average relative SAR and of proportion of total energy absorbed by anatomical location and frequency band—figures shown are in anatomical locations in the right hemisphere of the brain for a phone held on the right side of the head.

			800–900 MHz Japanese phones			900 MHz European phones			1500 MHz Japanese phones			1800 MHz European phones		
Brain hemisphere	Structure	Number of cells in structure	Average relative SAR (%)	5–95th percentile	25–75th percentile	Average relative SAR (%)	5–95th percentile	25–75th percentile	Average relative SAR (%)	5–95th percentile	25–75th percentile	Average relative SAR (%)	5–95th percentile	25–75th percentile
Average Relative SAR relative to the cube of the brain with the highest absolute SAR														
Right	Brainstem	15	2.4	0.5–4.4	1.2–3.6	3.2	0.9–6.6	1.3–4.7	0.6	0.1–1.1	0.2–1.0	0.3	0.1–0.8	0.1–0.6
	Cerebellum	88	9.5	1.1–32	2.8–12	6.9	0.4–29	1.0–7.0	5.5	0.3–24	0.9–6.1	2.4	0.1–9.9	0.3–2.5
	Frontal	203	1.6	0.2–4.5	0.5–2.0	5.7	0.9–17	1.7–8.0	0.5	0.0–1.8	0.1–0.6	1.6	0.0–8.3	0.1–1.8
	Occipital	117	3.8	0.2–18	0.6–3.5	2.2	0.1–8.1	0.5–2.0	2.1	0.0–12	0.1–1.2	0.8	0.0–4.0	0.1–0.5
	Parietal	105	1.1	0.1–3.5	0.3–1.5	5.1	0.7–16	1.5–7.4	0.5	0.0–1.9	0.1–0.7	1.5	0.0–6.4	0.1–1.8
	Temporal	165	11.5	0.5–39	2.3–14	15.5	1.3–49	3.3–19	6.2	0.1–24	0.6–6.5	5.0	0.0–22	0.4–5.0
Proportion of total energy absorbed in the brain (average relative SAR relative to the energy absorbed in the entire brain)														
Right	Brainstem	15	1	0.6–1.3	0.8–1.1	1	0.2–1.7	0.4–1.3	0.4	0.3–0.6	0.4–0.5	0.2	0.0–1.1	0.0–0.4
	Cerebellum	88	22	17–27	21–24	12	2–20	9–15	25	20–31	23–29	13	1.1–35	5.7–16
	Frontal	203	8	3–13	7–9	19	9–43	14–22	4	2–5	3–4	14	1.0–41	7.0–17
	Occipital	117	12	6–21	10–13	5	1–9	4–7	13	8–16	12–15	5	0.4–12	3.0–7.4
	Parietal	105	3	2–4	3–4	9	4–14	9–10	3	2–4	2–3	7	0.5–21	2.8–11
	Temporal	165	50	42–59	49–53	50	41–63	46–53	53	46–62	49–57	60	32–92	51–67
	Total	693	96.7			96.8			99.1			99.5		
Left	Total	738	3.3			3.2			0.9			0.5		
Number of phones measured			31			34			45			31[a]		

[a] Three phones excluded at 1800 MHz because it was not possible to estimate decay factor.

Table 2. Distribution of average relative SAR and of proportion of total energy absorbed by anatomical location, frequency band, marketing year and type of antenna—for a phone held on the right side of the head and in anatomical locations in the right hemisphere of the brain (French phones only as no information available on Japanese phones).

	Marketing year				Type of antenna			
	Before 2001		2001 or later		Helix		Patch	
	900	1800	900	1800	900	1800	900	1800
Average relative SAR (%)								
Brainstem	3.3	0.3	3.1	0.4	3.2	0.2	3.1	0.6
Cerebellum	6.9	2.1	6.9	2.5	7.0	1.9	6.5	3.3
Frontal	4.2	0.6	6.4	2.0	5.6	0.7	6.2	3.0
Occipital	1.9	0.7	2.3	0.9	2.1	0.5	2.2	1.5
Parietal	4.4	1.4	5.4	1.5	4.9	0.7	5.3	2.8
Temporal	14.4	3.5	16.0	5.7	15.4	3.5	15.9	7.6
Proportion of total energy absorbed in the brain (%)								
Brainstem	1.0	0.3	0.8	0.2	0.8	0.2	0.9	0.2
Cerebellum	12.7	14.3	11.8	11.9	12.3	13.8	11.2	10.8
Frontal	16.8	9.6	20.6	15.9	19.0	12.5	20.8	17.1
Occipital	4.6	6.3	5.1	5.0	5.0	5.2	4.7	5.9
Parietal	9.7	9.5	9.3	6.0	9.4	5.7	9.4	9.2
Temporal	51.8	59.6	49.3	60.4	50.4	62.2	49.9	56.1
Number of phones measured								
	10	9	24	23	21	19	12	11

Table 3. Distribution of average relative SAR by anatomical location, frequency band and position of the phone during the measurements—for a phone held on the right side of the head and in anatomical locations in the right hemisphere of the brain.

	Tilt				Cheek			
	800–900 PDC and CDMA	900 GSM	1500 PDC	1800 GSM	800–900 PDC and CDMA	900 GSM	1500 PDC	1800 GSM
Average relative SAR (%)								
Brainstem	2.1	2.7	0.5	0.4	3.3	3.4	0.7	0.3
Cerebellum	9.5	6.5	5.6	2.5	9.4	6.4	5.0	2.1
Frontal	1.3	5.3	0.5	1.4	2.8	5.4	0.8	1.8
Occipital	3.9	2.1	2.2	0.9	3.7	1.9	2.0	0.8
Parietal	1.0	5.0	0.5	1.5	1.5	4.2	0.8	1.1
Temporal	10.5	14.2	5.9	4.7	15.4	15.8	7.8	5.8

and 85–94 mm from the right side of the reference head ($S3_R$ passes through the orbit of the right eye and $S6_L$ also corresponds to the slice 75–84 mm from the left side of the head) (figure 1). The average relative SAR diminished rapidly with depth in the brain, particularly at higher frequencies. In 800 and 900 MHz phones, the average relative SAR was less than or equal to 10% in the $S3_R$ layer in all anatomical structures except the cerebellum; at 1500 and 1800 MHz, the average relative SAR was less than 10% in the $S2_R$ layers in all structures but the cerebellum. By the $S6_R$ layer, the average relative SAR was of the order of 1% or less at all frequencies and in nearly all structures except the cerebellum.

Table 4. Distribution of the average relative SAR by anatomical location, saggital layer and frequency band, expressed as % of the SAR in the brain cube with the highest absolute SAR value—figures shown are in anatomical locations in the right half of the brain for a phone held on the right side of the head.

Anatomical layer[a]	Temporal lobe	Frontal lobe	Parietal lobe	Occipital lobe	Cerebellum
800–900 MHz Japanese phones (%)					
S0R-	40	NA[b]	NA	NA	NA
S1R-	21	5	4	32	NA
S2 R-	13	4	2	11	31
S3 R-	7	2	1	5	16
S4R-	4	1	0.7	2	8
S5R-	2	0.8	0.4	1	4
S6 R-	0.4	0.5	0.2	0.6	2
-S6 L	0.2	0.2	0.1	0.3	1
900 MHz European phones (%)					
S0R-	51	NA	NA	NA	NA
S1R-	28	21	16	19	NA
S2 R-	18	13	9	6	24
S3 R-	10	8	5	3	11
S4R-	6	5	3	1	5
S5R-	3	3	2	0.8	3
S6 R-	1	1	1	0.4	1
-S6 L	0.6	0.7	0.6	0.2	0.5
1500 MHz Japanese phones (%)					
S0R-	34	NA	NA	NA	NA
S1R-	13	2	2	27	NA
S2 R-	5	1	1	6	22
S3 R-	2	0.7	0.4	2	9
S4R-	0.9	0.4	0.2	0.6	4
S5R-	0.4	0.2	0.1	0.3	1
S6 R-	0.1	0.1	0.1	0.1	0.5
-S6 L	0.02	0.03	0.02	0.04	0.2
1800 MHz European phones (%)					
S0R-	34	NA	NA	NA	NA
S1R-	10	8	6	12	NA
S2 R-	4	4	3	2	11
S3 R-	1	3	1	0.8	4
S4R-	0.5	1	0.8	0.2	1
S5R-	0.2	0.3	0.4	0.1	0.5
S6 R-	0.04	0.1	0.1	0.04	0.2
-S6 L	0.02	0.03	0.04	0.02	0.1

[a] See text for definition.
[b] N.A.: not applicable—indicates that there is no relevant tissue (or very little) in a particular sagittal layer.

In the temporal lobe, the average relative SAR in the first layer ranged from 34% to 51% of the SAR in the cube with the highest exposure. In the fourth layer, the corresponding values were 1% at 1800 MHz and 10% at 900 MHz (table 4 and figure 5).

In the outermost layers, the highest average SAR values were seen in the temporal lobe, followed by the cerebellum and occipital lobes (table 4).

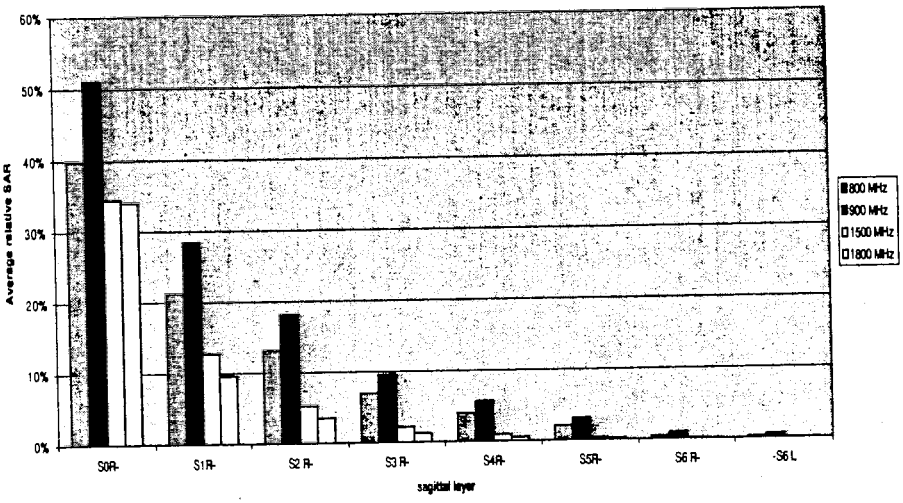

Figure 5. Distribution of average relative SAR (expressed as % of the SAR in the brain cube with the highest absolute SAR value) in the temporal lobe, as a function of frequency and sagittal layer—for a phone held on the right-hand side of the head and in anatomical locations in the right hemisphere of the brain.

4. Discussion

Results of analyses presented here suggest that the average RF energy absorption from mobile phones is generally highest in the temporal lobe and that this structure, on the side of the head to which the phone is held, generally absorbs at least half of all of the RF energy absorbed in the brain. As observed previously (Kuster *et al* 2004), the absorption is also highest in the outermost layers of the brain on the side of the head where the phone is held.

There are a number of uncertainties in our estimation of SAR in the head. They are related to

- the fact that we estimate SAR in a heterogeneous head using measurements performed in a homogeneous head; this uncertainty is, however, reduced by averaging over 1 cm^3;
- human anatomical variability: depending on the shape of the head and on the internal anatomy, the SAR in the brain can vary; a recent study (Wiart *et al* 2008) performed with different adult heads has shown that the standard deviation of the maximum 10 g average SAR is about 30%;
- uncertainties in the exact localization of the different anatomical structures in the relatively coarse 1 cm^3 grid, particularly relatively small ones such as the cerebellum;
- the measurements themselves are subject to variability, as a measurement uncertainty of 30% is allowed in the standards for measurement procedure in IEC 62209–1 (IEC 2005), IEEE 1528 (IEEE 2003) and CENELEC (CENELEC 2001);
- uncertainties related to the position in which the phone is held, although results of measurements made in tilt and cheek showed generally similar results;
- the interpolation and extrapolation methods used to derive the SAR distribution in our three-dimensional grid also are subject to uncertainty.

While the distribution is likely to be relatively well characterized in the region close to the maximum SAR, it is more uncertain further away as, for compliance purposes, the

phantoms used have been designed to be larger than average European and Japanese heads, particularly towards the back of the head. In particular, the average relative SAR estimated in this paper in the cerebellum and the occipital lobe may be overestimated. Although part of the cerebellum is located close to the region of maximum SAR (and the maximum SAR over 1 g in the cerebellum is close to the SAR over 1 g in the brain (Wiart *et al* 2008) and although the cerebellum is relatively small, most of the organ is not in fact close to the region of maximum SAR. Numerical simulations performed with FDTD with various adult head models and different handsets indicate an average SAR in the cerebellum of the order of 3% of the maximum SAR over 1 g in the brain. Furthermore, results of the sensitivity analyses comparing SAM and TWIN phantoms show that the average relative SAR is very similar in a given frequency band in the temporal, frontal and parietal lobes. However, in the structures located further back in the head, the occipital lobe and the cerebellum, it is nearly twice as high at 900 MHz for the phones measured on SAM; although these differences may reflect uncertainties related to extrapolating from measurements made on a restricted volume, they could also be related to the size of the SAM phantom, which is the bigger of the two phantoms.

Despite these uncertainties, however, our results appear to be fairly robust; the maximum SAR and the highest average relative SAR are seen in the temporal lobe for the vast majority of the phones measured and, although phones have become smaller and the type and position of the antenna have changed over time, this appears to have relatively little impact on the anatomical distribution of the SAR.

These results suggest that analyses of risk by location of tumour are important for the interpretation of results of epidemiological studies of brain tumours in relation to mobile phone use.

5. Conflicts of interest

EC, ID, SM, MT, KW have no conflict of interest to declare. JW worked for the research center of France telecom, as did NV from 2004 to 2005; she is now working toward a PhD degree at Tokyo Metropolitan University, Tokyo, Japan.

Acknowledgments

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Wiart J, Hadjem A, Wong M F and Bloch I 2008 Analysis of RF exposure in the head tissues of children and adults *Phys. Med. Biol.* submitted

EXHIBIT D

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Variability analysis of SAR from 20 MHz to 2.4 GHz for different adult and child models using finite-difference time-domain

2008 Phys. Med. Biol. 53 1511

(http://iopscience.iop.org/0031-9155/53/6/001)

IOP PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. 53 (2008) 1511–1525 doi:10.1088/0031-9155/53/6/001

Variability analysis of SAR from 20 MHz to 2.4 GHz for different adult and child models using finite-difference time-domain

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Abstract

This paper deals with the variability of body models used in numerical dosimetry studies. Six adult anthropomorphic voxel models have been collected and used to build 5-, 8- and 12-year-old children using a morphing method respecting anatomical parameters. Finite-difference time-domain calculations of a specific absorption rate (SAR) have been performed for a range of frequencies from 20 MHz to 2.4 GHz for isolated models illuminated by plane waves. A whole-body-averaged SAR is presented as well as the average on specific tissues such as skin, muscles, fat or bones and the average on specific parts of the body such as head, legs, arms or torso. Results point out the variability of adult models. The standard deviation of whole-body-averaged SAR of adult models can reach 40%. All phantoms are exposed to the ICNIRP reference levels. Results show that for adults, compliance with reference levels ensures compliance with basic restrictions, but concerning children models involved in this study, the whole-body-averaged SAR goes over the fundamental safety limits up to 40%.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

To ensure protection for public and workers against radio frequency (RF) overexposure, the ICNIRP have established guidelines for limiting electromagnetic fields' exposure (ICNIRP 1998). They define basic restrictions which specify a specific absorption rate (SAR) not to be exceeded and reference levels in terms of an electric field, magnetic field or power density. The reference levels were derived from basic restrictions several years ago from a highly simplified human model. Since then, a number of realistic human models have been developed and used in dosimetry studies.

Since 1997, several studies have been performed to analyze adults and also children the behavior of toward electromagnetic exposure (Dimbylow 1997, 2002, 2007, Dimbylow and

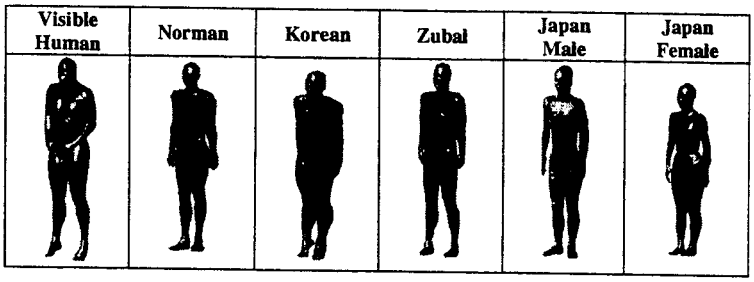

Figure 1. The six adult models gathered for this study.

Mann 2006a, 2006b, Findlay and Dimbylow 2005, 2006). These studies have pointed out that the whole-body-averaged SAR may exceed the basic SAR limit under the reference level for children. Dimbylow's work is focused on the English numerical model named Norman. A Japanese team confirmed Dimbylow's results using Japanese numerical models (Wang *et al* 2006a, 2006b, Hirata *et al* 2006, 2007).

The main limitation of a number of studies is linked to the variability. The human population is highly diverse and it is impossible to generalize any result obtained on one model. The objective of this paper is to push back this limitation using several adult models. Six numerical human models have been compared, and their variability in terms of morphology and behavior toward RF exposure for frequencies from 20 MHz to 2.4 GHz has been analyzed. Historically, the first numerical models of children have been obtained by homothetic transformation of adult models. But a child is not a simple scale of an adult. Numerous studies have already dealt with the case of realistic child heads (Wang and Fujiwara 2003, Hadjem *et al* 2004, Wiart *et al* 2005, 2008). For this study, we have constructed more realistic child models using a piecewise reduction of adult models respecting child morphologic data.

The electromagnetic properties of tissues are important to assess the SAR in specific tissues. In this paper, we consider that in the range of our study (above 5-years old), the variation of dielectric properties with age can be neglected (Wang *et al* 2006a). In line with this, we use the dielectric properties of tissues that are commonly used (Gabriel 1996).

The paper is focused on the assessment of the SAR not only averaged on the whole body as usually done, but also averaged on different parts of the body such as the head, the legs, the arms or the torso. Another original aspect concerns the SAR averaged in particular tissues such as skin, muscles, fat or bones.

2. Numerical phantom models

2.1. Adults

2.1.1. Models. In recent years, several voxel phantoms have been developed on the basis of tomographic data of real individuals. For this study, five male adult models and one female adult model have been gathered (figure 1): Visible Human (VH) (Ackerman 1995), the model developed at HPA-NRPB named Norman (Dimbylow 1996), the models developed at NICT named here Japan Male and Japan Female (Nagaoka *et al* 2004), the model developed in Korea later named Korean (Lee *et al* 2006) and the model developed by Yale University named Zubal (Zubal *et al* 1995).

These six adult models do not look like each other. Initial models also do not have the same segmentation. The size of voxels varies from 1 mm^3 to 3.6 mm^3 and the number of

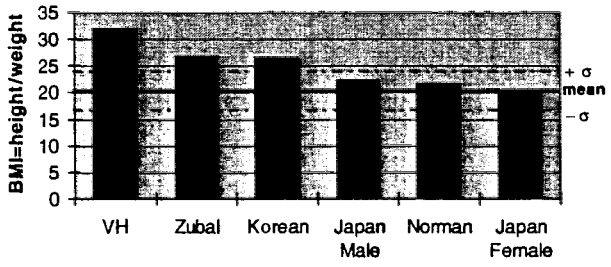

Figure 2. Repartition of the BMI of adult models around mean value.

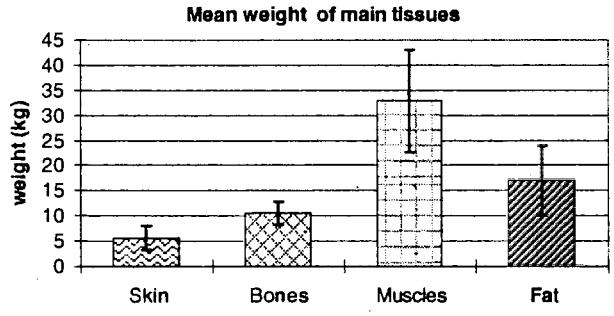

Figure 3. Mean weight of the four main tissues of phantoms (skin, bones, muscle and fat) and associated standard deviations.

tissues from 29 to 55. For the purpose of standardizing the input data, all the models have been remeshed with a common voxel size of 2 mm^3.

2.1.2. Morphological characteristics. Before assessing the RF exposure of different models, we have to compare external and internal morphologies of phantoms. The external geometry is characterized among others by the height, the weight, the body mass index (BMI) which can be used as a measure of body fat:

$$\mathrm{BMI} = \frac{\text{height (m)}}{\text{weight (kg)}^2}.$$

The six adult models represent different types of morphologies. The mean phantom has a weight of 76 kg with an important standard deviation of 18.5 kg and a height of 1.73 m with a standard deviation of 7 cm. Figure 2 shows repartition of the BMI around the mean value.

The Visible Human and the Japan Female emerge as two extremes. Visible Human is tall and fat with the highest BMI, while the Japan Female is small and light with the smallest BMI. Between both the extremes, we find Zubal and the Korean on the one hand and the Japan Male and Norman on the other hand that have almost the same height, weight and so almost the same BMI.

Concerning the internal morphology, the weight repartition of main tissues reveals that four tissues constitute around 85% of the total weight whatever the model: skin, muscles, bones and fat. For each of these four tissues, the mean weight and associated standard deviation have been plotted in figure 3.

Figure 3 points out an important variability of adult models in term of tissue weights. Tissues that are most important quantitatively (i.e. muscles and fat with mean values of 33 kg

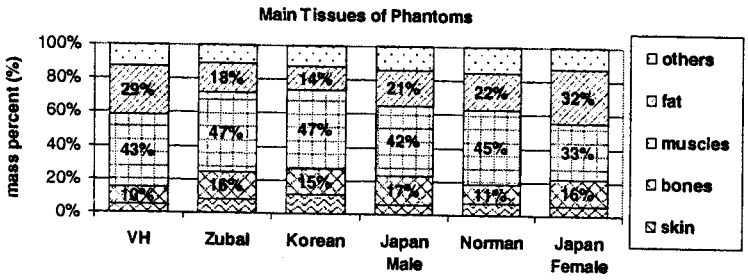

Figure 4. Internal morphology–weight repartition of main tissues.

and 17 kg, respectively) are also those that have the highest standard deviations (i.e. 10 kg for muscles and 7 kg for fat). The repartition in the weight ratio of the main tissues (skin, muscles, fat and bones) is summed up for each model in figure 4.

Skin is a highly important tissue because it is the first tissue which is met by the incident field. Figure 4 shows quite an important variability in the skin–weight ratio. It varies from around 5% for VH to almost 12% for the Korean. The Korean model had the largest initial size of voxel with 3.6 mm, which involves a higher skin thickness. Concerning the muscle–weight ratio, the Japan Female distinguishes herself with a lower ratio (about 33%) than the ratios of male models (between 42% and 47%). About fat, Visible Human and the Japan Female differ from the others with a higher fat–weight ratio (about 30%). The shape of both these models (figure 1) shows that they are fat.

2.2. *Child*

2.2.1. Method of morphing. The first problem encountered with child models is the lack of magnetic resonance images (MRI) of children. Uniform scaling has been used (Dimbylow 2002), but this method supposes that growth is perfectly proportional which is not valid. To obtain more realistic child models, we suggest making a piecewise reduction of the adult model with respect to the main anatomical parameters. From the literature, the external shape of human heads and bodies and their transformation versus age have been analyzed (Sempé *et al* 1979, Farkas 1994, Hadjem *et al* 2004, Burguet *et al* 2004). The numbers of head and body parameters have been taken into account to build models corresponding to the mean value of the three classes of ages (12-, 8- and 5-year olds).

Head parameters. Head growth is particularly important because it is absolutely not linear. Children have bigger heads than adults. Specific studies on child head RF exposure have been conducted (Hadjem *et al* 2004, Wiart *et al* 2007).

Body parameters. Concerning body proportions, as for the head, a number of parameters have been considered to obtain the three classes of ages (see figure 5).

All child models have been constructed on the basis of mean values of morphologic data. So even if they come from six highly variable adults, child models present, by construction, a weaker variability than adult models.

2.2.2. Morphological characteristics depending on age. The mean values of main tissue weight ratios versus age are shown in figure 6. Skin and bone ratios are quite stable during the

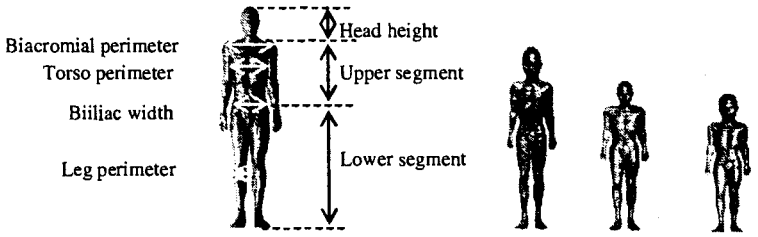

Figure 5. Morphological description of the body model. Example from left to right of Norman at adulthood, 12-, 8- and 5-year olds.

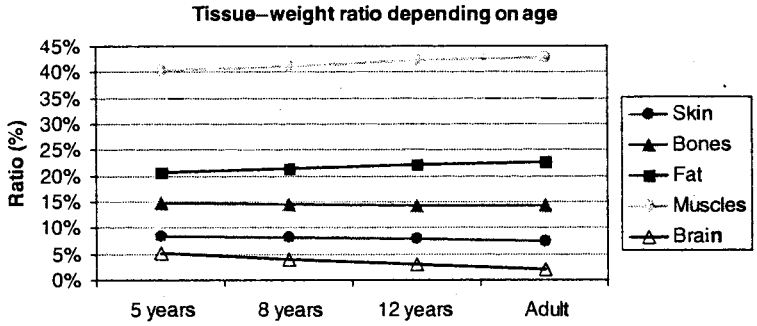

Figure 6. Evolution depending on the age of mean weight ratios of main tissues.

growth (about 8% for skin and 15% for bones). As for fat and muscles ratios, they increase during the growth by about 2%.

The brain–weight ratio is the only one to decrease with age. It decreases from 5% to 2% on average. This traduces that a child's brain grows quickly before the age of three and afterwards grows slowly. The brain–weight ratio reaches the adult level between 6 and 14 years of age.

As for adults, skin, muscles, bones and fat represent around 85% of total weight. The mean repartition of these tissues is quite stable at the different ages studied. Muscles represent the heaviest ratio with an average of 41% of the total weight.

By comparing weight repartitions in a child obtained by the morphing method and in a child obtained by a simple scaling, it appears that the homothetic transformation does not enable us to take into account the disparities in the human growth. For example, the brain homothetic reduction would be too drastic and opposite; muscles and fat homothetic reductions would not be important enough.

3. Numerical method

3.1. Exposure parameters

This study is focused on exposure assessment to an incident front plane wave for isolated conditions. The incident field is vertically polarized and arrives face to the phantom. Exposure is quantified by the SAR. The SAR is given by the well-known relationship

$$\mathrm{SAR} = \frac{\sigma E^2}{\rho},$$

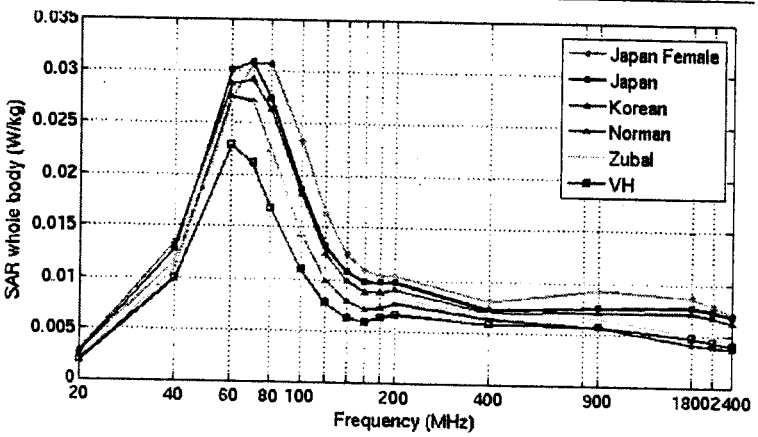

Figure 7. Whole-body-averaged SAR for different adult models on a large frequency range from 20 MHz to 2400 MHz for an incident power density of 1 W m^{-2}.

where σ is the conductivity, ρ is the mass density and E is the electric field strength induced in tissues.

Different numerical methods can be used to assess the electric field induced in human body. The most employed is the finite difference in time domain (FDTD) (Taflove 2000). In our study, an in-house FDTD code has been used. To simulate an infinite space and to avoid spurious reflection at the boundary of the limited numerical domain, absorbing boundary conditions have to be imposed in this study. The in-house code enables using the uniaxial perfectly matched layer (UPML) (Berenger 1994). To propagate a plane wave, a Huygens box is placed five cells from the UMPL layers. The phantom is also placed five cells away from the Huygens box as described.

The choice of different parameters has been tested by comparing FDTD calculations with the analytical Mie series solution (Stratton 1941) for a homogeneous muscle sphere. The calculation domain consists in 2 mm cubical cells and the absorbing boundary conditions employed were six UMPLs (Gedney 1996) with an order of 4. The Huygens box is placed five cells away from the UMPL. The incident field was a plane wave vertically polarized propagating along the horizontal axis from front to back. A comparison between the FDTD and Mie calculations gives a very good agreement. At 900 MHz, the local error on the electric field is very weak with an absolute maximal deviation of 7% and an absolute averaged error of less than 1%. Similar comparisons at 70 MHz and 2100 MHz yield maximal differences of 5% and 10% and averaged differences of 1% and 2%, respectively.

4. Results on variability of models

4.1. Adults

4.1.1. Averaged whole-body SAR. We are now going to consider the whole-body-averaged SAR of each adult phantom depending on frequency (figure 7).

The well-known resonance region around 70 MHz clearly appears in figure 7. The resonance frequency depends on the height of the phantom. The tallest phantom Visible Human (respectively the smallest phantom Japan Female) has the lowest (respectively the highest) resonance frequency.

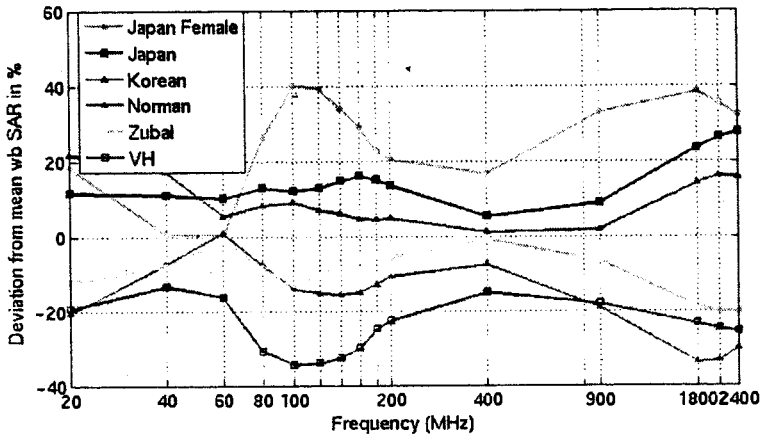

Figure 8. Deviation of the whole-body SAR of each adult model from the mean whole-body SAR.

Table 1. Mean values on frequency for each adult model of the deviation from mean whole-body SAR.

	Visible Human	Korean	Zubal	Norman	Japan Male	Japan Female
Mean deviation from mean whole-body bSAR	−25%	−15%	−9%	+9%	15%	+25%

The whole-body-averaged SAR level can be compared to the BMI level or to the body surface area (BSA) level. The lowest (respectively highest) whole-body-averaged SAR fits with the highest (respectively lowest) BMI or the highest (respectively lowest) BSA. Concerning Japan Male and Norman, they have roughly the same BMI and BSA, and yet Japan Male has a whole-body-averaged SAR slightly higher than that of Norman. This discrepancy can be explained by anatomical considerations. Japan Male has less skin than Norman, and skin has a relative high permittivity and conductivity.

Figure 8 displays deviations of the whole-body SAR of each adult model from the mean whole-body SAR depending on the frequency. The variability of the adult model appears strong. As expected, the highest deviations are visible for both the extreme models: the Japan Female and Visible Human.

In table 1, the mean deviation of the whole-body SAR averaged on the frequency range is given for each adult.

On the frequency range studied, the standard deviation is highly variable contained between 9% at 60 MHz and 30% at 2100 MHz. The mean value is 20% and, for example, values at 100 MHz, 400 MHz and 900 MHz are 25%, 10% and 20% respectively.

4.1.2. Averaged part-body SAR. In this part, the whole body is split into four main parts: the head, the legs, the torso and the arms. The mean values of the averaged SAR induced in each part are displayed in figure 9.

Whatever the part of the body, the resonance around 60 MHz of the whole body is visible. Each part participates in the whole-body resonance. For the legs and torso, the resonance at 60 MHz is highly marked because the legs and torso constitute the parts of the whole body which start resonating. In contrast, head and arms are separate parts of the body. The head

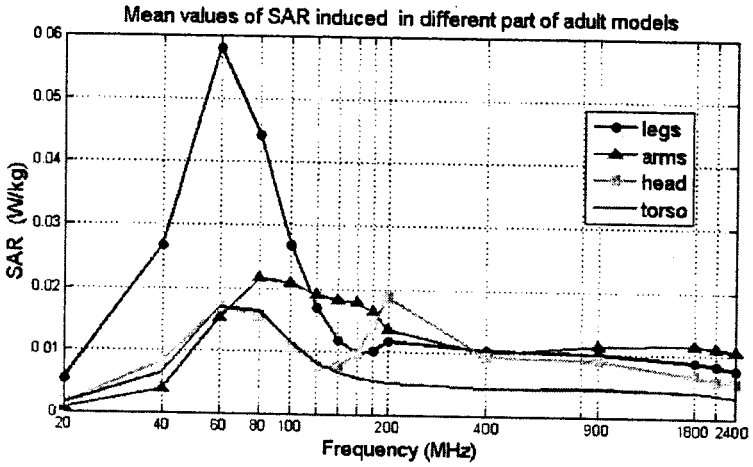

Figure 9. Mean values of SAR induced in different parts of adult models.

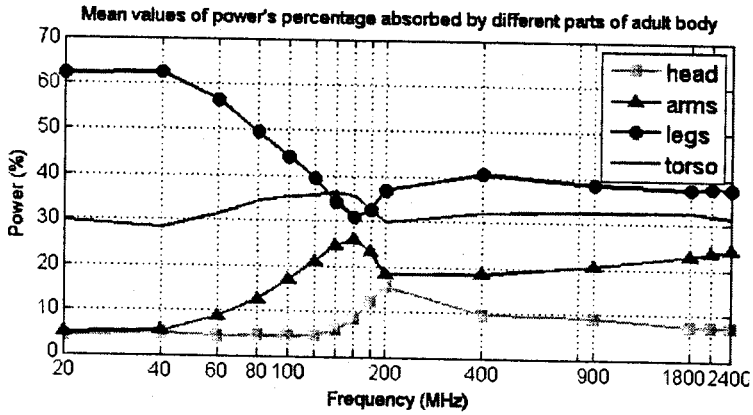

Figure 10. Mean values of power's percentage absorbed by each part of body: head, arms, legs and torso.

subjects the whole-body resonance around 60 MHz, but another resonance also appears around 200 MHz. This resonance is a characteristic of the head's geometry and internal properties. The arms are parallel to the body; this should explain the large zone of resonance between 80 MHz and 180 MHz. On the one hand, a homogeneous cylinder of a size which is typically the size of adult arms resonates around 180 MHz and, on the other hand, the whole body resonates around 70 MHz. A combination of both phenomena induces this large resonance region from 80 MHz to 180 MHz.

To enable quantitative comparisons, figure 10 displays the percentage of power absorbed by the main parts of the body. As expected, the legs and torso absorbed most of the power, specifically at low frequencies. The legs absorb until more than 60% of the total absorbed power and the torso until 30% at the lowest frequencies. When the frequency increases, the arms and head start their specific resonances and, as a result, they will absorb more in proportion.

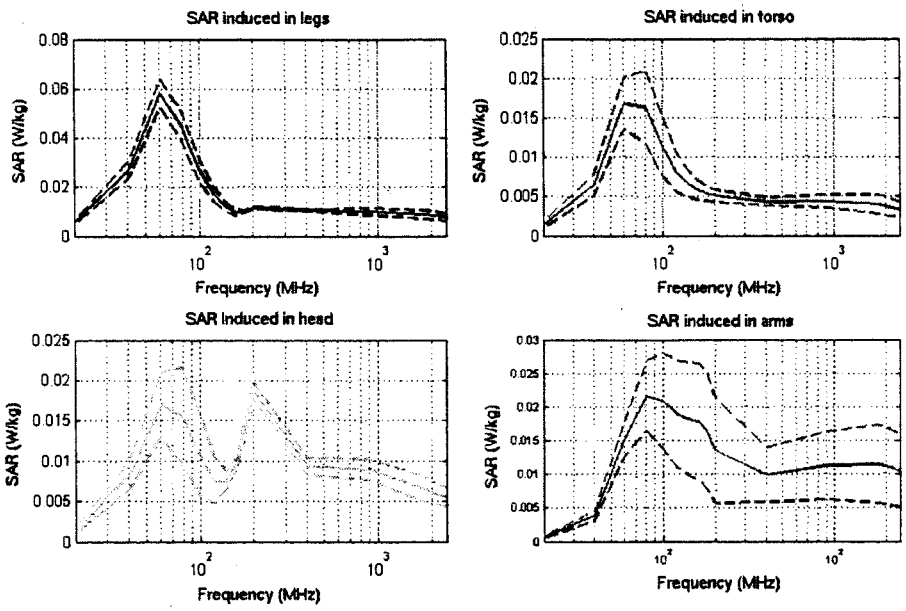

Figure 11. Variability of the SAR induced in different parts of adult models: legs (a), torso (b), head (c) and arms (d). The continuous lines are the mean values and the dotted lines are lower and upper bounds of the interval [mean $-\sigma$ mean $+\sigma$].

To point out the variability of used models, figure 11 shows mean trends of the SAR induced at different parts of the adult body. The lower and upper bounds of interval [mean $-\sigma$ mean $+\sigma$] are also indicated by dotted lines.

First of all, the SAR induced in legs is noted to be very variable. The standard deviation σ is low. The SAR induced in the torso presents a variability analogous to that of the whole body. The SAR induced in the head presents a variability analogous to that of the whole body around the whole-body resonance. But around the resonance characteristic of the head (about 200 MHz), the variability is lower. This can be explained by the lower variability of head models than that of the whole body. As for arms, the posture of different models is different. For example (see figure 1), the Korean model has his arms very close to his body while Visible Human has his hands in front of him and other models have their arms slightly separated from their bodies. These differences may explain the high variability in the SAR induced in arms.

4.1.3. Averaged SAR depending on the tissue type. In the morphological analysis of adult models in section 1, we have noted that only four tissues of adult models absorbed about 85% of the total power absorbed by the whole body. These tissues are skin, bones, muscles and fat. Figure 12 displays the mean values of the SAR induced in these four tissues.

As expected, the whole-body resonance around 60 MHz is visible in each tissue. In the resonance region, the SAR values are much higher in muscles and skin than in fat and bones because conductivity values of muscles and skin are much higher than those of fat and bones. Above this resonance region, the higher the frequency is, the more the absorption is superficial and, in this way, the SAR induced in skin increases while the SAR induced in muscles decreases.

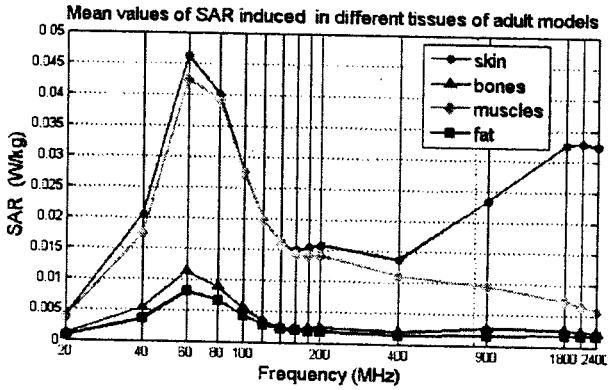

Figure 12. Mean values of the SAR induced in main tissues of an adult model: skin, bones, muscles, fat and brain.

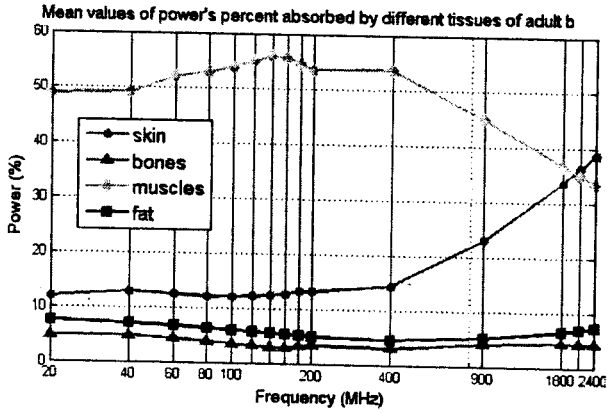

Figure 13. Percentages of power absorbed by main tissues of adult models depending on frequencies.

As for the study of absorption by different parts of the body, we display in figure 13 percentages of power absorbed by five main tissues.

Figure 12 shows that skin and muscles have almost the same behavior in terms of induced SAR at low frequencies. But concerning the percentage of absorbed power, muscles absorb most of the power at low frequencies (until 55% of the total absorbed power) because the human body has much more muscles than skin. In adulthood, muscles represent on average 43% of the total weight. But by increasing the frequency, the absorption becomes more superficial and then the skin becomes the predominant tissue concerning the absorbed power. At 2400 MHz, the skin absorbed on average 40% of the total absorbed power while it represents only 7% of the total weight.

In figure 14, distributions of power absorption depending on tissues for a low frequency of 20 MHz and a high frequency of 2400 MHz are displayed. At 20 MHz, it clearly appears that absorption is through the whole body with most of the power absorbed by muscles. In

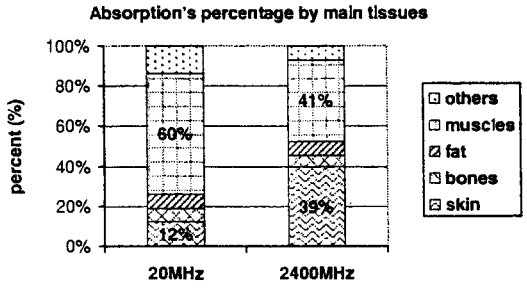

Figure 14. Mean distribution of power absorption in adult models at 20 MHz and 2400 MHz.

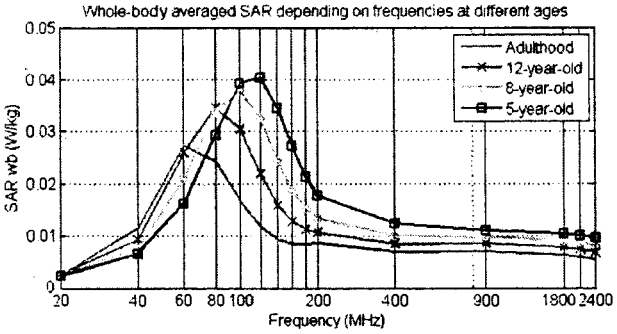

Figure 15. Mean whole-body SAR depending on frequencies for different ages.

contrast, at 2400 MHz, absorption is more superficial and the skin absorbs a high part of the incident power.

4.2. Child

As described in section 2.2, for each type of model (VH, Zubal, Norman, Japan Male, Japan Female and Korean) three 5-, 8- and 12-year-old children have been constructed by morphing. In figure 15, the whole-body-averaged SAR depending on the frequency is displayed averaged for the six types of models.

Whatever the model, children and adults have qualitatively the same behavior. But the younger the model, the higher the resonance frequency and the stronger the resonance. So, the whole-body SAR induced in children is higher than the one induced in adults.

On average, the resonance frequency is shifted from 60 MHz at adulthood to 80, 100 and 120 MHz at respectively 12, 8 and 5 years of age. Concerning amplitudes, the whole-body-averaged SAR at resonance increased by 26%, 38% and 48% from adulthood to respectively 12, 8 and 5 years of age.

As for the adult study, the SAR induced in each part of the body is interesting data to understand the absorption by the body. Figure 16 displays the SAR induced in each part of the body of adult and children, on average of the six types of model depending on frequency. The same conclusions as for an adult are valid. The legs and torso constitute the global shape of the body and present the whole-body resonance. Concerning heads, as for the adult one, besides resonating at the whole-body resonance frequency, they have a characteristic resonance at higher frequency. As for the whole-body resonance frequency, the resonance characteristic

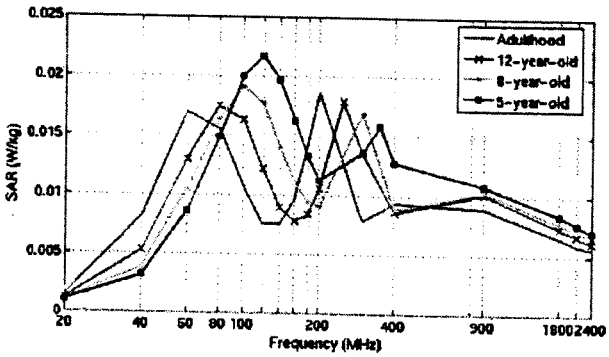

Figure 16. SAR induced in heads, averaged on six types of model for different ages of model (adulthood, 12-, 8- and 5-year-old) depending on frequency.

of the head is shifted with age. It is located at 200 MHz, 250 MHz, 300 MHz and 350 MHz for the heads of respectively an adult, a 12-, a 8- and a 5-year-old child.

5. SAR and reference levels

The ICNIRP has recommended limits to protect the general public against overexposure to electromagnetic fields. These limits are stated in terms of basic restrictions and of reference levels. Basic restrictions define among others a limit value for the whole-body-averaged SAR. For public exposure, this ICNIRP basic restriction is 0.08 W kg^{-1}. Reference levels have also been defined in order to ensure respect for these basic restrictions. For our range of frequency, the ICNIRP public exposure reference levels are given as a power density denoted as S:

$$\begin{aligned} &\text{for} \quad F < 400\,\text{MHz}, && S = 2\,\text{W m}^{-2} \\ &\text{for} \quad 400\,\text{MHz} < F < 2\,\text{GHz}, && S = \tfrac{F}{200}\,\text{W m}^{-2} \\ &\text{for} \quad F > 2\,\text{GHz}, && S = 10\,\text{W m}^{-2}. \end{aligned}$$

Figure 17 displays the whole-body-averaged SAR for the six adult models for an incident power density equal to ICNIRP public exposure reference levels. Compared to the whole-body-averaged SAR induced by constant incident power density (figure 8), a second peak region appears in the 2 GHz region directly induced by the reference levels proportional to the frequency in this region.

Around 2 GHz, the whole-body-averaged SAR of the Japan Female and that of the Male are very close to the basic restriction (SAR values reach 92% and 99% of the basic restriction). It was previously shown that the standard deviation of the whole-body SAR is about 30% around 2 GHz. It is therefore reasonable to consider that some human models that will exceed basic restrictions.

Concerning child exposure, ICNIRP reference levels are the same as for an adult. The behavior of the whole-body SAR of children for incident power density equal to ICNIRP reference levels (see figure 18 for trends averaged on the six models) is qualitatively the same as for an adult. The artificial peak around 2 GHz also appears and is stronger than for an adult. Adults were not so far off the basic restriction; it also makes sense that the SAR induced in children exceeds the ICNIRP basic restriction under these conditions of exposure. The most problematic region is the region around 2 GHz. At these frequencies, almost all children have a whole-body-averaged SAR exceeding the basic restriction. The whole-body-averaged

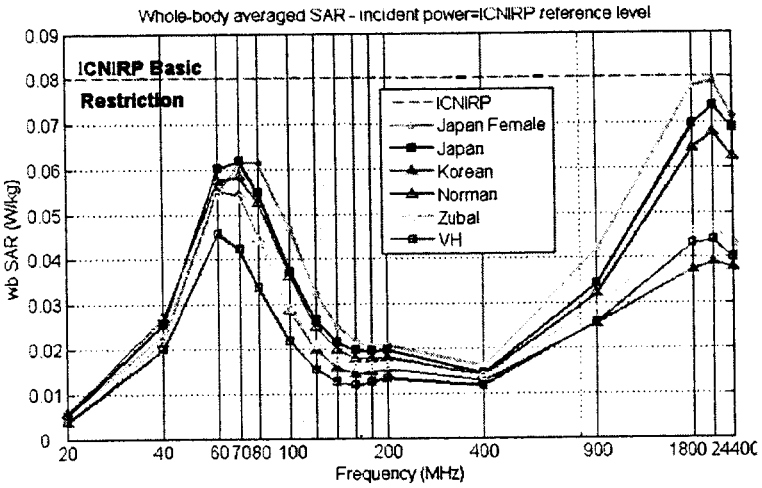

Figure 17. Whole-body-averaged SAR for the six adult models depending on frequency for an incident power density fixed by ICNIRP reference levels.

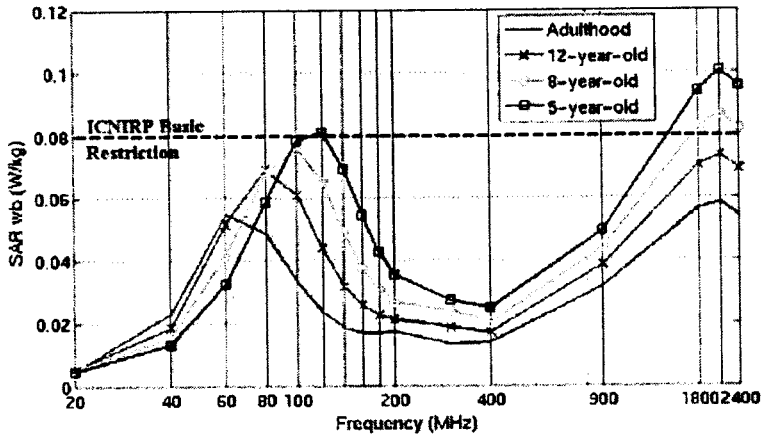

Figure 18. Whole-body-averaged SAR for the mean model (for adult and children) depending on frequency for an incident power density fixed by ICNIRP reference levels.

SAR of 5-year-old children reached on average 125% of the ICNIRP basic restriction with a standard deviation of 25%, that of 8-year-old children reached 108% with a standard deviation of 23% and that of 12-year-old children reached 96% with a standard deviation of 13%.

Concerning the resonance region, SAR values are very close to restrictions particularly for 5-year-old children. The whole-body-averaged SAR of a 5-year-old child reached on average 101% of the ICNIRP basic restriction with a standard deviation of 7%.

6. Conclusions

FDTD calculations have been performed at a common 2 mm resolution of different voxel models of adult human for isolated conditions: Norman, Zubal, Korean, Japan Male and

Female and Visible Human. From these adults, 5-, 8- and 12-year-old children have been built by using a morphing method enabling us to respect numerous morphological parameters. This paper presented an analysis of calculations of an averaged SAR from 20 MHz to 2.4 GHz.

Before any calculation, the morphology variability of adult models used in this study has been pointed out. Indeed, the six used adult models do not have the same appearance. This has been traduced by relatively high standard deviations of morphological parameters of adult models. For example, the body mass index (BMI) assessing body fat has a standard deviation of 18% and concerning internal morphology, muscles that represent the highest weight ratio of humans have a standard deviation of 30%.

The morphology variability affects an induced SAR in models. FDTD calculations have pointed out an important variability of the whole-body-averaged SAR implying a standard deviation from 10% to 30% depending on the frequency.

On the one hand, calculation of the tissues-averaged SAR has shown that skin has a high impact on high frequencies because absorption is more superficial. At a low frequency, absorption is more volumic and most of the power is absorbed by muscles. Muscles represent on average 40% of the total mass for an adult, and they absorbed at low frequencies until 55% of the total absorbed power.

On the other hand, assessment of the averaged SAR in different parts of body has shown that the legs and torso introduce the whole-body resonance visible around 70 MHz for an adult. The heads and arms undergo whole-body resonance, but also present their own resonances around 200 MHz for an adult's head and around 160 MHz for an adult's legs.

By subjecting adult models to ICNIRP reference levels of public exposure, we point out that all the adult models used in this study respect basic restrictions but are not so far from them. Moreover, the variability of models leads to envisage models that might exceed basic restrictions.

Concerning children, the morphing method enables us to obtain more realistic models than by a simple homothetic transformation. Children have a behavior similar to adults. A whole-body resonance appears at a frequency and with amplitude increasing with a decreased age. Heads have a characteristic resonance between 200 MHz and 350 MHz depending on the age. Legs have a resonating plateau between 100 MHz and 200 MHz.

By subjecting children models to ICNIRP reference levels of public exposure, we point out that a number of the child models used in this study exceed basic restrictions around the gigahertz region. The whole-body-averaged SAR of 5-year-old children goes up to 40% over basic restrictions.

Further work will consist, on one hand, of studing the localized SAR exposure. On the other hand, it will be interesting to vary exposure by using an aside exposure or ground conditions for example.

Results on children should be confirmed by calculations on voxel models obtained, for example, from MRI images.

Acknowledgments

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EXHIBIT E

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

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Mobile Phone Radiation Induces Reactive Oxygen Species Production and DNA Damage in Human Spermatozoa *In Vitro*

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Abstract

Background: In recent times there has been some controversy over the impact of electromagnetic radiation on human health. The significance of mobile phone radiation on male reproduction is a key element of this debate since several studies have suggested a relationship between mobile phone use and semen quality. The potential mechanisms involved have not been established, however, human spermatozoa are known to be particularly vulnerable to oxidative stress by virtue of the abundant availability of substrates for free radical attack and the lack of cytoplasmic space to accommodate antioxidant enzymes. Moreover, the induction of oxidative stress in these cells not only perturbs their capacity for fertilization but also contributes to sperm DNA damage. The latter has, in turn, been linked with poor fertility, an increased incidence of miscarriage and morbidity in the offspring, including childhood cancer. In light of these associations, we have analyzed the influence of RF-EMR on the cell biology of human spermatozoa in vitro.

Principal Findings: Purified human spermatozoa were exposed to radio-frequency electromagnetic radiation (RF-EMR) tuned to 1.8 GHz and covering a range of specific absorption rates (SAR) from 0.4 W/kg to 27.5 W/kg. In step with increasing SAR, motility and vitality were significantly reduced after RF-EMR exposure, while the mitochondrial generation of reactive oxygen species and DNA fragmentation were significantly elevated ($P<0.001$). Furthermore, we also observed highly significant relationships between SAR, the oxidative DNA damage bio-marker, 8-OH-dG, and DNA fragmentation after RF-EMR exposure.

Conclusions: RF-EMR in both the power density and frequency range of mobile phones enhances mitochondrial reactive oxygen species generation by human spermatozoa, decreasing the motility and vitality of these cells while stimulating DNA base adduct formation and, ultimately DNA fragmentation. These findings have clear implications for the safety of extensive mobile phone use by males of reproductive age, potentially affecting both their fertility and the health and wellbeing of their offspring.

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Introduction

Male infertility is a distressingly common condition affecting about 1 in 20 of the male population [1]. In a majority of cases, the male partner produces sufficient numbers of spermatozoa to achieve fertilization but there are functional defects in these cells that prevent conception from occurring [2]. Despite several decades of research, the causes of such functional deficiencies in human spermatozoa remain largely unresolved. However, one contributory factor that has recently emerged is the quality of the sperm DNA delivered to the oocyte at the moment of fertilization [3]. Fragmentation of DNA in the male germ line has been associated with impaired fertilization, poor embryonic development, high rates of miscarriage and an increased incidence of morbidity in the offspring, including childhood cancer [3,4]. In view of the seriousness of these clinical outcomes, attention has recently focused on the environmental and genetic factors that might be involved in the aetiology of DNA damage in the male germ line.

These investigations have suggested that one of the environmental factors potentially involved in the etiology of DNA damage in human spermatozoa is an increased exposure to radio-frequency electromagnetic radiation (RF-EMR) emitted from mobile phones. This association was initially suggested by an epidemiological study which found negative correlations between mobile phone usage and various attributes of semen quality, particularly motility [5]. This was immediately followed by an experimental study involving exposure of male mice to RF-EMR, which revealed a significant impact on the integrity of both the mitochondrial and nuclear genomes [6]. Recently, the negative impact of mobile phone usage on semen quality in human males was confirmed in a study that found the duration of exposure to be

correlated with defects in sperm count, motility, viability, and normal morphology [7]. In light of these data, there is now an urgent need to determine whether exposure of human spermatozoa to RF-EMR can also induce DNA damage and to resolve the cellular mechanisms involved.

Several studies have found an association between human health and exposure to RF-EMR, with emphasis on a range of clinical conditions including childhood leukaemia, brain tumours, genotoxicity and neurodegenerative disease [8,9]. While the cellular mechanisms underpinning these effects have not been completely resolved, it has been suggested that oxidative stress could be a key factor [10]. However, extensive analysis of the importance of oxidative stress in mediating the pathological effects of RF-EMR has generated conflicting results, possibly due to differences in the fundamental redox susceptibility of the cell lines employed in these analyses [11]. In this context, it is significant that human spermatozoa are uniquely sensitive to oxidative stress for a variety of reasons. Firstly, these cells are largely devoid of the cytoplasm that in somatic cells houses the antioxidant enzymes that offer a first line of defense against free radical attack [12]. Secondly, these cells possess abundant targets for the induction of peroxidative damage including polyunsaturated fatty acids and DNA [12–14]. Thirdly, these cells are professional generators of reactive oxygen species, that appear to emanate largely from the sperm mitochondria and, possibly, plasma membrane NAD(P)H oxidases [15,16]. Thus if any cell type would be vulnerable to the oxidative stress reportedly generated on exposure to RF-EMR, it would be human spermatozoa.

In light of these considerations, we have conducted a careful analysis of the biological consequences of exposing human spermatozoa to RF-EMR. The study design involved overnight exposure to RF-EMR at a defined frequency (1.8 GHz), over a range of SAR values that both covered the emission characteristics of mobile phones and generated sufficient dose-response data to shed light on the underlying pathophysiological mechanisms. Moreover, the temperature of the incubations was maintained at 21°C to avoid any secondary heating effects. The results clearly demonstrate that exposure to this type of radiation not only stimulates free radical generation by the sperm mitochondria but also creates a state of oxidative stress characterized by the formation of oxidative base adducts and DNA fragmentation. These data clearly have important implications for the safety of mobile phone use and highlight the potential importance of RF-EMR in the etiology of male infertility and childhood disease.

Results

RF-EMR disrupts human sperm motility and vitality and induces intracellular reactive oxygen species (ROS) production

In an initial experiment, functional human spermatozoa isolated from the high density region of Percoll gradients and suspended in BWW medium were exposed to RF-EMR at an SAR of 27.5 W/kg. This exposure induced a highly significant decline in both vitality ($p<0.001$; Figure 1A) and motility ($p<0.01$; Figure 1B) compared with the unexposed controls. Exposed spermatozoa also produced significantly higher amounts of ROS than background levels as measured by both the dihydroethidium (DHE) ($p<0.001$; Figure 1C) and MitoSOX red (MSR) probes ($p<0.001$; Figure 1D) suggesting that free radical generation had been initiated as a consequence of RF-EMR and that the mitochondria were significantly involved in this response.

RF-EMR has a negative impact on human spermatozoa over a range of SAR values

In light of these results we then extended the range of SAR values over which the consequences of RF-EMR radiation were examined (0.4 W/kg–27.5 W/kg) to include the values covered by conventional mobile phones (0.5 W/kg–1.5 W/kg).

High quality spermatozoa selected in discontinuous Percoll gradients displayed a decline in both vitality and motility after exposure to RF-EMR in a dose-dependent manner. The control populations maintained an average vitality of 89%; however, significant reductions in vitality were observed at exposure levels as low as 1.0 W/kg ($p<0.01$) (Figure 2A). Similarly, the control populations maintained motilities at an average of 86% over the incubation period, however after exposure to RF-EMR at levels of 1.0 W/kg, motility was observed to significantly decrease to 68% ($p<0.05$) and decreased still further at higher SAR exposures (Figure 2B).

Reactive Oxygen Species are central to the RF-EMR response

Exposure of human spermatozoa to RF-EMR over a range of SAR levels resulted in a dose-dependent activation of ROS generation, as detected by the DHE probe (Figure 3A). In this analysis, a significant increase in ROS positive cells was observed after exposure at 1.0 W/kg ($p<0.05$); thereafter ROS production rose rapidly with SAR values up to 4.3 W/kg and then began to plateau reaching a peak of 30% at the highest exposure levels assessed (Figure 3A). To determine whether such increases in ROS production might originate from the sperm mitochondria, MSR was employed as a probe. Spermatozoa exposed to increasing levels of RF-EMR, generated a significant, dose-dependent increase in ROS generation by the mitochondria. The response rose rapidly following RF-EMR exposure reaching statistical significance ($p<0.001$) at an SAR value 2.8 W/kg at which point 16% of the exposed cells were MSR positive. At SAR values above 4.3 W/kg, RF-EMR induced mitochondrial ROS begun to plateau reaching 30% at the maximal SAR values assessed (Figure 3B). By plotting the DHE positive cells against the MSR response for the entire data set (Figure 3D) we observed an extremely strong correlation ($R^2 = 0.823$) between these signals, suggesting that a majority of the ROS production elicited by RF-EMR involved electron leakage from the mitochondrial electron transport chain.

In order to control for bulk thermal effects of RF-EMR exposure, spermatozoa were also incubated at temperatures ranging from 21°C–50°C for 2 h (Figure 3C). This analysis did reveal an effect of heat on free radical generation by human spermatozoa possibly due to the activation of an apoptotic response, however these effects were only significant above 40°C. Thus at the temperature at which these experiments were performed (21°C) the highest observed RF-EMR-induced temperature rise (+0.4°C at 27.5 W/kg), could not of itself account for the increased ROS response observed across the range of SAR settings evaluated in this study.

RF-EMR induces oxidative DNA damage (8-OH-dG)

In order to determine whether the ROS generation induced on exposure of human spermatozoa to RF-EMR resulted in a state of oxidative stress, we monitored the expression of 8-hydroxy-2′-deoxyguanosine (8-OH-dG), a marker for oxidative damage to sperm DNA. As the SAR level was increased, the amount of oxidative DNA damage expressed in the spermatozoa became elevated (Figure 4A). A significant increase in 8-OH-dG expression

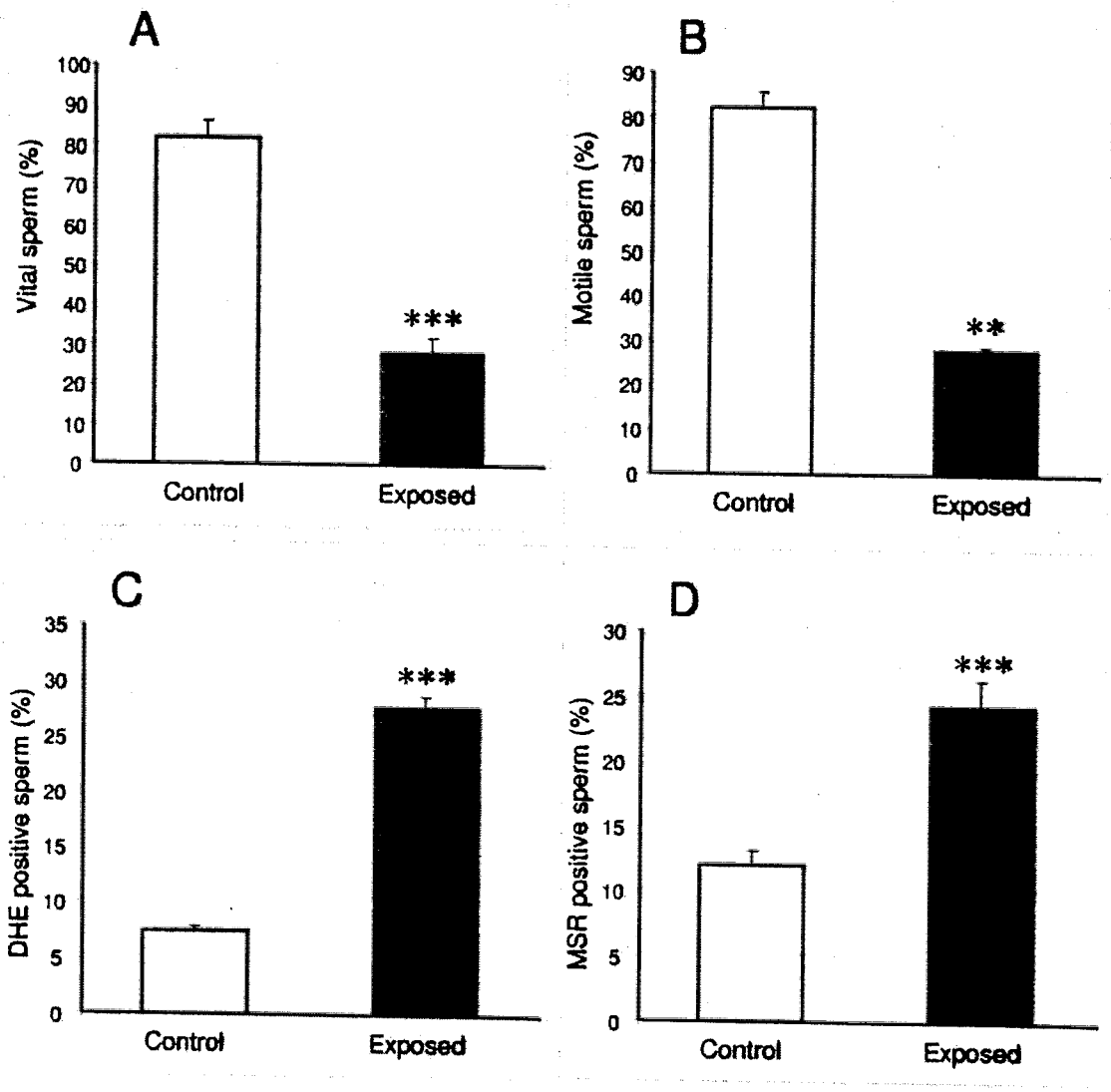

Figure 1. RF-EMR exposure decreases motility and vitality of human sperm while also inducing intracellular ROS. Percoll-purified spermatozoa (5×10^6 cells) were suspended in 1 ml BWW in a 35 mm Petri dish and placed within the waveguide while control cells placed outside the waveguide. A frequency of 1.8 GHz at a SAR of 27.5 W/kg was used and all samples were incubated for 16 h at 21°C. **A,** Sperm vitality was significantly reduced from the control value of 82%±4% to 29%±4% for the exposed cells (***$p<0.001$). **B,** Sperm motility was also significantly reduced from the control value of 82%±4% to 28%±1% (**$p<0.01$). **C,** ROS production was increased after RF-EMR exposure such that 28%±1% of the cells were producing ROS, while only 7%±0.4% of the controls contributed to ROS production (***$p<0.001$). **D,** 24%±1% of the exposed cells generated mitochondrial ROS, while the only 12%±1% of the control cells produced ROS from this source (***$p<0.001$). All results are based on 4 independent samples.
doi:10.1371/journal.pone.0006446.g001

became apparent at low SAR values (<5.0 W/kg) rising to a maximum of around 20% at the highest levels of exposure (27.5 W/kg). By plotting the 8-OH-dG positive cells against the MSR signal (Figure 4B) it was apparent that a strong positive correlation existed between the two parameters ($R^2=0.727$); the higher the level of mitochondrial ROS generation, the greater the degree of oxidative DNA damage in the spermatozoa.

RF-EMR induces DNA fragmentation in human spermatozoa

To determine whether the oxidative DNA base damage precipitated by RF-EMR-induced ROS generation had any impact on DNA stand breaks in human spermatozoa, the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay was utilized. As illustrated in Figure 5A, human spermatozoa responded to RF-EMR exposure, with a significant increase in DNA strand breaks at an SAR of 2.8 W/kg ($p<0.05$) that increased rapidly with rising SAR values and then reached a plateau so that at the highest SAR level assessed (27.5 W/kg), 29% of the cells expressed significant DNA fragmentation. This DNA damage was highly correlated with free radical generation by the sperm mitochondria giving a correlation coefficient of $R^2=0.861$ (Figure 5B). Moreover, the level of DNA fragmentation was highly correlated with 8-OH-dG formation ($R^2=0.725$; Figure 5C) such that sperm cells exhibiting high levels of oxidative DNA damage, also possessed high levels of DNA fragmentation.

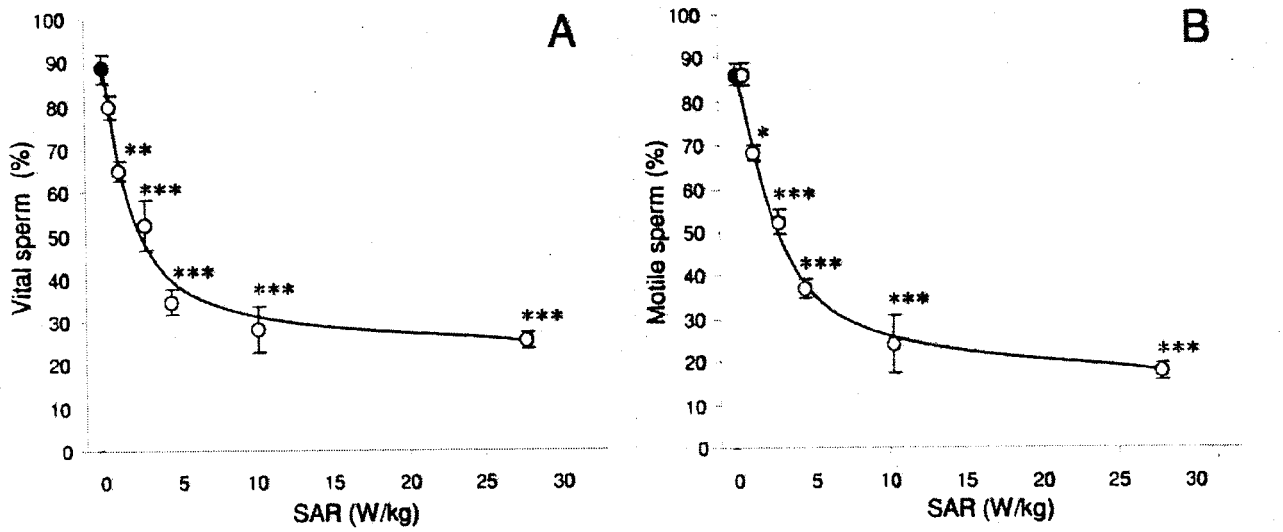

Figure 2. RF-EMR exposure reduces motility and vitality of human spermatozoa, in an SAR dependent manner. Percoll-purified spermatozoa (5×10^6 cells) were suspended in 1 ml BWW in a 35 mm Petri dish and placed within the waveguide while control cells (closed circles) were placed outside the waveguide. Cells in the waveguide were exposed to 1.8 GHz RF-EMR at SAR levels of 0.4, 1.0 2.8 4.3 10.1 and 27.5 W/kg (open circles) for 16 h at 21°C. Both vitality and motility were reduced in a dose dependent manner. **A,** Vitality was significantly reduced at a SAR of 1.0 W/kg from 89%±3% to 65%±1% (**p<0.01). **B,** Motility was also significantly reduced at a SAR of 1.0 W/kg from 86%±2% to 68%±2% (*p<0.05). All results are based on 4 independent samples.
doi:10.1371/journal.pone.0006446.g002

Discussion

While a high proportion of the male population suffers from infertility associated with defective sperm function [17], the ctiology of this condition remains largely unresolved. Notwithstanding the general paucity of information in this area, recent studies have highlighted the interesting finding that male infertility patients are frequently characterized by high levels of DNA damage to their spermatozoa [18]. In light of these data, we have hypothesized that the disruption of sperm fertilizing potential and the concomitant presence of high levels of DNA damage in the sperm nucleus involves a common causative mechanism in the form of oxidative stress [19].

Oxidative stress has been known for some time to limit the fertilizing potential of human spermatozoa through the induction of peroxidative damage to the sperm plasma membrane [13,20]. Oxidative stress is also known to be associated with DNA damage in human spermatozoa [21]. Furthermore, the source of the free radicals rcsponsible for generating such stress appears to be the mitochondria [15]. However, the factors responsible for inducing the mitochondria to leak electrons and propagate the production of ROS have not been elucidated. The research described in this article suggests that one of the key environmental factors involved in the stimulation of sperm mitochondria to produce high levels of ROS, might be excess exposure to RF-EMR from sources such as mobile phones.

In a pilot study, human spermatozoa were found to respond to RF-EMR (at 1.8 GHz with a SAR of 27.5 W/kg) with a range of negative changes including dramatic declines in both sperm vitality and motility. We also observed significant increases in both cytoplasmic ROS levels (DHE) as well as mitochondrial ROS levels (MSR) after RF-EMR exposure. We have previously shown that the chemical induction of mitochondrial ROS production with rotenone can precipitate a state of oxidative stress leading to high levels of lipid peroxidation and a loss of sperm motility [15]. Therefore, these data highlight the particular vulnerability of human spermatozoa to oxidative attack and the potential significance of sperm mitochondria in the generation of free radicals.

To assess whether similar effects could be observed at lower power densities, closer to the SAR values associated with mobile phones (0.5–1.5 W/kg) a dose-dependent analysis was conducted. In addition to the conventional assessments of motility and vitality, assays were included to assess the potential for RF-EMR to induce sperm DNA damage and further, whether the DNA damage was oxidative in nature. Confirmation of the detrimental effects of RF-EMR on human sperm was again observed. Over the power density range employed, a significant ($P<0.001$) dose-dependent response for all sperm parameters was observed, including motility, vitality, ROS generation by the whole cell, ROS generation by the mitochondria, oxidative DNA damage and DNA fragmentation. Furthermore, the profiles of all the observed effects with respect to SAR were intriguingly similar, suggesting a common underlying mechanism.

Specifically, all of the responses examined showed an extremely rapid change at low SAR exposures that then reached a plateau at a point where around 30% of the sperm population was affected. This suggests that while we were careful to use only Percoll-purified, high quality spermatozoa in this analysis, there exists within this cell population, a cohort of spermatozoa that are particularly vulnerable to the induction of oxidative stress by RF-EMR. These spermatozoa may have compromised mitochondria, poorly remodeled chromatin or a combination of such factors [15,22]. Heterogeneity within the sperm population is a feature of the human condition. However, this does not mean that a majority of spermatozoa would not, ultimately, be affected by RF-EMR in vivo; much would depend on the duration of exposure. In vitro, we are limited by the inability of human spermatozoa to survive for

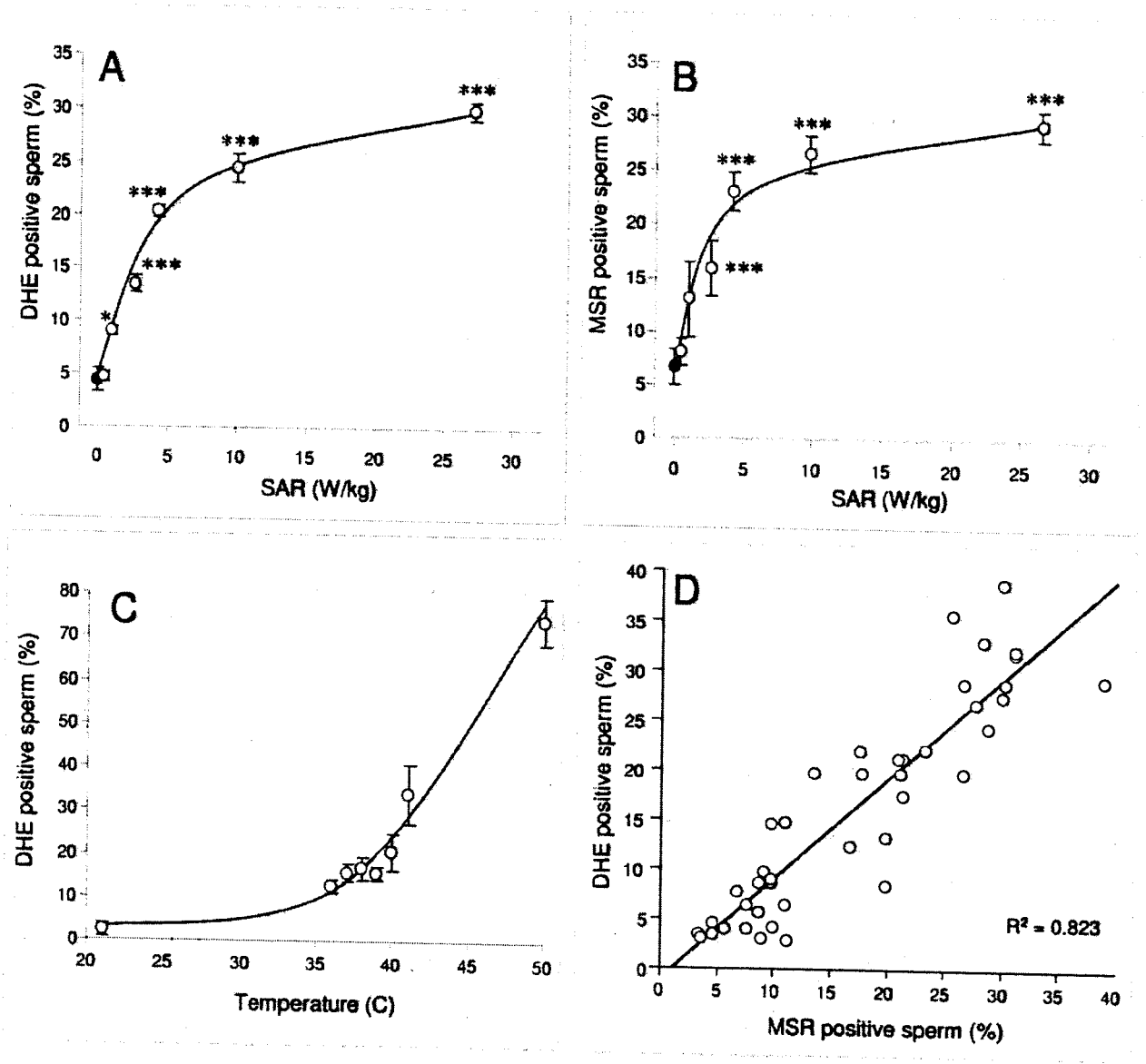

Figure 3. RF-EMR induces ROS generation in human spermatozoa, in an SAR-dependent manner unrelated to thermal effects. Percoll-purified spermatozoa (5×10^6 cells) were suspended in 1 ml BWW in a 35 mm Petri dish and placed within the waveguide while control cells placed outside the waveguide (closed circles). Cells in the waveguide were exposed to 1.8 GHz RF-EMR at SAR levels between 0.4 and 27.5 W/kg (open circles) for 16 h at 21°C. Also, purified sperm cells were subjected to incubation temperatures ranging from 21°C–50°C for 2 h. As the power levels were increased, the cellular generation of ROS increased in a dose-dependent manner. ROS levels were also observed to increase as a result of incubation temperature, but such results were not significant until the temperature exceeded 40°C. **A,** ROS generation (DHE response) was significantly increased from control levels after exposure to 1.0 W/kg (*$p<0.05$) and above (***$p<0.001$). **B,** RF-EMR induces ROS generation by the sperm mitochondria as monitored by MSR; significant increases were observed at SAR values of 2.8 W/kg (***$p<0.001$) and above. All results are based on 4 independent samples. **C,** In order to control for thermal effects, the impact of temperature of cellular ROS generation was monitored; a significant increase in ROS generation was observed as temperatures rose above 40°C ($p<0.001$). **D,** Across the entire data set, the total level of ROS generation by human spermatozoa (DHE positive cells) was highly correlated with the level of ROS generation by the mitochondria (MSR positive cells: $R^2=0.823$).

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more than 24 hours in a simple defined culture medium. In vivo, spermatozoa may take up to a week to move from the seminiferous tubules in the testes to the cauda epididymis and during the whole of this time they would be vulnerable to RF-EMR exposure [23].

We recognize that these studies were conducted using spermatozoa suspended in a simple defined culture medium rather than the epididymal plasma in which they would be suspended in vivo. Nevertheless the fact that effects on sperm quality have previously been observed in both whole animal radiation experiments [3] and in epidemiological studies of human subjects exposed to various levels of mobile phone radiation [5,7,24], emphasizes the biological and clinical relevance of these findings. Moreover, another recent study has found that exposing human spermatozoa to mobile phone radiation for 1 hour leads to significant declines in motility and

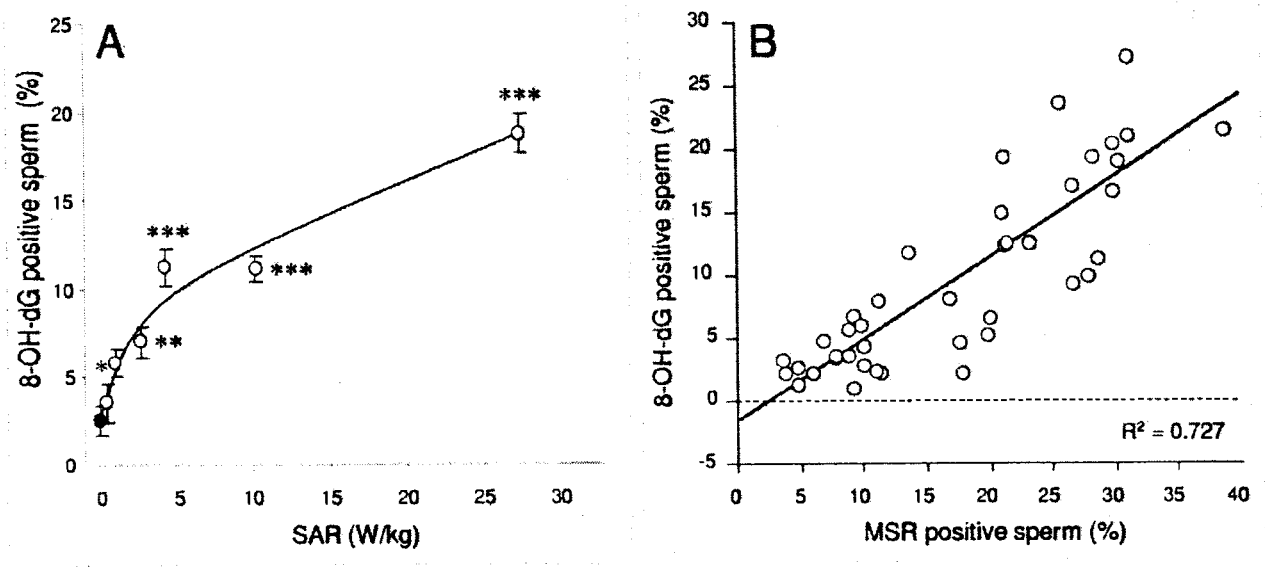

Figure 4. RF-EMR induces oxidative DNA damage in human spermatozoa. Following Percoll fractionation, 5×10^6 high density, spermatozoa were suspended in 1 ml BWW. The cells were placed in 35 mm Petri dishes and placed inside a waveguide. 5×10^6 cells in 1 ml BWW were placed outside the waveguide as a control (closed circle). The cells in the waveguide were exposed to 1.8 GHz RF-EMR at SAR levels between 0.4 and 27.5 W/kg (open circles) and all samples were incubated for 16 h at 21°C. Following incubation, Fe^{2+} and H_2O_2 was added to cells to act as a positive control, incubated for 1 h, then 100 µl 2 mM DTT/BWW solution was added and incubated for 45 min at 37°C. Cells were fixed and labeled with 100 µl charcoal purified anti-8-OH-dG, FITC tagged antibody at a dilution of 1:50, incubated at 21°C for 1 h, washed and then assessed by flow cytometry. **A,** As the power levels were increased, the amount of oxidative DNA damage expressed also increased. A significant amount of oxidative DNA damage was observed in cells exposed to 2.8 W/kg (*$p<0.05$) RF-EMR and above (**$p<0.01$; ***$p<0.001$). Results are based on 4 independent samples. **B,** The levels of 8-OH-dG expression were positively correlated with the levels of ROS generation by the mitochondria ($R^2=0.727$).
doi:10.1371/journal.pone.0006446.g004

vitality in concert with an increase in cellular reactive oxygen species generation [25]. The levels of RFEMR exposure were not quantified in this study nor were the sources of ROS identified. Nevertheless, these findings reinforce the general conclusions generated in this paper, particularly with respect to central role played by oxidative stress. The ever-increasing prevalence of mobile communications technology means that humans are now exposed to higher amounts of RF-EMR than ever before. Mobile phones are commonly carried in bags or in pockets in very close proximity to the body. In addition to this, these devices can be stored adjacent to the same part of the body for extended periods of time. In this context, exposure of the male reproductive system to RF-EMR is clearly a significant issue.

The particular significance of the present study is that it not only demonstrates a direct effect of RF-EMR on sperm motility, vitality and DNA integrity but also identifies a potential causative mechanism involving electron leakage from the mitochondrial electron transport chain and the induction of oxidative DNA damage. In part, these mechanistic insights have been achieved because the cell type used in these studies, the human spermatozoon, has an extremely simple cellular architecture, lacking significant cytosol and possessing few cellular organelles other than the sperm nucleus, flagellum and mitochondria. One consequence of this structure is that these cells are uniquely vulnerable to oxidative stress. Moreover, such stress is already known to induce the functional and structural lesions observed in this study including both a loss of motility mediated by peroxidative damage to the sperm plasma membrane, as well as the formation of DNA base adducts in the sperm nucleus that ultimately lead to DNA fragmentation [26,27].

Notwithstanding the specialized nature of mammalian spermatozoa, the mechanisms suggested by this study may also apply to RF-EMR-mediated damage in other cell types. The RF-EMR used for communications, including mobile phone networks, is not of high enough power to be classed as ionizing radiation. The latter has sufficient energy to pull away electrons, dramatically altering the properties of affected molecules and typically creating extremely reactive radical species. RF-EMR does not contain sufficient energy for these processes. Nevertheless, this form of radiation may have other effects on larger scale systems such as cells and organelles, which stem from the perturbation of charged molecules and the disruption of electron flow [28,29]. Mitochondria have one of the largest standing membrane potentials in the body and their energetic functions are entirely dependent on the regulated movement of electrons and protons within the inner mitochondrion membrane. Theoretically, such fluxes might be susceptible to disruptions in local electric fields induced by RF-EMR, offering a potential link between this form of radiation and the non-thermal biological effects observed in this study.

This study clearly demonstrates that RF-EMR can damage sperm function via mechanisms that involve the leakage of electrons from the mitochondria and the creation of oxidative stress. These findings have immediate implications for the high rates of male infertility seen in our species, a majority of which is idiopathic. Furthermore, the fact that sperm DNA is damaged by this form of radiation has additional implications for the health and wellbeing of children born to fathers who have experienced high levels of occupational or environmental exposure to RF-EMR around the time of conception. Overall, these finding raise a number of related health policy and patient management issues that deserve our immediate attention. Specifically we recommend that men of reproductive age who engage in high levels of mobile phone use, do not keep their phones in receiving mode below waist level.

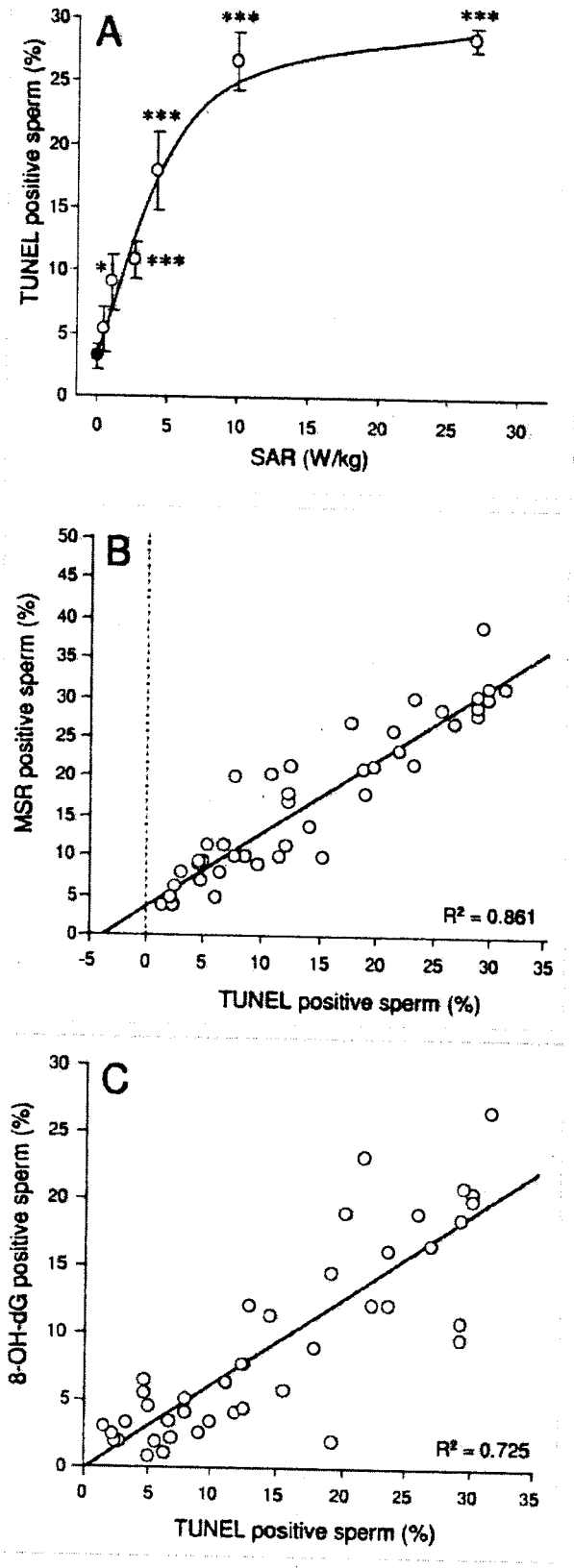

Figure 5. RF-EMR induces DNA fragmentation in human spermatozoa. Following Percoll fractionation, 5×10^6 high density spermatozoa were resuspended in 1 ml BWW, pipetted into 35 mm Petri dishes and placed inside a waveguide. 5×10^6 cells in 1 ml BWW were placed outside the waveguide as a control (closed circle). The cells in the waveguide were exposed to 1.8 GHz RF-EMR at SAR levels between 0.4 and 27.5 W/kg (open circles) and all samples were incubated for 16 h at 21°C. Following incubation, cells were fixed; DNase-I was used as a positive control. After 1 h incubation at 37°C, 50 µl of label and enzyme master mixes were added to the cells and incubated for 1 h at 37°C. Cells were then washed and assessed by flow cytometry. **A,** Significant levels of DNA fragmentation was observed in exposed spermatozoa at 2.8 W/kg (*$p<0.05$) and above (***$p<0.001$). **B,** DNA fragmentation was positively correlated with ROS production by the mitochondria as monitored by MSR ($R^2=0.861$). **C,** 8-OH-dG was also positively correlated with DNA fragmentation ($R^2=0.725$). Results are based on 4 independent samples.

Methods

Ethics Statement

This study was conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the University of Newcastle (H-712-0799). All patients provided written informed consent for the collection of samples and subsequent analysis.

Reagents and Solutions

All chemicals and reagents used in this research were obtained from Sigma Aldrich (Sigma Chemical Co., St. Louis, MO) unless stated otherwise. All reagents used were of research grade. All fluorescent probes were purchased from Molecular Probes Inc. (Eugene, OR). Biggers, Whitten and Whittingham (BWW) media supplemented with 1 mg/ml polyvinyl alcohol (PVA) was used in all experiments [30]. It was prepared fresh as required and kept at 37°C with an osmolarity in the range of 290–310 mOsm/kg.

Human spermatozoa

Institutional and State Government ethical approval was secured for the use of human semen samples for this research. The donors were students from the University of Newcastle donor program who had no known prior male reproductive pathologies including varicocele and infection. From this pool, 22 normozoospermic donors were used in this study. The average (±SEM) age of these donors was 24.1±1.1 y. After allowing at least 30 min for liquefaction to occur, spermatozoa were separated from seminal plasma on a discontinuous two-step Percoll gradient, as described [16]. The isolated spermatozoa were washed with 10 ml BWW, centrifuged at 600× g for 15 min and finally resuspended in HEPES-buffered BWW at a concentration of 20×10^6/ml supplemented with 1 mg/ml PVA. After acquiring each sperm fraction, the vitality, motility and cell density of the spermatozoa were evaluated. Vitality was determined by transferring 5 µl of each cell fraction onto a microscope slide followed by the addition of 5 µl of 0.5% eosin; the percentage of non-viable cells staining pink was then assessed by light microscopy. Motility was assessed by transferring 6 µl of the same sample onto a slide which was then covered with a coverslip and examined by phase contrast microscopy. For both the vitality and motility assessments, 100 cells were counted and the results expressed as a percentage.

Radio Frequency Electromagnetic Radiation and Waveguide

In this study, a cylindrical waveguide copied from the design by Gajda *et al* [31] was constructed such that 1.8 GHz radiation could

propagate along the waveguide and also so that 35 mm Petri dishes could be accommodated within the waveguide. To produce the radiation, a 3 GHz function generator (E4431B; Agilent, Palo Alto, CA) was used to generate a pure tone of 1.8 GHz. This signal was amplified by a linear radio-frequency (RF) amplifier and the amplifier output was split and connected through a matching network to antennae in the waveguide. The antenna matching circuit was tuned for maximum energy transfer to the antenna. The waveguide was encased in a brass mesh Faraday cage and the end was filled with 15 cm thick carbon-impregnated foam (RFI Industries, Bayswater, Victoria, Australia), which absorbs RF radiation, minimizing the reflection of radiation back into the waveguide and reducing the RF power by more than 50 dB outside the Faraday cage compared to the power at the amplifier output. A spectrum analyser (Advantest, Tokyo, Japan) connected to a Hameg HZ530 E-field probe (Hameg GmbH, Mainhausen, Germany) was used to check radiation levels and frequency prior to irradiation. The SAR values for the irradiations were calibrated by measuring the temperature rise in saline solution at power levels 20 dB or 100× higher than for the normal irradiations. The calibration procedure is complicated because (i) the saline solution loses heat energy to the surroundings at the same time as it is heated by the RF radiation and (ii) the temperature rise must be measured by an electronic thermometer to achieve the 0.1°C resolution required; however, the RF field interfered with the thermometer operation. As a consequence of these factors, the saline temperature was measured as a function of the time delay after the RF field was turned off and the temperature change extrapolated back to zero delay. Multiple measurements were made for RF irradiation times varying from 15 to 120 s and temperature increases up to 2.2°C above the ambient temperature were measured. After allowing for heat losses to the surroundings, the power level of 38.8 dBm at the amplifier output used in these measurements gave rise to a saline temperature rise of $0.053\pm0.008°Cs^{-1}$, giving a SAR of 220 ± 33 Wkg^{-1}. This error is similar to the variation in SAR observed in reference paper as a function of probe position [31]. The values of SAR reported in this paper were calculated from the above SAR, linearly scaled by the amplifier output power.

Following sperm purification and initial analysis, the high density Percoll fraction was prepared as a 1 ml suspension in BWW containing 5×10^6 cells and transferred into 35 mm Petri dishes. The cells to be irradiated were placed inside the waveguide while the control cells where placed adjacent to the waveguide but outside the Faraday cage. The SAR levels (0.4–27.5 W/kg) were fixed by setting the RF source to the appropriate dBm value. For all RF-EMR exposures (and respective controls) spermatozoa were incubated at room temperature (21°C) for a period of 16 h. Motility and vitality was measured prior to as well as after treatment. ROS and DNA damage assays were completed on both the exposed cells and respective controls after incubation.

Dihydroethidium Assay

Dihydroethidium (DHE) is a poorly fluorescent 2-electron reduction product of ethidium that on oxidation produces DNA sensitive fluorochromes that generate a red nuclear fluorescence when excited at 510 nm. The results obtained with this probe have been validated as a measure of the ability of human spermatozoa to generate ROS, including definitive identification of the superoxide anion [32]. For the assay, DHE and the vitality stain, SYTOX® Green (Molecular Probes), were diluted in BWW/PVA and added to 2×10^6 spermatozoa in a final volume of 200 µl comprising 175 µl of purified sperm suspension, 5 µl of test compound and 20 µl of the DHE:SYTOX® green mixture to give final concentrations of 2 µM DHE and 0.5 µM SYTOX® green. The cells were then incubated in the dark at 37°C for 15 min, washed once (600×*g* for 5 min) and the resultant red and green fluorescence measured on a FACSCalibur flow cytometer (Becton Dickinson, San Jose, CA), as described [32]. The unstained control displayed 0.09%±0.03% DHE positivity, the DHE positive control (treated with 100 µM arachidonic acid) displayed 99%±1% DHE positivity and the SyG positive control (frozen-thawed cells) displayed 98%±1% SyG positivity. The inclusion of SyG in this assay ensured that the production of ROS was only being assessed in live cells.

MitoSOX Red (MSR) Assay

MSR is a poorly fluorescent compound similar to DHE but carrying a charge that results in the selective accumulation of this probe within the mitochondria. Following reaction with the superoxide anion, MSR produces DNA sensitive fluorochromes that generate a red fluorescence when excited at 510 nm that can be detected by flow cytometry.

As with the DHE assay, SyG was used in order to ensure that only live cells were evaluated in this assay. MSR and SyG stock solutions (in DMSO) were diluted in BWW/PVA and 20 µl of each added to each treatment to give final concentrations of 2 µM and 0.05 µM respectively in a final volume of 200 µl. The cells were incubated at 37°C away from light for 15 min, centrifuged at 600× *g* for 5 min and the supernatant discarded. The pellet was then washed in 200 µl BWW/PVA, resuspended in 1 ml of this medium and transferred to 5 ml FACS tubes for analysis by flow cytometry. [15] The unstained control displayed 0.66%±0.32% MSR positivity, the MSR positive control (treated with 100 µM arachidonic acid) displayed 96%±3% MSR positivity and the SyG control displayed 96%±1% SyG positivity.

Assay for 8-hydroxy-2′-deoxyguanosine (8-OH-dG)

The formation of the 8-OH-dG base lesion, which is a biomarker for oxidative stress, was measured using an anti-8-OH-dG antibody (supplied in the Biotrin OxyDNA test Kit, Biotrin International Ltd, Dublin, Ireland) which was conjugated with a fluorescent label, fluorescein isothiocyanate (FITC). The level of FITC fluorescence was then measured using flow cytometry. For the positive control, spermatozoa were incubated for 1 h at room temperature with H_2O_2 (2 mM) and $FeCl_2{\cdot}4H_2O$ (1 mM) in a final volume of 200 µl BWW. The initial H_2O_2 concentration was determined by measuring absorbance at 240 nm ($\varepsilon = 43.6$ M^{-1} cm^{-1}). The cells were then washed twice in BWW, resuspended in 100 µl of 2 mM dithiothreitol (DTT) in BWW and incubated for 45 min at 37°C. After centrifugation at 600× *g* for 5 min, the cells were then fixed by resuspending the pellet in 100 µl Phosphate Buffered Saline (PBS) and 100 µl 4% paraformaldehyde and incubated at 4°C for 15 min. The cells were then washed in PBS and stored in 200 µl 0.1 M glycine at 4°C and stored for a maximum of 1 week. Fixed cells were washed and resuspended in 100 µl 0.2% Triton-X and incubated at room temperature for 15 min. Cells were then washed in Wash Solution (Biotrin OxyDNA test Kit, Biotrin International Ltd.) and 50 µl blocking solution (Biotrin OxyDNA test Kit, Biotrin International Ltd.) added before incubation at 37°C for 1 h. The anti-8-OH-dG antibody was further purified by adding approximately 1 mg of activated charcoal powder, followed by incubation at room temperature for 1 h and centrifugation at 600× *g* for 5 min. This step was repeated once more for complete removal of the charcoal. The supernatant containing the purified antibody was then added in a 1:50 dilution to the fixed cells in wash solution with a final volume of 100 µl. Finally, cells were washed twice, resuspended in

1 ml PBS and transferred to 5 ml FACS tubes for flow cytometric analysis. The unstained control and positive (H_2O_2/Fe^{2+}) control displayed 0.09%±0.02% and 97%±1% 8-OH-dG positivity, respectively.

TUNEL Assay

Spermatozoa were centrifuged (600× *g* for 4 min) before resuspending the pellet in 100 µl of fresh permeabilization solution (10 mg sodium citrate, 10 µl triton-X in 10 ml dH_2O) and incubating for 2 min at 4°C. The cells were then centrifuged (600× *g* for 4 min) and the pellets washed with PBS. The positive control samples were treated with 100 µl of DNase I (1 mg/ml) for 30 min at 37°C in a humid environment. TUNEL labeling was achieved with the In Situ Cell Death Detection Kit (Roche Diagnostics, Indianapolis, IN) according to the manufacturer's instructions. Cells were then washed twice in PBS, diluted to a final volume of 500 µl in PBS and kept in the dark for analysis using flow cytometry.

Analysis by Flow Cytometry

For flow cytometry analysis, Falcon 35 (2008) 5 mL polystyrene round bottom tubes were used for aspirating the sample into the fluorescence activated cell sorter (FACS). At least 5,000 cells were analyzed for each assay using a FACS™ calibur (Becton Dickinson) and the gates were set, based on forward and side scatter, such that only spermatozoa were assessed [15]. Fluorescence was measured upon excitation by a 15 mW argon-ion laser at 488 nm and was paired with emission measurements using 530/30 band pass (green/FL-1), 585/42 band pass (red/FL-2) and >670 long pass (far red/FL-3) filters. The FL-1 and the FL-2 filters were used for the vitality stain (SyG) and ROS stain (DHE) respectively. For TUNEL and 8-OH-dG analysis, only the FL-1 filter was used and for these assays. The software used to analyze the data was CellQuest Pro (BD Biosciences, San Jose, CA).

Statistics

All experiments were repeated at least 3 times on independent samples and the results analyzed by ANOVA using the Super-ANOVA programme (Abacus Concepts Inc, CA) on a MacIntosh G5 computer; post hoc comparison of group means was determined by Fisher's PLSD test. Differences with a P value of <0.05 were regarded as significant. All data are presented as the mean value±SEM.

Author Contributions

Conceived and designed the experiments: GNDI RJA. Performed the experiments: GNDI RJN BVK. Analyzed the data: GNDI RJA. Contributed reagents/materials/analysis tools: GNDI BVK RJA. Wrote the paper: GNDI RJA.

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EXHIBIT F

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Electromagnetic Absorption in the Head of Adult and Children Due to Mobile Phone Operation Close to the Head

Alvaro. A. A. de Salles [1], Giovani Bulla [2] and Claudio E. Fernández Rodriguez [3].

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

Index Terms — **Mobile Phones, Cell Phones, Specific Absorption Rate – SAR, Finite Difference Time Domain – FDTD, Biological Effects.**

I. INTRODUCTION

There has been a significant expansion of cell phones systems all over the world and particularly in Brazil in the last decades. There are now more than 1.8 billion cell phone user's in the world, and more than 94 million cell phone user's in Brazil, with perspective to grow fast in the next years. In parallel with this, an increased concern from the scientific community, the authorities and the population regarding the safety of these phones has arisen. A major problem is the distance between the antenna and the user's head, specially when conventional monopole (or whip) or helix antenna are used. These radiate nearly symmetrical around them. In this situation, the electromagnetic (EM) energy absorbed in the head tissues is significant and can result in serious risks for the users.

Several authors have used the Finite Difference Time-Domain (FDTD) method to simulate the Specific

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Absorption Rate (SAR) in the cell phone user's head (e.g., Jensen and Rahmat-Samii,, 1995; Ghandi et al, 1996; Fernández et al., 2004). It is currently the most appropriate choice when highly non-homogeneous structures are involved for which boundary techniques have fundamental limitations. The SAR results estimated and measured show exposure levels close (or even above) the limits of the available recommendations (IEEE/ANSI, 1991; ICNIRP, 1998). These consider only the thermal effects of the electromagnetic absorption.

Recently the use of cell phones by young and children has been strongly stimulated. Some authors have focused this, and different results were presented (Ghandi et al., 1996; Schönborn et al., 1998; Wang and Fujiwara, 2003; Anderson, 2003; Martinez-Búrdalo et al., 2004). In (Ghandi et al., 1996), the model of the children head was based on a scaled adult model and a SAR increase (compared with the adult) of around 120 % has been obtained. In (Schönborn et al., 1998), the head model was based on MRI using similar electromagnetic parameters as those for the adults, and no significant differences between adult and children SAR results were observed. In (Anderson, 2003), the head model was approximated by spheres considering some variation of the electromagnetic parameters, and an increase of around 20 % in the calculated SAR was shown. In (Martinez-Búrdalo et al., 2004), using also scaled model for the children's head with adult electromagnetic parameters, no significant variation for the average SAR in the whole head was observed, and an increase of around 35% in the SAR was calculated when considering the brain.

In this article, the FDTD method was used to simulate the SAR in the head of adult and a child, and to compare the results simulated for the child with those obtained for the adults. Adult and child head model were previously developed and presented by our research group, (Salles et al., 2002, 2003; Fernández et al., 2004, 2005). The electromagnetic parameters for the child were fitted to this age. Comparisons also were made with SAR calculated in the children model when using adult human electromagnetic parameters values. Simulations were performed using CRAY T 94 supercomputer from CESUP (www.cesup.ufrgs.br).

All the SAR results were calculated using planar microstrip (or patch) directional antennas and quarter wavelength monopole antennas.

The monopole antennas are now widely used in mobile phones. Their radiation pattern on the horizontal plane is

nearly symmetrical around them. Then, in the usual situation of operation, when these antennas are placed very close to the head, most of the radiated energy is absorbed in the user's head (e.g. in the brain tissues, in the eyes, etc.) and a smaller portion of energy is radiated to the nearest base station. This is an undesired situation, since there is degradation on the communication's quality, the battery drain and the user's health risk are increased.

The use of planar antennas with moderate directivity for mobile phones has been suggested previously (Jensen and Rahmat-Samii, 1995; Salles et al., 2003; Fernández et al., 2004). These antennas radiate more in the direction opposed to the head, improving the quality of communication, reducing the battery drain and the user's health risk. They can have small dimensions and a compact form, integrated to the cell phone box. Also, they can be very low cost, resulting therefore in an interesting alternative to this application.

II. ANTENNA MODELS

The cell phones were modelled using microstrip (or patch) planar antennas and quarter wavelength monopole antennas. The patch antennas were designed following the cavity models described by (Taflove,1998; Garg et al., 2001) and the monopole antennas were simulated using a quarter wavelength thin wire. The antenna dimensions were adjusted according to the cell grid shown in Table I. Special care was taken to feed the antenna at the exact resonance frequency. S11 simulations using FDTD and FFT show the resonance frequency. This was the frequency used to feed the antenna. The antenna is feed with an harmonic signal; 1850 MHz and 850 MHz frequencies were used as the feed frequency. As the delivered power to the antenna may be different for each case, due to principally mismatch in the impedance input, these were normalised. The value of 600mW was used for 850 MHz antennas and 125mW was used for 1850 MHz antennas. Among others, a main objective of this work is to compare the child and adult exposures in three different situations (cases A, B, and C, as described below), and for each antenna.

III. SAR SIMULATIONS IN THE ADULT HEAD

SAR simulations for the adult human are performed using a model based on the visible man (available at www.vhd.org.br) as described in previous works (Salles et al., 2002; Salles et al., 2003; Fernández et al., 2004). This is based in medical images. From this the numerical domain is developed, where the field is calculated. Each cell in this domain matrix is associated to a spatial place and to the corresponding tissue in each place. The derivation of the mesh which is used for the domain of calculations based in the discretization of the adult head has been described in a previous paper (Salles et al., 2002). No interpolation or smoothing were implemented to prevent staircasing. A three-dimensional view of the adult head is shown in Fig. 1 (a) and (b). The head is rotated to put the ear-to-mouth line vertically. This facilitates the cell phones antennas positioning.

In this work, the physical and electrical parameters used for the different tissues in the adult head were analogous to those used by other authors (Jensen and Rahmat-Samii, 1995; Salles et al., 2002; Watanabe et al., 1996; Bernardi et al., 2001). The permittivity, the equivalent conductivity and the density are associated to each kind of tissue, in function of the frequency of operation.

In Table II the parameters used at 1.85 GHz are indicated. These values are close to those recommended by FCC-Federal Communications Commission, from USA (available at www.fcc.gov/fcc-bin/dielec.sh).

If the hand were placed close to the antenna, it could substantially modify some radiation parameters, such as the antenna input impedance, the radiation pattern, as well as the SAR values. The exact influence of this effect would be a function of the relative position between the antenna and the hand. In (Watanabe et al., 1996) it has been shown that, if the hand is not placed directly over the antenna, SAR values are disturbed only a little.

The electric field intensity ($20\times\log | E |$) for the two antennas are shown in Fig. 2, on the left for the $\lambda/4$ monopole, and on the right for the patch antenna, in frontal cut (xz plane) (at the $\lambda/4$ monopole antenna plane) and coronal cut (xz plane) (at the bottom of the $\lambda/4$ monopole antenna), above and below, respectively. It can be observed that the fields inside the head can be substantially reduced (by more than 10 to 13 dB) when the planar antenna is used. These results are in close agreement to those described in (Jensen and Rahmat-Samii, 1995). The distance between the head and the antenna is 5.4 mm.

The SAR distribution in dB (10×log [SAR]) for the same frontal and coronal cuts are shown in Fig. 3. These SAR values are normalised to an average power of P_{del} = 600 mW delivered to the antenna, then 0 dB corresponds to a SAR = 1 mW/*g*. Again, it can be observed that reduced SAR levels (at least 10 to 13 dB down) are obtained when the patch antenna is used, if compared to the λ/4 monopole antenna. The maximum human exposure limit recommended by ICNIRP (ICNIRP, 1998), is a SAR = 2 mW/*g*. This is the same as recommended by the Brazilian agency ANATEL (ANATEL, 2002). It is observed that under the conditions of these simulations, when the monopole antenna is used, the SAR in the head can be several times above the 2 mW/g limit. This is in very close agreement to the results described elsewhere (Jensen and Rahmat-Samii, 1995; Watanabe et al., 1996; Iskander et al., 2000; Bernardi et al., 2001) . However, as it has been shown in previous paper (Salles et al., 2002), if the antenna were operated at a distance sufficiently apart from the user's head (e.g. d ≥ 2.5 cm from the head), then the SAR in the head would be below the ICNIRP limit of 2 mW/*g*.

Among others, one of the purposes of this paper is to compare the relative specific absorption rates when monopole and planar antennas are used, showing a reduction in the SAR when planar antennas are used. This is true even when spatial average or punctual SAR values are taken into account. The microstrip (or patch) antenna simulations show that the field intensity and the SAR in the head are reduced to levels below the ICNIRP limits (Fernández et al., 2004). Similar results obtained for other planar antennas were reported elsewhere (Jensen and Rahmat-Samii, 1995; Watanabe et al., 1996; Iskander et al., 2000; Bernardi et al., 2001).

In order to calculate the radiation efficiency, the power absorbed in the user's head is added to the antenna losses and this is named overall absorbed power P_{abs}. Since the power absorbed in the user's head is reduced when the planar antennas are used, then an increase on the radiation efficiency $\eta = (P_{del} - P_{abs})/P_{del}$ is obtained, as compared to the use of λ/4 monopole antennas. This was discussed earlier (Jensen and Rahmat-Samii, 1995).

IV . SAR Simulations in a Child Compared With Adult

In order to compare the simulated SAR due to cell phones operated close to the head in adults and children, the model of the children previously developed (Fernández et al., 2005) was used. The geometric and the

electromagnetic parameter differences between the adult and the child were considered in the simulations. Three-dimensional view of these models are shown in Fig 1. Both models were rotated to put the ear-to-mouth line vertically. This facilitates the cell phones antennas positioning.

Three different simulation cases were implemented. In case A, the adult model with the adult parameters (Gabriel and Gabriel, 1996) was used. In case B, the 10 years old child model with adult electromagnetic parameters was considered. In case C, the 10 years old child model with the electromagnetic parameters fitted to this age was used. These were obtained from comparison with the results obtained for rats (Peyman et al., 2001). The electromagnetic parameters for adult human are well established, with accuracy better than 5% (Gabriel and Gabriel, 1996). However data for children are still not available. A study with rats (Peyman et al., 2001) shows that conductivity and permittivity decrease with age. For 10 day and younger rats, the values are around 20% higher than for sexually mature (adult) rats (e.g. 50 days). One reason for this could be the higher salt-water concentration in the tissues of the young. The measured results for adult individuals in different animal species show that there is a parameter variation lower than 5% from animal to animal when considering the same type of tissue. This was the rationale, and using similar correspondence between parameters values and age for humans as for rats, we obtained the fitted parameters for the children. These values are shown in Table II.

The cranial perimeters in both models were approximated from ellipsis. The calculated values are in close agreement with those shown in (Schönborn et al., 1998). To adjust for the corresponding dimensions and in order to save processor memory, FDTD simulation were performed having different cell dimensions for each of the three cases (Taflove, 1995; Taflove, 1998). Then, the distance between the antenna and the head are slightly different. These are shown in Table I.

The simulated peak SAR and average SAR (1g and 10g) are presented. The 1g-SAR and the 10g-SAR were calculated as spatial averages of boxes with $11\Delta x \times 6\Delta y \times 5\Delta z$ (1g-SAR, Case A), $24\Delta x \times 11\Delta y \times 11\Delta z$ (10g-SAR, Case A), $10\Delta x \times 6\Delta y \times 5\Delta z$ (1g-SAR, Cases B and C), $23\Delta x \times 12\Delta y \times 11\Delta z$ (10g-SAR, Case B and C). Since there is not a great variation in the densities of the different tissues, this can be considered a reasonable approximation.

As mentioned before, the child and the adult head models were rotated in order to a better positioning of the cell phone, and then the vertical cuts do not correspond exactly to coronal cuts. Fig. 4 shows the SAR calculated in all

cases.

In Tables III-VI the maximum simulated SAR results in the brain for all the cases are shown. In accordance with the IEEE/ANSI and the ICNIRP recommendations (IEEE/ANSI, 1991; ICNIRP, 1998) one of major parameters to be considered is the 1g mean SAR. It is observed that an increase in the 1g-SAR was obtained for the children model with the adult parameters (Case B) and for the children model with the fitted parameters (case C). The 1g-SAR in the child head for the antennas fed at 1850 MHz shows an increase relative to the adult of about 32% for case B and 60% for case C, independently of the type of antenna used. At 850 MHz this relative increase was even higher, but different for each antenna type. The patch antenna at 850 MHz shows an increase of 98% between the 1g-SAR of the adult and the child in case B and 131% between the adult and the child in case C. Also it is observed an increase in the mean SAR (whole head) simulated in the child (cases B and C) when compared to the adult (case A). However, a significant difference between the mean SAR (whole head) for the child in case B and in case C was not observed.

IV. Discussions and Conclusions

The SAR in an adult and in a 10 years old child was calculated and comparison of the SAR results obtained for the adult and the child with planar microstrip (or patch) and $\lambda/4$ monopole antenna, at 1850 MHz and 850 MHz were shown. It is observed that under the conditions of these simulations, when the $\lambda/4$ monopole antenna is used, the SAR in the head of an adult can be several times above the 2 mW/g ICNIRP thermal limit. When the directional antenna is used, a SAR reduction in the head between 20 to 30 times is estimated.

SAR results around 60% higher than those simulated for the adults were observed for the children with fitted parameters, independent of antenna type or frequency. The relation between the 1g-SAR calculated with the child model and the 1g-SAR calculated using the adult model was higher at 850 MHz than at 1850 MHz. This is probably due to the wavelength, since at 850 MHz it is of the same order of magnitude as the child head dimensions.

The increase in the mean SAR in the whole head, between the adult and the child, is expected due to the reduced dimensions in the child head, as well as the higher values of the permittivity and of the conductivity in the child

brain tissues. Also, children's growing skulls are thinner than those of adults, and therefore less resistant to radiation. This is in accordance with the results obtained by other authors (Gandhi et al., 1996).

It is important to remark that only the thermal limit has been considered so far. In principle, as the digital phone radiates lower mean power in comparison to the analogue phones, their risk associated with the heating of tissues is then reduced. However, since most mobile communication systems now are pulse-like in nature, modulated at low frequencies, such as the GSM, UMTS, CDMA, TDMA systems, then they are able to induce currents in the brain tissues and this can result in some low level non thermal effects, e.g., blood brain barrier (BBB) alterations, single and double strand DNA breaks, chromosomal aberrations, etc., at RF energy levels substantially below the thermal threshold. Several papers and reports have already shown adverse health effects at exposure levels well below the thermal limits (e.g., Salford et al, 1994; Lai and Singh, 1996; Reflex, 2005; Lai, 2005). Further to that, a recent epidemiological study has shown 1.7 to 5.9-fold increase in risk for malignant brain tumours, with > 10 years latency period for long-term mobile phone and cordless phone users (Hardell, 2006). As a substantial percentage of the population now uses mobile phones for a long time during each day and for several years, operating the antenna very close to their head, then this exposure can effectively represent a serious risk for their health.

Finally, due to the increased use of mobile phones by adult and children, and since compliance tests use head phantoms based exclusively on adult data, the results shown in this paper may suggest that further theoretical and experimental research must be immediately done in order to evaluate these issues aiming to reduce risks, specially for the children. This is in accordance to the WHO – World Health Organisation – effort, included in the WHO Children's EMF Research Agenda, recommending research studies relevant to the risk of adverse health effects in children from exposure to electromagnetic fields – EMFs (WHO, 2004).

Meanwhile, since the present guidelines are questionable in protecting the cell phone user's, the Precautionary Approach should be promptly adopted, and the cell phone exposure should be kept to a minimum, following the ALARA principle (As Low as Reasonably Achievable). For example, the responsible health public authorities should disseminate some basic recommendations for the cell phone user's, such as to make only short and essential calls, to use always hands free kits and maintain the antenna far away from their body during the calls. In order to reduce irreparable public health damage, it is clear that the adoption of the Precautionary

Approach, until more detailed and scientifically robust information on any health effects becomes available, should not be further delayed.

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TABLE CAPTIONS

TABLE I – Spatial discretization

TABLE II – Physical properties for the adult man and fitted for the 10 years old child at 1850 MHz

TABLE III – SAR – Quarter wavelength monopole (1850 MHz), power=125mW.

TABLE IV – SAR – Quarter wavelength monopole (850 MHz), power=600mW.

TABLE V – SAR – Microstrip (or patch) antenna (1850 MHz), power=125mW.

TABLE VI – SAR – Microstrip (or patch) antenna (850 MHz), power=600mW.

TABLES

TABLE I

Model	*Adult*	*10 years old*
Cases	***A***	***B and C***
Scale factor	*l*	*l*
Cranial perimeter (mm)	563.5	523.9
Δx (mm)	0,910	0,9460
Δy (mm)	1.887	2.269
Δz (mm)	1.968	1.601
device distance (mm)	Δx	Δx

TABLE I I

Age		adult		10 years old	
Properties	ρ (g/cm^3)	ε_r	$\sigma(\Omega^{-1}/m)$	ε_r	$\sigma(\Omega^{-1}/m)$
Air	0.00	1.00	0.00	1.00	0.00
Average Skull	1.85	15.56	0.43	18.48	0.54
Skin (Wet)	1.01	43.85	1.23	54.63	1.53

Average Muscle	1.04	54.44	1.39	61.68	1.57
Average Brain	1.03	43.54	1.15	52.52	1.44
Vitreous Humour	1.01	68.57	2.03	81.81	2.47
Fat (Mean)	0.92	11.02	0.19	13.15	0.23
Eye Tissue (Sclera)	1.17	53.57	1.60	63.91	1.95
Brain Spinal Fluid	1.01	67.20	2.92	80.17	3.55
Nerve (Spinal chord)	1.04	30.87	0.84	36.83	1.02
Lens Nucleus	1.10	34.65	0.79	41.34	0.96

TABLE III

Model	*Adult*	*10 years old child*	
Electromagnetic parameters	*Adult parameters*	*Adult parameters*	*Children parameters*
	SAR values (W/kg)		
Peak SAR (one *voxel*)	1.490	3.58	4.40
1g-SAR	0.527	0.794	0.885
10g-SAR	0.362	0.556	0.596
Mean SAR (whole head)	0.021	0.032	0.032

TABLE IV

Model	*Adult*	*10 years old child*	
Electromagnetic parameters	*Adult parameters*	*Adult parameters*	*Children parameters*
	SAR values (W/kg)		
Peak SAR (one *voxel*)	3.68	5.97	6.20
1g-SAR	1.8	2.38	2.89
10g-SAR	1.7	1.74	2.05
Mean SAR (whole head)	0.149	0.193	0.191

TABLE V

Model	*Adult*	*10 years old child*	
Electromagnetic parameters	*Adult parameters*	*Adult parameters*	*Children parameters*
	SAR values (W/kg)		
Peak SAR (one *voxel*)	0.091	0.190	0.207
1g-SAR	0.055	0.109	0.131
10g-SAR	0.036	0.086	0.086
Mean SAR (whole head)	0.0058	0.0085	0.0085

TABLE VI

Model	*Adult*	*10 years old child*	
Electromagnetic parameters	*Adult parameters*	*Adult parameters*	*Children parameters*
	SAR values (W/kg)		
Peak SAR (one *voxel*)	0.670	1.16	1.26
1g-SAR	0.359	0.477	0.590
10g-SAR	0.231	0.342	0.347
Mean SAR (whole head)	0.0451	0.0516	0.0524

FIGURE CAPTIONS –

Fig. 1. Three-dimensional images from both head models: (a) adult head without a quadrant ; (b) adult skull; (c) child head without a quarter of the head top; (d) brain, eyes, spinal chord on the child model.

Fig 2. Frontal (xy plane) and coronal (xz plane) images showing the electric field distribution (20 x log | E |) obtained at the end of the simulations: (a) monopole antenna (frontal); (b)microstrip antenna (frontal); (c) monopole antenna (coronal); (d) microstrip antenna (coronal).

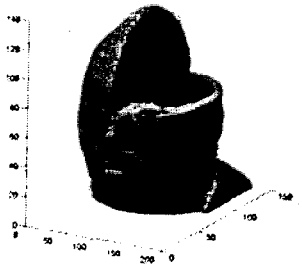
Fig 3. Frontal (xy plane) and coronal (xz plane) images showing the SAR distribution (10 x log | E |) obtained at the end of the simulations. Left: λ/4 monopole and right: microstrip patch antenna.

Fig. 4. SAR distribution on adult and child head. A logarithmic scale was $10*\log_{10}(SAR(mW/g)/1.6(mW/g))$.

(a) adult with quarter wavelength monopole at 850 MHz and 600mW,
(b) adult with quarter wavelength monopole at 1850 MHz and 125 mW,
(c) adult with microstrip (or patch) antenna at 850 MHz and 600mW,
(d) adult with microstrip (or patch) antenna at 1850 MHz and 125mW,
(e) child with adult parameters with quarter wavelength monopole at 850 MHz and 600mW,
(f) child with adult parameters with quarter wavelength monopole at 1850 MHz and 125 mW,
(g) child with adult parameters with microstrip (or patch) antenna at 850 MHz and 600mW
(h) child with adult parameters with microstrip (or patch) antenna at 1850 MHz and 125mW
(i) child with fitted parameters with quarter wavelength monopole at 850 MHz and 600mW,
(j) child with fitted parameters with quarter wavelength monopole at 1850 MHz and 125 mW,
(k) child with fitted parameters with microstrip (or patch) antenna at 850 MHz and 600mW,
(l) child with adult parameters with microstrip (or patch) antenna at 1850 MHz and 125mW.

FIGURES

Figure 1



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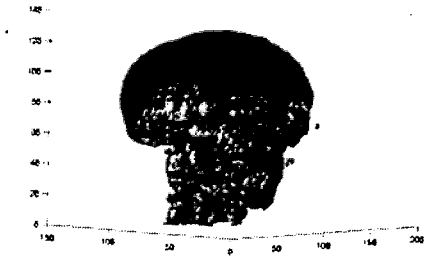

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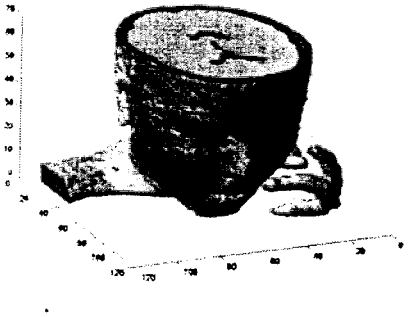

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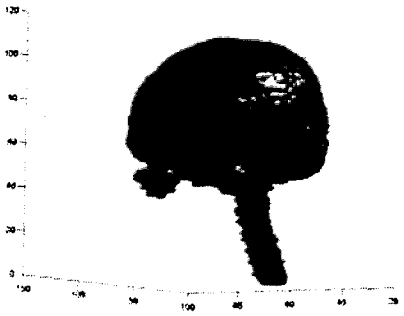
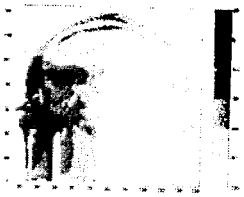


(d)

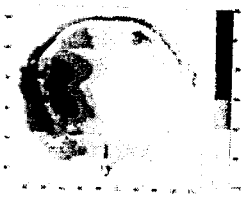
Figure 2

(a)



(b)

(c)



(d)

Figure 3

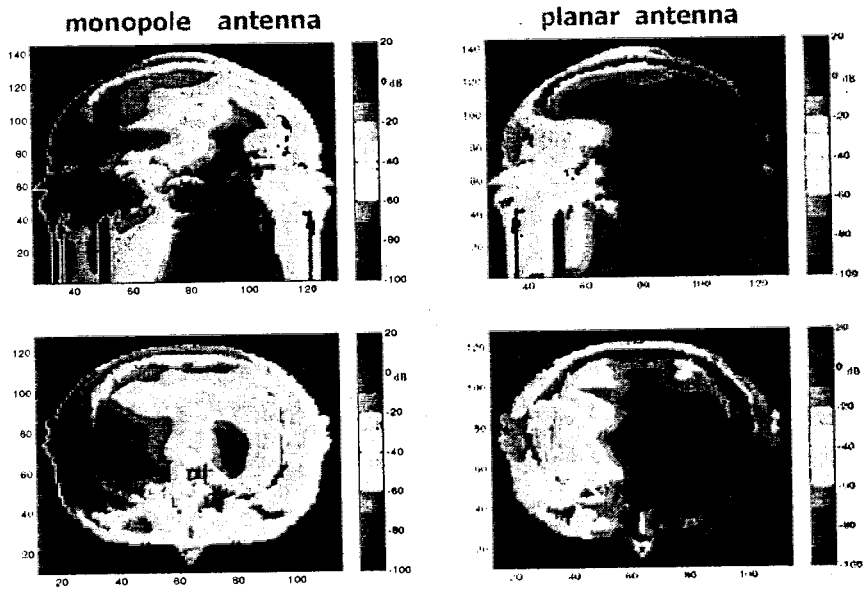


Figure 4

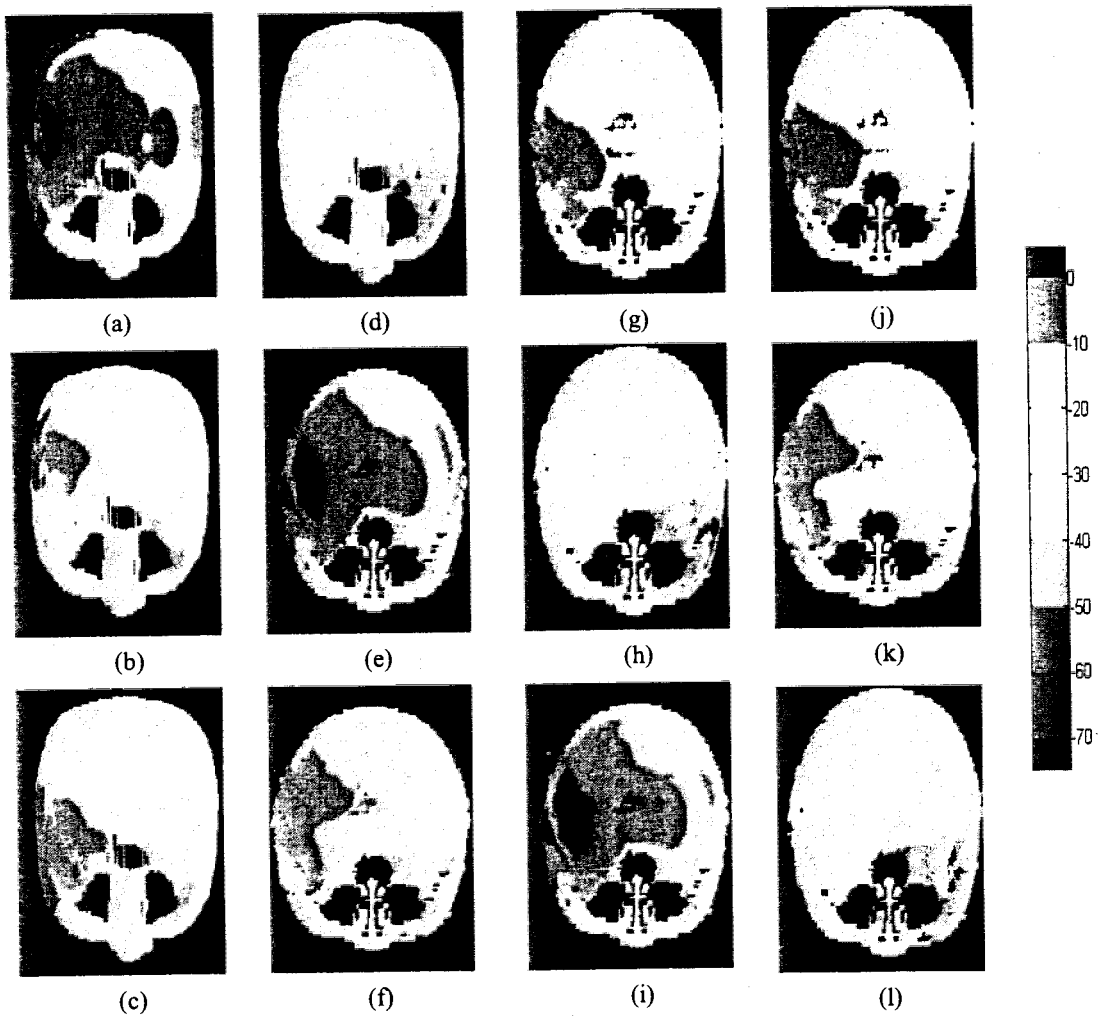


EXHIBIT G

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

ORIGINAL ARTICLE

Prenatal and Postnatal Exposure to Cell Phone Use and Behavioral Problems in Children

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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 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.

(*Epidemiology* 2008;19: 000–000)

Exposure to radiofrequency fields is increasingly common, but the potential influence on health has not been thoroughly investigated, especially in children. Between 2003 and 2008, there were more than 900 million new cell phone subscribers worldwide, with a total of more than 2 billion subscribers.[1] Fetuses and children may be more vulnerable than adults to external exposures in general.[2] In 2000, the Stewart Report recommended a precautionary approach to the use of cell phones until more detailed and scientifically robust information became available, especially for children.[3] Numerous reviews, including 1 by the World Health Organization,[4] stress the need for studies in children and on cognitive effects, because of the importance of cognitive abilities and learning in early development.

Most epidemiologic studies of exposure to radiofrequency fields have focused on brain and acoustic cancers as outcomes[5–11] or on subjective symptoms such as headaches.[12,13] A number of laboratory studies have examined physiologic effects after short-term exposure,[14–18] but a variety of other outcomes are yet to be investigated, and none has included potentially susceptible populations such as fetuses and very young children.

Children are potentially exposed during fetal life by maternal use of cell phones and then later in childhood when they themselves become users of cell phones. Exposures early in life may have particular importance because this is during vulnerable stages of brain development.

There is limited information on the association between radiofrequency field exposure during pregnancy and reproductive outcomes (spontaneous abortions, birth weight, sex ratio, and congenital malformations), mostly from occupational studies. Occupational exposures are typically much higher than exposures from cell phone use. Some studies have reported increased risk of spontaneous abortions and congenital malformations, although these results come from poorly designed studies.[19]

Since no established mechanism is known for radiofrequency exposure—except for what may be caused by an increased temperature in the exposed regions—it is impossible to exclude any health outcomes from consideration. Experimental research indicates exposure might affect nonspecific neurologic performance such as attention. In a preliminary cross-sectional analysis of 13 year-olds in the MoRPhEUs study, differences in certain cognitive abilities related to cell phone use were observed (Rodney Croft personal communication, 16 December 2007).

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An increasing number of children are being diagnosed with attention-deficit hyperactivity disorder (ADHD) as classified in the DSM-IV or hyperkinetic disorder in the ICD-10 classification. These behavioral problems include hyperactivity, impulsivity, and difficulty in concentrating. Known risk factors for these conditions include sex of child, smoking during pregnancy, family psychiatric history, and socioeconomic status (SES).[20,21] To date, no epidemiologic studies have investigated cell phone use as a possible risk factor for behavioral outcomes with similarities to ADHD.

In this analysis, we explored the association of cell phone use during pregnancy and during early childhood with behavioral problems in children.

METHODS

This study was based on the Danish National Birth Cohort, which recruited study participants from March 1996 through November 2002. A total of 101,032 pregnancies were enrolled in the cohort.[22,23] Mothers and live-born children constitute 2 fixed cohorts that are to be followed for decades in a life-course perspective. Detailed information on life-style factors, dietary habits and environmental exposures were collected by means of 4 telephone interviews; 2 of these were conducted during pregnancy and 2 when the newborn child reached 6 and 18 months of age.[24]

A new round of data collection from mothers that focuses upon the child's health status was initiated when the children reached the age of 7 years. This analysis is based on the information collected about children born between 1997 and 1999. This Age-7 Questionnaire contained questions on cell phone use among children, as well as among mothers during pregnancy. In addition, the questionnaire included data on social conditions, family lifestyle, and diseases in childhood, including behavioral problems as defined by the Strengths and Difficulties Questionnaire. Specifically, we asked about mother's use of cell phone during pregnancy (the number of times spoken per day, proportion of time the phone was on), use of hands-free equipment during pregnancy (proportion of time) and location of the phone when not in use (handbag or clothing pocket), and for children, current use of cellular and other wireless phones.

Letters were sent to participants' homes instructing them about how to respond to the questionnaire via the Internet, as well as informing them that they may request a questionnaire to return by ordinary mail using a prepaid envelope. If they did not respond within a 4-week period, a reminder letter was sent. If, at the end of a second 4-week period, the Internet version still had not been completed, a paper-based questionnaire was provided via mail. Formats of the 2 questionnaire were identical.

This study was approved by the Danish Data Protection Agency and by regional science ethics committees in Denmark as well as the University of California, Los Angeles Office for the Protection of Research Subjects.

Outcome Measures

Behavioral problems in children were assessed using the Strengths and Difficulties Questionnaire.[25,26] Mothers completed a list of 25 questions with scaled responses (very true, partly true, or not true) regarding their child's behavior. The assessment of disorders was based upon scores over a particular group of questions with a priori defined cutoff points. The questionnaire assessed overall behavioral problems or disorders, as well as specific emotional, conduct, hyperactivity, peer and social disorders.

Based on the specific numerical score, children were classified as abnormal, borderline, or normal for overall behavioral problems as well as for the specific outcomes such as emotional, conduct, hyperactivity, or peer problems.[27]

Statistical Analysis

Comparisons were made between baseline characteristics (ie, sex of child, social-occupational status, and mother's psychiatric history and smoking) as well as prenatal and postnatal cell phone exposure.

We used an ordinal logistic regression model (adjacent category logistic model) to estimate the odds of the outcomes of behavioral problems (2 = abnormal, 1 = borderline, 0 = normal) in children according to combined prenatal and postnatal exposure to cell phones, prenatal exposure only, and postnatal exposure only. The model imposes the same odds in going from "normal" to "borderline" as from "borderline" to "abnormal." Tests for heterogeneity were conducted to verify this assumption. Regression analyses were adjusted for several potential confounders (child's sex, mother's age, mother's psychiatric history, social-occupational status, and smoking during pregnancy). We computed odds ratios (ORs) and 95% confidence intervals (CIs).

To evaluate possible dose-response patterns, we considered proxies of prenatal exposure intensity (times per day spoken, location of the phone when not in use, proportion of time the phone was turned on, and use of an earpiece with cell phone). For each specific characteristic of use, the reference category was defined as the lowest possible category (ie, no use, 0–1 times per day spoken). For location of phone when not in use, the reference category was "carried in bag" versus "carried in dress/pant pocket."

RESULTS

Mothers completed an Age-7 Questionnaire for 13,159 children, which is about 65% of the eligible mothers who were contacted through November 2006. Thirty percent of children were using a cell phone at the age of 7 years, but fewer than 1% used a cell phone for more than 1 hour per week. About 11% of children were exposed to cell phones both prenatally and postnatally (Table 1). Nearly half had neither prenatal nor postnatal exposure, and another 8% (n = 1091) were coded as do not know or missing in the analysis

TABLE 1. Distribution of Covariates and Behavioral Problems Score by Prenatal and Postnatal Exposure to Cell Phone Use (n = 13,159)

	No Exposure (n = 6471)	Prenatal Exposure Only[a] (n = 1895)	Postnatal Exposure Only[b] (n = 2281)	Both Prenatal and Postnatal (n = 1421)	Do Not Know/Missing (n = 1091)
Covariates					
Sex of child					
Boy	53.3	53.6	47.0	46.7	51.2
Girl	46.6	46.4	52.9	53.1	48.8
Missing	0.1	0.0	0.1	0.2	0.0
Social-occupational status					
High	53.5	50.9	52.1	45.3	48.6
Medium	35.2	36.4	36.7	38.9	38.3
Low	7.5	10.0	7.3	12.1	9.9
Missing	3.8	2.7	3.9	3.7	3.2
Mother ever suffered from mental disorder or neurosis					
Yes	5.2	5.9	6.6	8.0	12.6
No	91.1	91.5	89.7	88.8	84.6
Do not know/missing	3.7	2.6	3.7	3.2	2.8
Mother ever had psychiatric illness					
Yes	10.1	11.9	13.5	16.8	34.7
No	87.7	84.9	83.9	81.0	57.7
Do not know	1.6	2.2	1.8	1.6	1.5
Missing	0.6	1.0	0.8	0.6	6.1
Mother's smoking status during pregnancy					
Entire pregnancy	15.1	19.3	20.4	24.8	17.0
Every day	80.0	85.0	79.6	83.0	82.7
Less than every day	10.6	5.5	12.0	7.4	6.5
Do not know frequency	9.4	9.6	8.4	9.6	10.8
Early in pregnancy only	6.5	6.2	7.3	8.2	7.3
Not a smoker	72.5	69.2	66.7	59.9	70.1
Do not know/missing	5.9	5.3	5.6	7.1	5.6
Behavioral problems score					
Overall behavioral problems score					
Normal (0–13)	95.0	91.6	93.8	89.9	89.5
Borderline (14–16)	2.5	4.1	3.7	5.4	3.6
Abnormal (17–40)	2.4	4.2	2.4	4.6	2.7
Missing	0.1	0.1	0.1	0.1	4.2
Emotional symptoms score					
Normal (0–3)	87.8	85.5	86.5	82.8	79.9
Borderline (4)	6.0	6.0	6.6	7.9	7.6
Abnormal (5–10)	6.1	8.4	6.9	9.2	8.4
Missing	0.1	0..1	0.0	0.1	4.1
Conduct problems score					
Normal (0–2)	87.1	83.9	86.4	80.2	81.3
Borderline (3)	8.1	9.9	8.7	11.1	8.9
Abnormal (4–10)	4.7	6.1	4.9	8.7	5.6
Missing	0.1	0.1	0.0	0.0	4.2
Hyperactivity score					
Normal (0–5)	91.8	88.9	91.8	88.1	87.6
Borderline (6)	3.5	4.5	3.3	4.3	3.2
Abnormal (7–10)	4.7	6.5	4.9	7.5	5.0
Missing	0.1	0.1	0.0	0.1	4.1
Peer problems score					
Normal (0–2)	92.5	90.0	91.6	89.1	88.5
Borderline (3)	3.5	4.3	4.6	5.2	3.7
Abnormal (4–10)	4.0	5.6	3.7	5.6	3.7
Missing	0.1	0.1	0.1	0.1	4.2

Values are given in percentage.
[a]Mother's use during pregnancy.
[b]Child's use.

because of incomplete information regarding mother's or child's cell phone use. For most characteristics and outcomes, the percent missing or not known was small (0%–7%) and similar across the 4 exposure groups. One exception was the percentage of mothers ever having psychiatric illness; nearly 35% of the 1091 who had incomplete information on exposure to cell phones answered "Yes" to this question. Nearly 90% of the children were reported as "normal" for all types of behaviors. Children with exposure to cell phones (prenatally, postnatally, or both) tended to have higher percentages of borderline or abnormal scores for emotional symptoms, conduct problems hyperactivity and peer problems.

The highest odds ratios for behavioral problems were observed for children who had both prenatal and postnatal exposure to cell phones compared with those who were not exposed during either time period (Table 2). For these children the adjusted OR for the overall behavioral score was 1.80 (95% CI = 1.45–2.23). For prenatal or postnatal exposure only, the adjusted odds ratios were 1.54 (1.32–1.81) and 1.18 (1.01–1.38), respectively. Adjusting for potential confounders moved the results towards the null.

For the combined prenatal and postnatal exposure, adjusted odds ratios (Table 3) were similarly increased for each of the 4 specific behavioral outcomes. The odds ratios were higher for prenatal exposure than for postnatal exposure, for each of the behavioral problems.

When analyses were stratified by the covariates the associations between cell phone use and behavioral problems were stable across the strata (Table 4). Associations with overall behavioral problems in children did not vary when considering the questionnaire administration format (paper-based or Internet-based) (data not shown).

Almost 85% of mothers carried their cell phone in a bag during pregnancy rather than on their person or elsewhere, and nearly 82% reported not using an earpiece (data not shown). In Table 5, nearly 56% of children with prenatal exposure had mothers who reported speaking 0–1 times per day during their pregnancy and 43% reported having the phone turned on at all times. For prenatal exposures—regardless of postnatal exposure—odds ratios for the overall behavioral problems score tended to be greater with higher potential for fetal exposure; however,

TABLE 2. Association of Prenatal and Postnatal Exposure to Cell Phone Use With Overall Behavioral Problems Score

	Postnatal Exposure					
	No		Yes		Prenatal Exposure[a]	
	Unadjusted OR	Adjusted OR (95% CI)[b]	Unadjusted OR	Adjusted OR (95% CI)[b]	Unadjusted OR	Adjusted OR (95% CI)[b]
Prenatal exposure						
No	1.0[c]	1.0[c]	1.25	1.18 (0.96–1.45)	1.0[c]	1.0[c]
Yes	1.77	1.58 (1.29–1.93)	2.16	1.80 (1.45–2.23)	1.74	1.54 (1.32–1.81)
Postnatal exposure[d]	1.0[c]	1.0[c]	1.26	1.18 (1.01–1.38)		

n = 12,068 with information about prenatal and postnatal exposure; n = 12,112 with information about prenatal exposure; n = 13,054 with information about postnatal exposure.
[a]OR for prenatal exposure adjusted for postnatal exposure.
[b]Adjusted for sex of child, age of mother, smoking during pregnancy, mother's psychiatric problems, and socio-occupational levels.
[c]Reference category.
[d]OR for postnatal exposure adjusted for prenatal exposure.

TABLE 3. Associations of Specific Behavioral Problems in Children With Prenatal and Postnatal Exposure to Cell Phone Use

	Prenatal Exposure Only		Postnatal Exposure Only		Both Prenatal and Postnatal Exposure	
	Unadjusted OR	Adjusted OR (95% CI)[a]	Unadjusted OR	Adjusted OR (95% CI)[a]	Unadjusted OR	Adjusted OR (95% CI)[a]
Behavioral problems						
Emotional	1.23	1.12 (0.97–1.30)	1.13	1.06 (0.92–1.23)	1.50	1.25 (1.07–1.47)
Hyperactivity	1.39	1.29 (1.08–1.53)	1.00	0.98 (0.82–1.17)	1.52	1.35 (1.12–1.63)
Conduct problems	1.29	1.21 (1.05–1.40)	1.06	1.02 (0.89–1.18)	1.69	1.49 (1.28–1.74)
Peer problems	1.36	1.27 (1.06–1.52)	1.11	1.08 (0.90–1.29)	1.51	1.34 (1.11–1.63)

Reference category is no prenatal or postnatal exposure to cell phone use.
[a]Adjusted for sex of child, age of mother, smoking during pregnancy, mother's psychiatric problems, and socio-occupational levels.

TABLE 4. Associations of Overall Behavioral Problems With Prenatal and Postnatal Exposure to Cell Phone Use Stratified by Covariates

Covariates	Prenatal Exposure Only OR (95% CI)	Postnatal Exposure Only OR (95% CI)	Both Prenatal and Postnatal Exposure OR (95% CI)
Sex of child			
Boy (n = 6201)	1.89 (1.48–2.40)	1.20 (0.92–1.58)	2.35 (1.81–3.06)
Girl (n = 5856)	1.55 (1.09–2.21)	1.44 (1.04–1.99)	2.12 (1.51–2.97)
Social-occupational level			
High level (n = 6259)	1.76 (1.27–2.46)	1.27 (0.90–1.79)	2.32 (1.63–3.30)
Medium level (n = 4359)	1.86 (1.39–2.51)	1.40 (1.04–1.89)	1.92 (1.40–2.64)
Low level (n = 1009)	1.22 (0.74–2.02)	0.67 (0.36–1.27)	1.56 (0.95–2.55)
Mother ever suffered from mental disorder or neurosis			
Yes (n = 710)	1.12 (0.56–2.27)	0.68 (0.33–1.42)	1.59 (0.84–3.01)
No (n = 10,937)	1.83 (1.48–2.26)	1.29 (1.03–1.60)	2.16 (1.72–2.69)
Mother ever had psychiatric illness			
Yes (n = 1424)	1.50 (0.96–2.3)	1.10 (0.71–1.69)	1.57 (1.02–2.41)
No (n = 10,349)	1.72 (1.36–2.17)	1.26 (0.99–1.60)	2.08 (1.62–2.66)
Mother's smoking status during pregnancy			
Smoked entire pregnancy (n = 2160)	1.75 (1.22–2.51)	0.89 (0.59–1.32)	1.71 (1.18–2.47)
Smoked early in pregnancy only (n = 822)	2.21 (0.99–4.96)	1.51 (0.68–3.37)	2.68 (1.24–5.80)
Not a smoker (n = 8378)	1.70 (1.31–2.20)	1.32 (1.01–3.37)	2.00 (1.50–2.66)

TABLE 5. Association of Characteristics of Mother's Cell Phone Use During Pregnancy With Overall Behavioral Problems Score in Children With Prenatal Exposure (n = 3322)

	No. (%)	Unadjusted OR	Adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[a,b]
Times spoken per day				
0–1	1873 (56.4)	1.00[c]	1.00[c]	1.00[c]
2–3	777 (23.4)	1.49	1.33 (0.99–1.79)	1.31 (0.97–1.77)
4+	347 (10.4)	1.60	1.51 (1.02–2.22)	1.47 (1.00–2.18)
Missing	325 (9.8)	—	—	—
P for trend	—	0.28	0.61	0.62
Percentage of time turned on				
0	397 (12.0)	1.00[c]	1.00[c]	1.00[c]
<50	500 (15.1)	0.70	0.62 (0.35–1.11)	0.62 (0.35–1.10)
50–99	954 (28.7)	1.20	0.93 (0.58–1.48)	0.91 (0.57–1.45)
100	1427 (43.0)	1.43	1.09 (0.70–1.70)	1.06 (0.68–1.65)
Missing	44 (1.2)	—	—	—
P for trend	—	0.15	0.13	0.13

[a]Estimates adjusted for sex of child, age of mother, smoking during pregnancy, mother's psychiatric problems, and socio-occupational levels.
[b]Also adjusted for postnatal exposure to cell phones.
[c]Reference category.

proxies for intensity of mother's phone use during pregnancy did not exhibit strong dose-response associations, and tests for trend were not statistically significant.

DISCUSSION

Use of cell phones during pregnancy was associated with an increased odds of behavioral problems in children in this study. These results were unexpected and should be interpreted with caution. Observed associations are not necessarily causal. We have no known biologic mechanisms to explain these associations, and confounding by unmeasured causes of behavioral problems could have produced these results. Furthermore, this is the first study of its kind. The highest exposure group differed somewhat on several factors that might relate to the risk of behavioral disorders in offspring: they were of lower social-occupational status, mothers were more likely to

have ever suffered from mental disorder or neurosis and to ever had psychiatric illness, and mothers were more likely to have smoked during pregnancy. Although the associations remained after adjustment for these factors, and the associations were actually stronger in the covariate strata associated with lower risk of behavior disorders in offspring, the possibility of residual confounding remains. Additionally, we did not have information on other potential confounders such as history of psychiatric disorders in fathers and history of lead exposure.[28]

Another possible explanation for the observed association might be the lack of attention given to a child by mothers who are frequent users of cell phones. It is also possible that behavioral correlates of maternal cell phone use, rather than radiofrequency exposure, affect perception or reality of children's behavioral problems. Thus confounding and other sources of bias may explain the associations observed.

The validity of our measure of behavioral problems based on the questionnaire is supported by the fact that the prevalence of observed behavioral problems is consistent with results from similar studies in which the questionnaire has been used and validated.[29,30] Additionally, we observed associations in the expected direction and magnitude for other risk factors for behavioral problems, such as sex of the child, age of mother, social-occupational status, psychiatric history of mother and smoking during pregnancy.[20,21] We measured mother's reports of their children's behavioral traits or patterns rather than clinical diagnoses such as ADHD.

While the questionnaire was designed to obtain history of cell phone use, we do not believe that differential recall bias explains the observed associations. The portion of the questionnaire asking about behavioral problems preceded the questions regarding cell phone use, but it is unlikely that mothers would be influenced by the knowledge of their child's behavioral status when providing data of phone use, as these behavioral problems have not previously been associated with cell phone use. A previous study has shown good accuracy for the simple reporting of use versus nonuse of cell phones, and reasonable reporting (underreporting of 10%) for times spoken per day.[31] Self-reported duration of calls was more problematic, being overestimated by 40%.

Because pregnancy leaves a strong impression on memory—allowing for mothers to recall events fairly well and actions during that time—we expect recall related to a specific pregnancy to provide better data than recall without such a stimulus, and a number of studies have supported this view.[32–35] Thus our estimates of exposure, which are based on cell phone use and number of calls, may be better than for the case-control studies of brain tumors published to date, although we do not expect the data to be without error.

Obtaining actual exposure dose measurements to radiofrequency fields in a large prospective cohort is unrealistic. Basing exposure data as collected by a well-designed questionnaire is the only practical way of obtaining cell phone use information for children in a large cohort study. It would be useful to know how well reported use of cell phone by mothers approximates exposure to the fetus. Adequate models estimating the specific absorption rate to a fetus from cell phones are still under development.[36] Based on the distance from outside the body to inside the uterus, the exposure reaching the fetus (either during conversation or when the phone is in a standby mode) is likely to be extremely low. Although unlikely, thermal effects due to localized increases in temperature should be considered, given that the temperature of the fetus is already about 0.5°C above that of the mother[37] and fetal heat dissipation to the mother (which occurs mostly at the placenta) is not fully efficient.

The specific absorption rate for children is somewhat higher than for adults due to differences in body size, shape, tissue distribution, as well as permittivity and conductivity of tissues. In addition, the relative penetration is deeper for children, a logical consequence of the smaller head diameter. Nevertheless, use of cell phones by children in this group was so infrequent and short term that the casual effect due to these exposures seems unlikely, according to our present knowledge.

About 30% of 7-year-olds used cell phones in Denmark, albeit infrequently. Although the difference in cell phone use by mothers and children between the 2 years of enrollment (1998 and 1999) was small, prevalence of use was increasing and will likely increase further as the children age. Many families will probably not have land-lines in the future, thus increasing frequency of cell phone use even more. In a recent Swedish study, nearly half of 7-year-olds had access to cell phones and prevalence increased sharply with age, to 98% of 14-year-olds.[38]

The immature nervous system is extremely vulnerable to toxicants, which can result in behavior-related toxicities that may not emerge until well into childhood, adolescence or adulthood.[39,40] Thus it will be useful to continue to follow this cohort of children.

Examination of the possible effect of prenatal and postnatal cell phone exposure on cognitive development and behavior is best done in a longitudinal study. Our results need to be replicated; they only suggest that cell phone use during critical periods of brain development in pregnancy and early childhood could be a potential risk factor for behavioral problems in children. We hope others will be able to pursue this question in other cohorts of children. The observed associations may be noncausal and due to unmeasured confounding; however, if they are real they would have major public health implications.

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EXHIBIT H

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

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ORIGINAL ARTICLE

Effects of Electromagnetic Radiation from a Cellular Phone on Human Sperm Motility: An *In Vitro* Study

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Background. There has been growing public concern on the effects of electromagnetic radiation (EMR) emitted by cellular phones on human health. Many studies have recently been published on this topic. However, possible consequences of the cellular phone usage on human sperm parameters have not been investigated adequately.

Methods. A total number of 27 males were enrolled in the study. The semen sample obtained from each participant was divided equally into two parts. One of the specimens was exposed to EMR emitted by an activated 900 MHz cellular phone, whereas the other was not. The concentration and motility of the specimens were compared to analyze the effects of EMR. Assessment of sperm movement in all specimens was performed using four criteria: (A) rapid progressive, (B) slow progressive, (C) nonprogressive, (D) no motility.

Results. Statistically significant changes were observed in the rapid progressive, slow progressive and no-motility categories of sperm movement. EMR exposure caused a subtle decrease in the rapid progressive and slow progressive sperm movement. It also caused an increase in the no-motility category of sperm movement. There was no statistically significant difference in the sperm concentration between two groups.

Conclusions. These data suggest that EMR emitted by cellular phone influences human sperm motility. In addition to these acute adverse effects of EMR on sperm motility, long-term EMR exposure may lead to behavioral or structural changes of the male germ cell. These effects may be observed later in life, and they are to be investigated more seriously. © 2006 IMSS. Published by Elsevier Inc.

Key Words: Mobile phone, Cellular, Electromagnetic field, Human, Sperm, Motility.

Introduction

Use of cellular phones has increased exponentially and become an important part of everyday life throughout the world. A growing concern for their possible adverse effects on human health evokes a flurry of scientific activity to evaluate this dilemma. Despite the increasing number of reports on the effects of electromagnetic radiation (EMR) in various biological systems, no satisfactory mechanism has been proposed to explain the effects of this radiation (1).

Radiofrequency (RF) energy is a type of nonionizing radiation, including EMR produced by cellular phone, and is not strong enough to cause ionization of atoms and molecules. Cellular phones emit low levels of RF in the microwave range while being used. Although high levels of RF can produce health effects (by heating tissue), exposure to low-level RF may not produce heating effects and causes no known adverse health effects. Several experimental studies demonstrated that exposure to electromagnetic or static magnetic fields had adverse effects on the reproductive system (2–10). However, it is likely that these effects were due to heating.

Recent epidemiological studies investigated the possible effects that EMR have comparing cell phone use and sperm

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quality of the individuals. Kilgallon et al. suggested that after other lifestyle variables had been accounted for, storage of cellular phones close to the testes had a significant negative impact on sperm concentration and percentage of motile sperm (11). Another important study performed by Fejes et al. suggested the effects of EMR radiated by cellular phones using *in vivo* experiments (12). It was the first human study performed on 371 healthy males. This study concluded that prolonged use of cellular phones might have negative effects on sperm motility characteristics. The other important study performed by Sun et al. investigated the effects of EMR emitted by computers on human sperm quality and did not find any adverse effects (13). However, epidemiologic studies might have many uncontrolled factors in the environment of these studies, which may reduce the reproducibility of their results.

In this study, we used an *in vitro* model in order to investigate the possible adverse effects of nonionizing radiation on semen parameters. Using this methodology, we can standardize the process and obtain reproducible results. We believe that the results of our *in vitro* tests may complement the *in vivo* studies.

Materials and Methods

Semen Samples

Study population was composed of healthy male volunteer individuals. Forty eight volunteering participants attending the urology clinic were tested for the existence of any abnormal situations including hormonal status and infections by routine blood and urine tests within the normal range of Gulhane Military Medical Academy. Subjects had no history of genitourinary abnormality or surgery. Donors were included if they had conventional sperm parameters within the normal range defined by World Health Organization (WHO) (1999) (14). Semen samples from 27 males (mean age 27 $\pm$ 3.2, range: 19–33) who satisfied these criteria were used in our experimental study. Samples were collected from the participants following the abstinence of ejaculation for a minimum of 48 h and no longer than 7 days before collection. All specimens were obtained by masturbation without using condom. Clean, wide-mouthed polypropylene containers (Sigma, St. Louis, MO) without residual chemicals were used for specimen collection, and specimens were kept at room temperature in the laboratory. The semen sample obtained from each participant was divided equally into two parts: control group (group 1) and EMR-exposed group (group 2).

Environmental Conditions

Environmental conditions were monitored in the semen analysis laboratory and the EMR exposure room throughout the study. All EMR measurements were performed using Triaxial Magnetic Meter, Model 4090 (Bell Technology, Orlando, FL). Basal and experimental levels of the environmental EMRs in the rooms were measured at the center of the working board of clean benches and on the stages of microscopes. EMR measurements of the experimental environment are shown in Table 1. The clean benches in the semen analysis laboratory and EMR exposure room are made out of marble. In the EMR exposure room, there are no other metal or ferromagnetic materials around the clean benches that would change the structure of the electromagnetic field. The use of any EMR-emitting device (such as an extra cellular phone, centrifuge, fluorescent light ballasts, and computers) was not allowed so that the EMR generated by this equipment would not interfere with the experimental environment.

Exposing Semen Samples to Electromagnetic Radiation

The method for exposing semen samples to EMR was established by modification of the technique described by Makler et al. (15). The collected semen samples for both groups were rested for 25 min without any intervention. At the end of the 25-min waiting period, the groups are separated from each other isolating the control group far from the source of the EMR. The EMR-exposure group specimens were taken to the exposure room and then exposed to the EMR emitted by a commercially available cellular telephone, GSM 900 type (900 MHz, 2 W peak power, average power density 0.02 mW/cm^2). The distance between the phone and specimen was 10 cm, and the duration of the exposure was 5 min (16).

Semen Analysis

Assessments of semen analysis were performed at the end of the 30-min period (25 min for liquefaction and 5 min for the EMR exposure or control) for both specimen groups (14). Sperm parameters of the two groups were analyzed at the same time to reduce time-dependent motility variations by using phase-contrast microscopes (Nikon, Alphaphot-2, YS-2, Tokyo, Japan) with phase objectives ($\times$20 magnification). Semen analyses were performed by two experienced and blinded observers. Semen samples were double checked by the observers to reduce interobserver variations. Concentration and motility were evaluated through a Makler counting chamber (Sefi-Medical Instrument, Haifa, Israel). WHO criteria (four categories of sperm movement; A-rapid progressive, B-slow progressive, C-nonprogressive and D-no motility) were used in the assessment of sperm movement (14).

Statistical Analysis

All results are given as mean $\pm$ SD. Sperm concentration and motility of exposure and control groups were compared by Wilcoxon Signed Ranks Test. SPSS for Windows

Table 1. Intensity of EMRs at experimental environment

	EMR value (μT)		
	Ambient level	Cell phone standby[a]	Cell phone working[a]
Semen analysis room			
On clean benches	0.1–0.3 μT	Ambient level	Ambient level
On microscopes	0.2–0.4 μT	Ambient level	Ambient level
Exposure room			
On clean benches	0.1–0.3 μT	0.1–0.2 μT	1.7–7.1 μT[b]

EMR, electromagnetic radiation; μT: microTesla.
[a]Cell phone is in the exposure room.
[b]EMR level produced by the cellular phone stays approximately constant during ringing and speaking.

(version 11.0, Windows, SPSS, Chicago, IL) was used for statistical analysis; $p < 0.05$ was considered statistically significant.

Results

Qualitative differences between the movement categories of the control and the EMR exposure groups are summarized in Table 2. We noted significant differences in percentages of rapid progressive, slow progressive, and no-motility categories of sperm movement. No significant differences were seen in nonprogressive motility between the two groups. Mean percentages of rapid progressive and slow progressive categories of sperm movement were higher in the control group. On the other hand, nonprogressive motility category of sperm movement was higher in the EMR exposure group. There was no statistically significant difference in the sperm concentration between the two groups.

There are more subjects with higher percentages of rapid progressive and slow progressive categories of sperm movement in the control group than the EMR exposure group. However, the EMR exposure group has more subjects with higher percentages of nonprogressive motility or no-motility categories of sperm movement compared to the control group.

Discussion

Available scientific evidence associates changes in semen quality with cellular phone usage. There are two important *in vivo* human studies in the literature about cellular phone usage and semen parameters. One suggests that lifestyle can influence semen quality. According to this study, the storage of mobile phones close to the testes can decrease semen quality (11). Another study claimed that the prolonged use of cell phones may have negative effects on sperm motility characteristics (12).

Radio waves of cellular phones do not have enough energy to cause ionization of atoms and molecules. Most DNA damage results from cellular phone EMR appear at the process of spermatogenesis and sperm maturation. Aitken et al. exposed mice to 900 MHz EMR for 7 days, 12 h/day to investigate the effects of EMR on sperm DNA (17). This study claimed that there is no increase in the single- or double-strand DNA breaks as a result of EMR exposure. However, the same study revealed that EMR exposure caused significant damage to both the mitochondrial genome and the nuclear β-globin locus caused by EMR exposure. These trends suggest that recent concerns over long-term exposure to electromagnetic irradiation emitted by mobile phones should be taken more seriously, given the growing trend for deterioration in the male germ line (18). Nonionizing radiation may cause hazardous effects by changing cellular molecules that lead to changes of cellular behaviors (reversibly or irreversibly). These changes may be passed to the next generation. This can be explained by the possible role of increased oxidative stress mediators (19) or some receptors such as seen in Merkel cells that can detect the EMR, show an exocytotic activity, and discharge its granules that lead the changes (20).

In this study we investigate the effects of electromagnetic radiation emitted by a typical cellular phone (900 MHz type) on sperm parameters. Semen collected from the participants was divided into two parts. Control group was kept at the laboratory where no EMR source exists. EMR exposure group was taken to another room and exposed to low-level nonionizing radiation generated by an activated cellular phone at a distance of 10 cm for 5 min. The 10-cm distance was accepted as physiologically reasonable limits for the individuals by measuring a high-dose radiation (70–140 μT) at ringing and speaking mode with the close touch position of cellular phone to the semen samples. Also, distance longer than 10 cm was not effective as measuring low-level (1–2 μT at 30 cm) EMR around the semen samples. Five-min exposure time was used as described by Panagopoulos et al. in their study about the effects 900-MHz cellular phone radiation on the reproductive capacity of *Drosophila melanogaster* during gonad development (16). The electromagnetic field applied to semen samples was about 20–70 times higher than the ambient EMR at the semen analysis laboratory where control group specimens were kept (see Table 1).

Table 2. Seminal findings in nonexposed and exposed groups

	Group 1 (not exposed to EMR)	Group 2 (exposed to EMR)	*z*	*p*
Movement categories (%)	Mean ± SD	Mean ± SD		
Rapid progressive (A)	13.6 ± 10.2	9.1 ± 7.9	−3.381	0.0007*
Slow progressive (B)	43.7 ± 19.4	33.9 ± 20.6	−3.377	0.0007*
Nonprogressive (C)	6.0 ± 2.6	6.4 ± 3.0	−0.756	0.4500
No motility (D)	35.9 ± 2.6	50.6 ± 22.7	−3.593	0.0003*
Sperm concentration ($\times 10^6$ mL^{-1})	59.8 ± 35.3	57.9 ± 37.6	−1.632	0.1028

EMR, electromagnetic radiation.
*p <0.001.

Our study controlled for semen analysis methodology. Our observers were trained to analyze semen samples using standardized protocols based on WHO guidelines. Our observers were also standardized by an internal quality control system for the semen analysis, although they may have used minimally different semen analysis techniques. The technique for the motility assessment outlined in the WHO guidelines is not a strictly quantifiable one, and it is possible that if a computer-assisted sperm analysis system had been used to assess motility, we may have found more precise sperm counts due to the reduced intra- and/or interobserver variations.

In vitro studies may play an important role when *in vivo* studies are weak or not definitive. Our *in vitro* study has a supporting or clarifying role on human studies. This study complements the work of Kilgallon and Simmons and Fejes et al. and confirms their results (11,12). Our *in vitro* method has a controllable environment and minimizes the uncontrolled subjective results of the *in vivo* tests.

In our study, exposure to EMR led to a significant decrease in sperm motility. Results of the semen analysis between the control and the EMR exposure group showed statistically significant changes in sperm motility in the progressive, slow progressive, and no-motility categories of sperm movement. Since all environmental factors, except the exposed EMR levels, were the same for the control and EMR exposure groups, we believe that the change in sperm motility between these groups was caused by the EMR produced by the cellular phone.

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EXHIBIT I

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Andrology Unit, Dept. of Obstetrics and Gynaecology, University of Szeged, Hungary

Is there a relationship between cell phone use and semen quality?

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Keywords: cell phone, electromagnetic field, male fertility, sperm

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Abstract

Our aim was to determine a possible relationship between regular cell phone use and different human semen attributes. Accordingly, the history-taking of male patients in our university clinic was supplemented with questions concerning cell phone use habits, including possession, daily standby position and daily transmission times. Semen analyses were performed by conventional methods. Statistics were calculated with SPSS statistical software. A total of 371 were included in the study. The duration of possession and the daily transmission time correlated negatively with the proportion of rapid progressive motile sperm (r=-0.12 and r=-0.19, respectively), and positively with the proportion of slow progressive motile sperm (r=0.12 and r=0.28, respectively). The low and high transmitter groups also differed in the proportion of rapid progressive motile sperm (48.75% vs. 40.62%). We therefore suggest that the prolonged use of cell phones may have negative effects on the sperm motility characteristics.

Introduction

The prevalence of infertility among couples of reproductive age has been estimated as up to 15%, with a tendency to increase in recent decades. In about half of these cases, the male partner exhibits some disturbance in the spermiogram [25, 31]. Idiopathic infertility is defined as a decreased sperm quality with no organic, genetic or endocrine alteration in the background, and no infection affecting the genital tract. Various environmental factors, such as heat or certain chemical agents, can deteriorate semen quality [25]. The use of cell phones has become widespread. The analogue NMT (Nordic Mobile Telephone) system introduced in the 1980s operated at an electromagnetic resonance of 902.5 MHz. A decade later, the GSM (General System for Mobile Communication) succeeded it, with a radiofrequency of 902.4 MHz, pulsing at 217 Hz. The recent DCS (Digital Cellular System), which uses a radiofrequency of 1,800 MHz, has spread rapidly [26]. Cell phones have a wide range of specific absorption rate (SAR): depending on the model used, it is approximately 0.1-2 W/kg. The emission level of cell phones is below the defined safety thresholds; however, the effects of the electromagnetic resonance emitted by cell phones on living cells and organs are still unclear. There have been publications concerning effects on the central nervous system, such as alterations in the EEG pattern, the sleeping pattern or even the neuroendocrine functions [1, 4, 15, 20]. There have also been reports on the breakage of DNA as the cause of tumours [12, 13, 14, 17, 24], but the role of cell phones in engendering tumours is debated [2, 3, 8, 11, 19, 29, 30].

Dasdag *et al.* [5] recently reported no effects of cell phone use on the testis of rats, whereas Davoudi *et al.* [6] observed declining levels of rapid progressive spermatozoa among a small study group of cell phone users. As far as we are aware, this is the first human study of the possible relationship between cell phone use and semen quality; more than 300 males were examined.

Materials and methods

Localization: Andrology Division of Department of Obstetrics and Gynaecology, University of Szeged, Hungary.

Our study involved consecutive male patients of reproductive age, who presented at our clinic because of infertility problems in their marriage. We supplemented the history-taking with questions concerning cell phone use habits. The main aspects were: duration of possession (in months), duration of standby position closer than 50 cm to the patient (in hours) and duration of daily transmission (in minutes).

The semen analysis and evaluation process was performed in accordance with the WHO 1999 standards criteria [32]. Sperm samples were produced by masturbation into a sterile, wide-mouthed calibrated glass container following a standardized 5 days of abstinence. After a 30-minute liquefaction period, the semen characteristics were quantified by using a Makler semen counting chamber (Sefi-Medical Instruments, Israel) under the 200x magnification of an Olympus CH 2 phase contrast light microscope (Olympus Optical Co. Ltd. Japan). The sperm concentration (10^6/ml) and the motile sperm ratio (%) were assessed by the same independent qualified assistant. The categories of motility were as follows: percentage of rapid progressive motile sperm (grade A), percentage of slow progressive motile sperm (grade B), percentage of non-progressive motile sperm (grade C) and percentage of immotile sperm (grade D), according to the WHO standards [32]. The total sperm count (ejaculate volume x sperm concentration), the total number of motile sperm cells (ejaculate volume x sperm concentration x motility/100) and the rapid progressive motile sperm count (ejaculate volume x sperm concentration x grade A motility/100) were calculated. After a 3-week period, sample taking was repeated under the same conditions. The better findings were analysed.

Exclusion criteria were: (1) some other potentially subfertility-causing factor in the patient's history, such as smoking (over 10 cigarettes/day), regular alcohol consumption (over 1 U/day) or drug abuse. (2) Any severe acute or chronic systemic non-gonadal illness (especially febrile illnesses) or trauma in the previous 6 weeks. (3) Some detectable organic alteration in the

reproductive organs on physical examination, such as varicocele, obstruction or absence of the deferent duct, the absence of testes or a testis volume below 12 ml, or any abnormal localization of the testes. (4) Some alteration in the levels of the spermatogenesis-related hormones. The normal levels were as follows: follicle stimulating hormone = 0.7-9.0 IU/l, luteinizing hormone = 0.8-7.6 IU/l, prolactin = 0.11-0.45 IU/l, testosterone = 6.9-28 nmol/l, sexual hormone binding globulin = 7.2-33 nmol/l. (5) Signs and symptoms of genital tract infection: cultures were made from every examined semen sample. In the event of the presence of pathogenic aerobic or anaerobic bacteria or fungi in the semen, the patient was excluded from the study.

Statistics were calculated with SPSS 11.0 for Windows statistical software (SPSS Inc. Chicago, IL, USA). The parametric t-test and the Pearson correlation tests were applied. Results are given as correlation coefficients or means ± SD. p values <0.05 were considered significant.

Control group 1 was subdivided into those who used a cell phone for less than 15 minutes/day (low transmitters) and those who used it for over 60 minutes/day (high transmitters). Control group 2 was subdivided into those patients who kept their cell phone in the standby position within a distance of 50 cm for less than 1 hour daily (short-standby group) and those who kept their cell phone in the standby position within a distance of 50 cm for more than 20 hours daily (long-standby group).

Results

A total of 611 consecutive Caucasian male patients were examined during the study period between 1 November 2002 and 31 March 2004. 39% of them (n = 240) did not meet the study criteria, and therefore the results on 371 of them were analysed. The mean age was 30.8±4.4 years (range 17-41). The subjects were from every social class.

The semen parameters of the study population are presented in Table 1 and the regression results in Table 2.

The duration of possession correlated negatively with the proportion of rapid progressive motile sperm, and positively with the proportion of slow progressive motile sperm ($r = -0.12$, $p = 0.023$, and $r = 0.12$, $p = 0.024$, respectively).

There was no significant correlation between the duration of the standby position and any of the semen parameters.

Although we found no changes in the total motility, the characteristics of the motile sperm had changed markedly. The results revealed a significant decrease in the proportion of rapid progressive motile sperm (grade A) with increase of the daily transmission time ($r = -0.19$; $p < 0.01$) (Figure 1), while the proportion of slow progressive motile sperm increased with increase of the duration of the daily transmission time (grade B) ($r = 0.28$; $p<0.01$) (Figure 2).

The low and high transmitter groups differed significantly in the proportion of rapid progressive sperm (48.75% vs. 40.62%, $p = 0.01$, $n = 195$ vs. $n = 58$). There was no difference in any characteristic between the short- and long-standby groups (Table 1).

We found no occupational hazard in the background of the deteriorated semen parameters among the high-transmitters.

Discussion

The number of couples presenting with infertility problems is increasing worldwide. In about 30% of the cases of male infertility, there is no obvious cause of the deteriorated semen parameters defined as idiopathic infertility [31]. The factors in the background of this state remain unknown. As far as we are aware, there has been no previous study of the effect of the electromagnetic field of cell phones on human semen on such a large population *in vivo*.

Our results suggest that standby communication signals do not have a significant effect on the sperm parameters. Conversely, the prolonged daily use of mobile phones may abrogate the motion characteristics of spermatozoa. The overall motility does not change, but the observed moderate decrease in grade A motility, together with the observed moderate increase in grade B motility, may be a consequence of the electromagnetic radiation emitted from cell phones. These findings are similar to those of Davoudi *et al.*, who observed a reduction in the proportion of rapid progressive sperm from 32.3% to 26.1% after 1 month of cell phone use for 6 hours daily [6]. Makler *et al.* examined the effects of 27 MHz electromagnetic resonance on human sperm velocity and survival *in vitro*, and found a decreased percentage motility and velocity, but no effect of UV light or X-rays [23].

The correlation between cell phone use and the changes in the motility parameters suggests that these effects accumulate.

Electromagnetic radiation has both thermal and non-thermal effects on living cells. There is no consensus among authors as to which effect predominates [5, 30]. We believe that the thermal effects possibly low at such low SAR levels as the cell phone emits.

We have formulated two hypotheses with which to interpret our results; however, both are in need of evidence.

First, as the brain region is close to the transmitting cell phone, the admittance is obvious: electromagnetic radiation affects the testis by changing the levels of hormones produced by glands inside the cranium. De Seze *et al.* found no alterations in the levels of pituitary hormones in

association with prolonged cell phone use [7]. According by we excluded those subjects who exhibited such an alteration. Burch *et al.* demonstrated a reduced 6-OHMS level in the urine among those using a cell phone for over 25 minutes/day; 6-OHMS is the urinary metabolite reflecting the therefore referring serum level of the pineal hormone melatonin [1]. Melatonin is known to be an antioxidant agent that protects against lipid peroxidation in the retina, brain, liver cells and even human sperm [9].

Secondly, the electromagnetic radiation of cell phones may cause DNA breakage in cells in the male genital tract, which can occur in a low-frequency electromagnetic field. *In vitro* studies appear justified to investigate the increased numbers of chromosome aberrations of the micronuclei in human leucocytes and DNA breaks [18, 21, 22]. A moderate correlation has been found between the sperm motility and the sperm chromatin structure which are probably brought about by distorted epididymal protamination [10].

A possible connection of the two theories is reactive oxygen species (ROS) production. ROS cause DNA fragmentation in somatic cells reducing protamination [28]. Melatonin inhibits ROS production.

A sedentary lifestyle and other occupational factors can lead to deteriorated semen parameters [25, 27]. These effects are mostly occupation-related. We found no specific profession among the high transmitters in our population to suggest that some particular occupation might be responsible for the deteriorated semen parameters rather than excessive cell phone use.

Our study has some limits: the effects of the non-ionizing radiation emitted by cell phones depend on a number of factors besides the duration of transmission, e.g. the type of cell phone and the distance from the cell phone tower [16]. We examined only the duration of use not specified to other variables, as this covered a fairly wide cross-section of males from the whole population.

The function of the accessory glands was not examined. Their secretion can improve sperm motion, and also affect the function in other ways.

Further, prospective, controlled studies on a larger population are required to prove whether the electromagnetic emission from cell phones affects the male fertilizing capacity, and to establish the mode of action of such a possible deteriorating effect.

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Tables

	Total population Mean± S.D.	Control group 1 Mean± S.D.	High-transmitters Mean± S.D.	Control group 2 Mean± S.D.	Long standby Mean± S.D.
Sperm concentration (10^6/ml)	68.38±48.86	67.6±44.56	68.47±46.43	69.32±45.97	63.77±42.3
Proportion of rapid progressive motile sperm (%)	47.17±21.21	48.75±20.62	40.47±21.62	47.85±21.4	46.17±20.65
Proportion of slow progressive motile sperm (%)	12.38±9.23	11.4±7.13	16.98±15.53	11.72±6.79	13.58±9.98
Proportion of non-progressive motile sperm (%)	7.99±5.4	8.34±5.76	7.73±4.37	9.12±5.67	7.59±4.94
Motility (%)	59.56±18.85	60.15±18.8	57.46±17.26	59.58±19.13	59.75±16.58

Table 1. Main semen characteristics of the study population (n=371), control group 1 (n=195), the high-transmitter group (n=59), control group 2 (n=106) and the long-standby group (n=88).

	Volume (ml)	Sperm conc. (10^6/ml)	Proportion of rapid progressive motile sperm (%)	Proportion of slow progressive motile sperm (%)	Proportion of non-progressive motile sperm (%)	Proportion of immotile sperm (%)	Total motility (%)	Total sperm count (10^6/ejaculate)	Total motile sperm count (10^6/ejaculate)	Total rapid progressive motile sperm count (10^6/ejaculate)
Duration of possession (months)	-0.02 p=0.64	-0.01 p=0.91	**-0.12 p=0.02**	**0.12 p=0.02**	0.07 p=0.15	0.06 p=0.28	-0.08 p=0.14	-0.01 p=0.81	-0.03 p=0.53	-0.06 p=0.26
Duration of daily standby (hours)	0.05 p=0.42	-0.01 p=0.39	-0.05 p=0.41	0.05 p=0.37	-0.05 p=0.37	0.04 p=0.47	-0.03 p=0.64	-0.05 p=0.41	-0.07 p=0.22	-0.08 p=0.15
Duration of daily transmission (min)	-0.01 p=84	0.04 p=0.84	**-0.19 p<0.01**	**0.28 p<0.01**	-0.03 p=0.56	0.08 p=0.12	-0.07 p=0.16	0.03 p=0.58	0.00 p=0.54	-0.08 p=0.14

Table 2. Correlations between parameters of cell phone use and semen characteristics (n=371). Bold numbers denote a significant correlation.

Figures

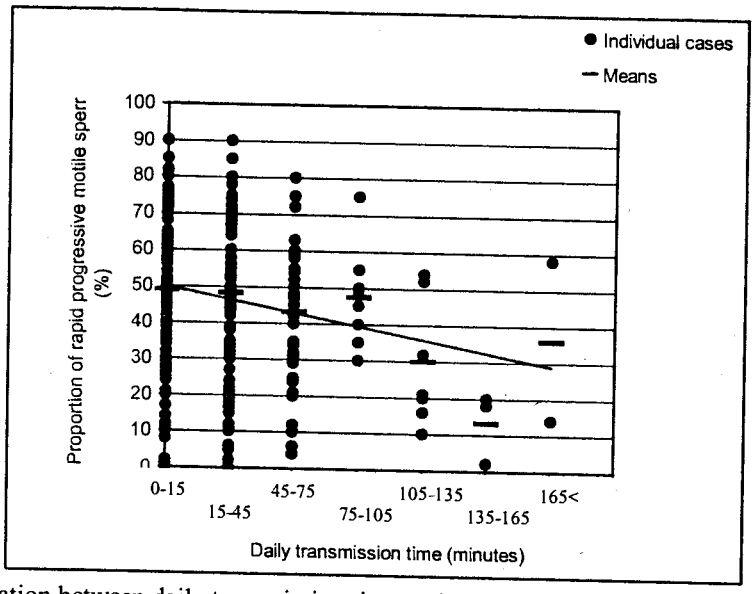

Figure 1. Correlation between daily transmission time and percentage of rapid progressive motile sperm ($r = -0.19$; $p<0.01$; $n = 372$)

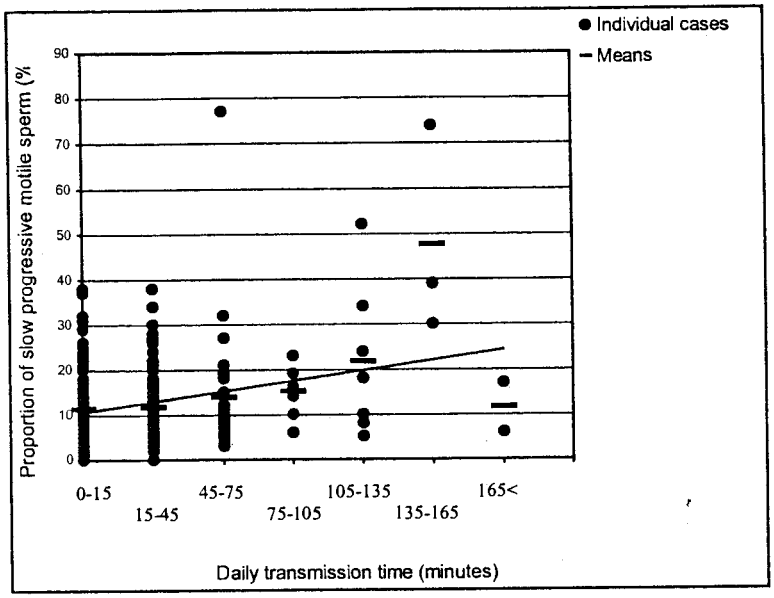

Figure 2. Correlation between daily transmission time of cell phone and proportion of slow progressive motile sperm ($r = 0.28$; $p<0.01$; $n = 372$)

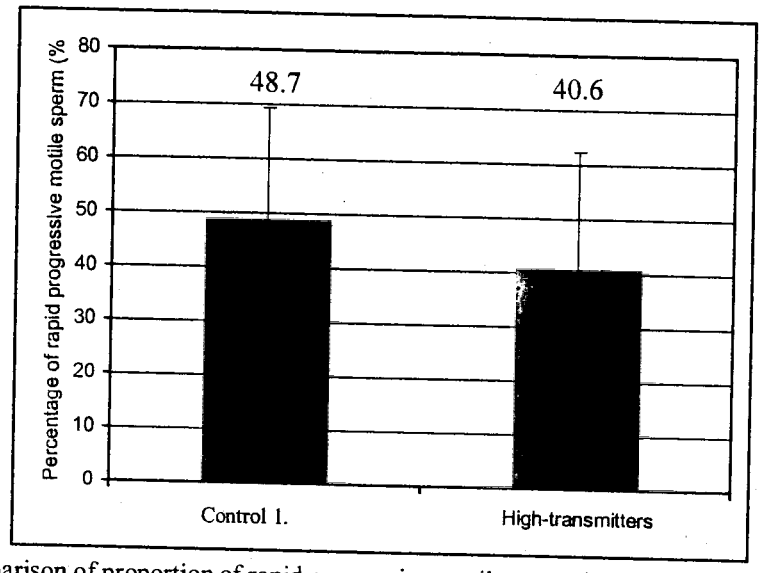

Figure 3. Comparison of proportion of rapid progressive motile sperm in low and high-transmitters (n = 195 vs n = 58; p = 0.01)

EXHIBIT J

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Electromagnetic Absorption in the Human Head and Neck for Mobile Telephones at 835 and 1900 MHz

Om P. Gandhi, *Fellow, IEEE*, Gianluca Lazzi, *Member, IEEE*, and Cynthia M. Furse, *Member, IEEE*

Abstract— **We have used the finite-difference time-domain method and a new millimeter-resolution anatomically based model of the human to study electromagnetic energy coupled to the head due to mobile telephones at 835 and 1900 MHz. Assuming reduced dimensions characteristic of today's mobile telephones, we have obtained SAR distributions for two different lengths of monopole antennas of lengths $\lambda/4$ and $3\lambda/8$ for a model of the adult male and reduced-scale models of 10- and 5-year-old children and find that peak one-voxel and 1-g SAR's are larger for the smaller models of children, particularly at 835 MHz. Also, a larger in-depth penetration of absorbed energy for these smaller models is obtained. We have also studied the effect of using the widely disparate tissue properties reported in the literature and of using homogeneous instead of the anatomically realistic heterogeneous models on the SAR distributions. Homogeneous models are shown to grossly overestimate both the peak 1-voxel and 1-g SAR's. Last, we show that it is possible to use truncated one-half or one-third models of the human head with negligible errors in the calculated SAR distributions. This simplification will allow considerable savings in computer memory and computation times.**

I. Introduction

CELLULAR telephones and mobile wireless communication systems are being introduced into society at a very rapid rate. This has resulted in public concern about the health hazards of RF electromagnetic fields that are emitted by these devices. In this paper, we describe a study of the electromagnetic absorption in the human body for some typical antennas used for these telephones and compare the mass-normalized rates of energy absorption (specific absorption rates or SAR's) with the ANSI/IEEE C95.1-1992 RF Safety Guidelines [1]. These safety guidelines are given in terms of the maximum permissible exposures (MPE) of electric and magnetic fields, or of power density for controlled and uncontrolled environments. Though simple to use for far-field, relatively uniform exposures, the MPE limits are not easy to use for highly nonuniform fields such as in the near-field region of a cellular telephone. An alternative procedure given in the following [1] has, therefore, been suggested to satisfy the safety guidelines for uncontrolled environments which are defined as situations where there is exposure of individuals who have no knowledge or control of their exposure.

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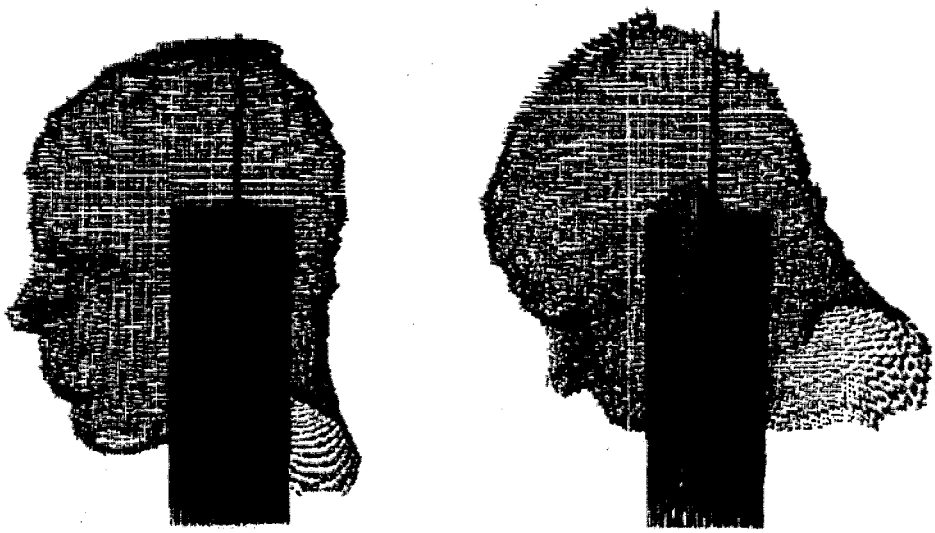
An exposure condition can be considered to be acceptable if it can be shown that it produces SAR's "below 0.08 W/kg, as averaged over the whole body, and spatial peak SAR values not exceeding 1.6 W/kg, as averaged over any 1 g of tissue (defined as a tissue volume in the shape of a cube)."

For calculations of the SAR distributions we have used the well-established finite-difference time-domain (FDTD) numerical electromagnetic method which has previously been used for a number of bioelectromagnetic problems pertaining to far-field or near-field exposures from ELF to microwave frequencies [2]. We have also used a newly developed millimeter-resolution model of the human body obtained from the magnetic resonance imaging (MRI) scans of a male volunteer. This whole-body model has a resolution of 1.875 mm for the two orthogonal axes in the cross-sectional planes and 3 mm along the height of the body [2]. The head and neck part of this model has previously been used to study SAR distributions for ten commercially available cellular telephones [2], [3] operating at transmission frequencies of 820–850 MHz (center frequency of 835 MHz). It has also been used to calculate electromagnetic absorption in the human head for some experimental handheld transceivers operating at 6 GHz [4]. This same anatomically based part-body model has also been used for the calculations given in this paper.

We are aware of some recent publications on the SAR calculations for mobile telephones using anatomically based models of the human head [5], [6]. Whereas a somewhat cruder model of the human head with a resolution of 6.56 mm was used in [5], a higher-resolution MRI-based model with 2-mm cell size has been used by Dimbylow and Mann [6] for calculations with $\lambda/4$ monopoles above a metal box and for $\lambda/2$ dipoles.

For calculations reported in this paper we have examined two different lengths of monopole antennas, $\lambda/4$ and $3\lambda/8$, mounted on plastic-coated handsets of dimensions that are typical of newer mobile telephones both at 835 and 1900 MHz. We have also studied the effect of tilting the handset as for typical usage at an angle of 33° relative to vertical and compared the results with the SAR's when the antenna is held vertically relative to the head. By scaling the model of the head and neck to obtain reduced-size models representative of 10- and 5-year-old children, we have calculated the SAR distributions and find deeper penetration of EM energy, and SAR's for internal tissues that are several times higher than



(a) (b)

Fig. 1. The two head models with the telephone used for the calculations: (a) vertical, (b) tilted 30° relative to vertical.

TABLE 1
DIELECTRIC PROPERTIES AND SPECIFIC GRAVITIES OF THE VARIOUS TISSUES ASSUMED AT THE MIDBAND MOBILE TELEPHONE FREQUENCIES OF 835 AND 1900 MHz [12]. ALSO INCLUDED ARE THE LOWER DIELECTRIC PROPERTIES FOR FAT, BONE, AND CARTILAGE PREVIOUSLY REPORTED IN THE LITERATURE [14], [16]

		835 MHz		1900 MHz	
Tissue	Spec. Gravity 10^3kg/m^3	ε_r	σ S/m	ε_r	σ S/m
muscle	1.04	51.76	1.11	49.41	1.64
fat	0.92	9.99	0.17	9.38	0.26
bone (skull)	1.81	17.40	0.25	16.40	0.45
cartilage	1.10	40.69	0.82	38.10	1.28
skin	1.01	35.40	0.63	37.21	1.25
nerve	1.04	33.40	0.60	32.05	0.90
blood	1.06	55.50	1.86	54.20	2.27
parotid gland	1.05	45.25	0.92	43.22	1.29
CSF	1.01	78.10	1.97	77.30	2.55
eye humour	1.01	67.90	1.68	67.15	2.14
sclera	1.17	54.90	1.17	52.56	1.73
lens	1.10	36.59	0.51	42.02	1.15
pineal gland	1.05	45.26	0.92	43.22	1.29
pituitary gland	1.07	45.26	0.92	43.22	1.29
brain	1.04	45.26	0.92	43.22	1.29
		Old properties [14, 16]		Old properties [14, 16]	
fat	0.92	7.20	0.16	9.70	0.27
bone (skull)	1.81	7.20	0.16	8.40	0.15
cartilage	1.10	7.20	0.16	9.70	0.27

TABLE II
DIELECTRIC PROPERTIES AND SPECIFIC GRAVITIES ASSUMED FOR TEST RUNS FOR COMPARISON WITH THE CALCULATIONS OF DIMBYLOW AND MANN [6]

Tissue	Spec. Gravity 10^3kg/m^3	835 MHz ε_r	835 MHz σ S/m	1900 MHz ε_r	1900 MHz σ S/m
muscle	1.04	58.00	1.21	56.00	1.76
fat	0.92*	9.99*	0.17*	9.38*	0.26*
bone (skull)	1.85	8.00	0.11	8.00	0.15
cartilage	1.10	35.00	0.60	32.00	0.57
skin	1.10	35.00	0.60	32.00	0.57
nerve	1.04*	33.4*	0.60*	32.05*	0.90*
blood	1.06	64.00	1.24	64.00	1.80
parotid gland	1.05*	45.25*	0.92*	43.22*	1.29*
CSF	1.06	72.00	2.13	72.00	2.50
eye humour	1.01	73.00	1.97	74.00	2.27
sclera	1.01	66.00	1.93	62.00	2.28
lens	1.05	44.00	0.80	42.00	1.19
pineal gland	1.05*	45.26*	0.92*	43.22*	1.29*
pituitary gland	1.07*	45.26*	0.92*	43.22*	1.29*
brain	1.03	49.00	1.10	47.00	1.42

* These values were not prescribed in [6].

for the model of the adult. Since the tissue properties are not as well characterized, and widely varying values have been reported for fat, bone, and cartilage, we have studied the effect that these properties can have on peak 1-g SAR's that need to be examined for compliance with the ANSI/IEEE safety guidelines. We have identified a problem with interpreting the ANSI/IEEE safety guidelines since unspecified and different subvolumes in the shape of a cube may be taken in order to obtain peak 1-g SAR's that should not exceed 1.6 W/kg for uncontrolled environments [1]. For slightly larger subvolumes involving the more superficial regions including the air pockets of the ear, considerably higher 1-g SAR's are obtained. This problem has been temporarily resolved with advice from the Dosimetry Working Group of WTR [see Section IV]. Finally, we have developed a procedure for using smaller truncated models by factors of 2–3 with minimal loss of accuracy in determination of SAR distributions for the exposed region of the head.

II. THE FDTD METHOD

The finite-difference time-domain method has been described in several publications and a couple of recent textbooks [7], [8]. This method has also been used successfully to obtain specific absorption rates for anatomically based models of the human body for whole-body or partial-body exposures to spatially uniform or nonuniform (far-field or near-field) electromagnetic fields from ELF to microwave frequencies [2], [9]. In this method, the coupled Maxwell's equations in differential form are solved for all points of the absorber (model of the human head and neck and the approximate model of the hand), as well as the space including the plastic-coated handset, the antenna embedded in a dielectric sheathing and the region to the absorbing boundaries which are generally taken to be at least 10 cells away from the telephone-head/neck coupled region. For all of the calculations reported in this paper we have used the retarded-time absorbing-boundary condition [10]. The time resolution $\delta t = \delta/2c = 3.29$ ps was taken to correspond to the smaller of the cell dimensions of 1.974 mm. To get converged results, we have used 8 time periods for each of the two frequencies of 835 and 1900 MHz that were used for the SAR distributions. It is recognized that different handset dimensions are being used for the cellular telephones, and the dimensions of the handset do influence the radiated fields and the SAR distribution patterns [11]. We have taken a handset dimension of $2.96 \times 5.73 \times 15.5$ cm typical of today's handsets for most of the calculations given in this paper. This includes a metal box of dimensions $14\delta_x \times 28\delta_y \times 51\delta_z (2.76 \times 5.53 \times 15.3$ cm) and 1-cell thickness δ of plastic coating of effective dielectric constant[1] K_e given by the following equation which is somewhat lower than the

[1] The effective dielectric constant K_e is derived by noting that the electric fields close to a metallic surface such as that of a handset are primarily normal and only a part of the FDTD-cell width is actually filled with the dielectric material. The required continuity of the normal component of $D = \varepsilon E$ with the outer region can be used to obtain K_e.

TABLE III
SAR DISTRIBUTIONS FOR THE SQUISHED-EAR MODEL OF THE ADULT MALE FOR $\lambda/4$ AND $3\lambda/8$ ANTENNAS AT 1900 MHz. TIME-AVERAGED RADIATED POWER = 125 mW

	$\lambda/4$ antenna	$3\lambda/8$ antenna
Peak 1-voxel SAR (W/kg)	3.90	2.66
Peak 1-g SAR (W/kg)[1]	0.52 (1.01 g; 98.7%)	0.32 (1.01 g; 98.7%)
Peak 1-g SAR (W/kg)[2]	1.11 (1.03 g; 81.0%)	0.69 (1.06 g; 86.0%)
Peak 1-g SAR (W/kg)[3]	1.03 (1.10 g; 82.4%)	0.69 (1.11 g; 86.1%)
Peak 1-g SAR for brain (W/kg)[2]	0.20 (1.00 g)	0.16 (1.00 g)
Peak 1-g SAR for brain (W/kg)[3]	0.19 (1.05 g)	0.16 (1.00 g)
Power absorbed by head and neck	35.6%	29.4%
Power absorbed by "hand"	13.8%	7.0%
Peak 1-voxel SAR for brain (W/kg)	0.29	0.26
CSF average (mW/kg)	8.0	8.3
Brain average (mW/kg)	7.6	7.6
Humour average (mW/kg)	3.2	2.6
Lens average (mW/kg)	1.5	1.3
Sclera average (mW/kg)	1.8	1.5

[1] $5 \times 5 \times 3$ cells; $0.987 \times 0.987 \times 0.9$ cm; 0.88 cm^3

[2] $5 \times 5 \times 4$ cells; $0.987 \times 0.987 \times 1.2$ cm; 1.17 cm^3

[3] $6 \times 6 \times 3$ cells; $1.184 \times 1.184 \times 0.9$ cm; 1.26 cm^3

It was not possible to obtain 1-g weight of the brain for subvolume 1; hence, the 1-g SAR for brain for this case is not given.

dielectric constant ε_r of the actual insulation layer of thickness w (generally 1 mm).

$$K_e = \frac{\delta//\varepsilon_r}{[\varepsilon_r(\delta - w) + w]} \quad (1)$$

Here δ is the dimension of the Yee cell which may be δ_x, δ_y, or δ_z depending on the surface of the metal handset.

III. A MILLIMETER-RESOLUTION ANATOMIC MODEL OF THE HUMAN BODY

We have recently developed a millimeter-resolution model of the human body from the magnetic resonance imaging (MRI) scans of a male volunteer of height 176.4 cm and weight 64 kg. The MRI scans were taken with a resolution of 3 mm along the height of the body and 1.875 mm for the orthogonal axes in the cross-sectional planes. Even though the height of the volunteer was quite appropriate for an average male, the weight was somewhat lower than an average of 71 kg, which is generally assumed for an average male. This problem can, to some extent, be ameliorated by assuming that the pixel dimensions for the cross sections are larger than 1.875 mm by the ratio of $(71/64)^{1/2} = 1.053$, i.e., 1.974 mm instead of 1.875 mm. Using a software package from the Mayo Clinic called ANALYZE, the MRI scans of the human body were converted into images involving 30 tissue types whose electrical properties (ε_r, σ) can then be prescribed at the mobile telephone midband frequencies of 835 MHz or 1900 MHz. The tissues taken for the whole-body model are: muscle, fat, regular bone, compact bone, cartilage, skin, nerve, intestine, spleen, pancreas, heart, blood, parotid gland, liver, kidney, lung, bladder, cerebrospinal fluid, eye humour, eye sclera, eye lens, stomach, erectile tissue, prostate gland, spermatic cord, testicle, ligament, brain, pineal gland, and pituitary gland. Since only the model of the head and neck is used for the present calculations, only 15 of these tissues are involved in this model. The new dielectric properties assumed for the various tissues at 835 and 1900 MHz are given in Table I. These are taken from the unpublished data of Gabriel [12]. We have considered two orientations of the handset, one that is held vertically relative to the head (tilt angle of 0°) and another that is held at a tilt angle of 30° relative to the head (see Fig. 1). To simulate a handset that is typically tilted forward by 30° for a vertically erect head, we have modified the MRI-based model so that it is tilted forward by 30°. As described in [13], the forward tilt is accomplished by a "best fitting" technique wherein each of the cells of the present model is assigned to a new corresponding cell only if no other cells have a better fitting to the new one. An error matrix proportional to the distance of the rotated cells from the cell centroid of the new cell is used and minimized to obtain the

TABLE IV
SAR DISTRIBUTIONS FOR THE UTAH MODEL OF THE ADULT MALE WITHOUT SQUISHED EAR FOR COMPARISON WITH DATA OBTAINED BY DIMBYLOW AND MANN USING THE NRPB MODEL [6]. FREQUENCY = 900 MHz. RADIATED POWER = 600 mW. DISTANCE OF THE SOURCE POINT TO THE EAR = 1.38 cm (7δ) AS AGAINST 1.4 cm IN [6]

	No hand $\lambda/4$ antenna above handset	No hand $\lambda/2$ dipole
Peak 1-voxel SAR (W/kg)	7.57	9.13
Peak 1-g SAR (W/kg)[1]	2.07* (1.00 g; 92.0%)	2.10† (1.00 g; 92.0%)
Peak 1-g SAR (W/kg)[2]	2.49* (1.07 g; 83.0%)	2.71† (1.07 g; 83.0%)
Peak 1-g SAR (W/kg)[3]	2.45* (1.18 g; 86.1%)	2.47† (1.13 g; 81.5%)
Peak 1-g SAR for brain (W/kg)[2]	1.36 (1.01 g)	1.54 (1.01 g)
Peak 1-g SAR for brain (W/kg)[3]	1.31 (1.10 g)	1.48 (1.10 g)
Power absorbed by head and neck	51.7%	52.0%
Peak 1-voxel SAR for brain (W/kg)	4.6	2.6
CSF average (mW/kg)	62.3	60.7
Brain average (mW/kg)	74.4	88.0
Humour average (mW/kg)	50.6	42.8
Lens average (mW/kg)	26.5	19.8
Sclera average (mW/kg)	43.4	33.1

Superscripts 1, 2, and 3 are for cell numbers and subvolumes given in the footnote of Table 3.

* SAR scaled from Table 2 of Reference [6] = 2.17 W/kg.

† SAR scaled from Table 2 of Reference [6] = 2.02 W/kg.

original cells that may occupy the new cell location. The 30° forward-tilted head thus obtained is shown in Fig. 1 together with the original untilted head model. For the tilted model, a vertical orientation of the handset and the antenna allows more accurate modeling of their shapes and dimensions. Models for each of the antennas and the handsets were assumed to be covered with insulating materials of $\varepsilon_r = 4.0$. Because of the different cell sizes used, particularly for the smaller models representative of 10- and 5-year-old children, different values of K_e obtained from (1) have been used for the various simulations for these cases.

Because of the proximity of the hand to the telephone, it is essential to also model the hand for numerical calculations. For the present calculations we have modeled the hand by a region of 2/3 muscle-equivalent material of thickness 1.974 cm ($10\delta_y$) wrapped around the handset on three sides, with the exception of the side facing the head, with height two-thirds that of the handset.

By scaling the cell sizes of the MRI-based model, we have developed smaller models of the head, neck, and hand to correspond to dimensions characteristic of 10- and 5-year-old children, respectively. In the dosimetry handbook [14], the heights and weights for average 10- and 5-year-old children are given as 1.38 and 1.12 m and 32.5 and 19.5 kg, respectively. These heights and weights are also in agreement with the averages for the boys given in [15]. To obtain models of these needed heights, we have scaled the cell size $\delta_z = 3$ mm of the MRI-based model of the adult male of height 176.4 cm to new dimensions $\delta_z = 2.3469$ and 1.9048 mm, respectively. Also, maintaining the square shapes of the pixels in the cross-sectional planes as for the MRI-based model, we have altered the dimensions $\delta_x = \delta_y$ from 1.875 mm of the adult male model of weight 64.0 kg to new cell sizes $\delta_x = \delta_y = 1.51$ and 1.2989 mm to obtain models of 10- and 5-year-old children of weights 32.5 and 19.5 kg, respectively. The approximate hand dimensions have been similarly scaled through these cell sizes so that the hands cover less than two-thirds of the heights of the assumed handsets for models of 10- and 5-year-old children.

It is well-known that considerably lower values of ε_r and σ have previously been reported for fat, bone, and cartilage in the published literature [14], [16] as compared to the higher values that have recently been determined by Gabriel [12]. These lower values of ε and σ reported for fat, bone, and cartilage are given at the bottom of Table II and have been taken instead of the newer values for some of the runs (see Table VI) to determine the effect of tissue properties on SAR distributions.

IV. THE PEAK 1-g SAR

According to the ANSI/IEEE C95.1-1992 RF safety guideline for uncontrolled environments, the spatial-peak SAR should not exceed 1.6 W/kg for any 1 g of tissue defined as a tissue volume in the shape of a cube [1]. Because of

TABLE V
SAR DISTRIBUTIONS FOR THE UTAH MODEL OF THE ADULT MALE WITHOUT SQUISHED EAR FOR COMPARISON WITH DATA OBTAINED BY DIMBYLOW AND MANN USING THE NRPB MODEL [6]. FREQUENCY = 1800 MHz. RADIATED POWER = 125 mW. DISTANCE OF THE SOURCE POINT TO THE EAR = 1.38 cm ($\bar{7}\delta$) AS AGAINST 1.4 cm IN [6]

	No hand $\lambda/4$ antenna above handset	No hand $\lambda/2$ dipole
Peak 1-voxel SAR (W/kg)	1.54	1.90
Peak 1-g SAR (W/kg)[1]	0.53* (1.00 g; 98.7%)	0.55† (1.00 g; 98.7%)
Peak 1-g SAR (W/kg)[2]	0.87* (1.03 g; 80.0%)	0.81† (1.04 g; 81.0%)
Peak 1-g SAR (W/kg)[3]	0.83* (1.13 g; 81.5%)	0.76† (1.16 g; 83.3%)
Peak 1-g SAR for brain (W/kg)[2]	0.27 (1.04 g)	0.41 (1.01 g)
Peak 1-g SAR for brain (W/kg)[3]	0.27 (1.02 g)	0.40 (1.07 g)
Power absorbed by head and neck	45.4%	46.4%
Peak 1-voxel SAR for brain (W/kg)	0.50	0.64
CSF average (mW/kg)	7.8	9.0
Brain average (mW/kg)	10.4	13.2
Humour average (mW/kg)	8.8	7.4
Lens average (mW/kg)	2.5	2.0
Sclera average (mW/kg)	5.7	4.5

Superscripts 1, 2, and 3 are for cell numbers and subvolumes given in the footnote of Table 3.

* SAR scaled from Table 3 of Reference [6] = 0.70

† SAR scaled from Table 3 of Reference [6] = 0.78.

TABLE VI
SAR DISTRIBUTIONS FOR DIFFERENT PROPERTIES OF THE VARIOUS TISSUES. A $\lambda/4$ ANTENNA ABOVE A HANDSET IS TAKEN FOR THE CALCULATIONS AT 835 MHz. RADIATED POWER = 600 mW

	New properties	Old properties	Homogeneous model
Peak 1-voxel SAR (W/kg)	10.86	8.52	15.98
Peak 1-g SAR (W/kg)	2.93 (1.00 g)	2.05 (1.00 g)	4.17 (1.03 g)
Peak 1-g SAR for brain (W/kg)	1.13 (1.09 g)	0.86 (1.02 g)	---
Power absorbed by head and neck	45.0%	44.0%	41.5%
Power absorbed by "hand"	9.2%	11.9%	8.4%
Peak 1-voxel SAR for brain (W/kg)	1.62	2.11	---
CSF average (mW/kg)	72.7	62.6	---
Brain average (mW/kg)	72.3	62.9	---
Humour average (mW/kg)	31.8	32.9	---
Lens average (mW/kg)	11.3	12.8	---
Sclera average (mW/kg)	17.8	19.4	---

the irregular shape of the body (e.g., the ears) and tissue heterogeneities, a tissue volume in the shape of a cube of, say, 1 × 1 × 1 cm will have a weight that may be in excess of, equal to, or less than 1 g. Larger or smaller volumes in the shape of a cube may, therefore, need to be considered to obtain a weight of about 1 g. Furthermore, for an anatomic model such as ours using unequal cell sizes (1.974 × 1.974 × 3 mm), it is not very convenient to obtain exact cubical volumes even though nearly cubic shapes may be considered. We have, therefore, considered 5 × 5 × 3, 5 × 5 × 4, and 6 × 6 × 3 cells for the model of the adult male to obtain subvolumes on the order of 1 cm^3. For each of these subvolumes selected close to and around the regions of the high SAR's, we have divided the absorbed powers by the weights calculated for

TABLE VII
COMPARISON OF THE POWERS ABSORBED AND PEAK SAR'S FOR THE $\lambda/4$ AND $3\lambda/8$ ANTENNAS AT 835 MHz. TIME-AVERAGED RADIATED POWER = 600 mW

Antenna length	Tilt	Peak 1-g SAR for Head	Peak 1-g SAR for Brain	% power absorbed by "hand"	% power absorbed by head and neck
$\lambda/4$	0°	2.93 (1.00 g)	1.13 (1.09 g)	9.2	45.0
$\lambda/4$	30°	2.42 (1.03 g)	0.93 (1.02 g)	12.4	39.8
$3\lambda/8$	0°	1.60 (1.00 g)	0.65 (1.05 g)	5.6	33.7

TABLE VIII
COMPARISON OF THE POWERS ABSORBED AND PEAK SAR'S FOR THE $\lambda/4$ AND $3\lambda/8$ ANTENNAS AT 1900 MHz. TIME-AVERAGED RADIATED POWER = 125 mW

Antenna length	Tilt	Peak 1-g SAR for Head W/kg	Peak 1-g SAR for Brain W/kg	% power absorbed by "hand"	% power absorbed by head and neck
$\lambda/4$	0°	1.11 (1.03 g)	0.20 (1.00 g)	13.8	35.6
$\lambda/4$	30°	1.08 (1.03 g)	0.20 (1.04 g)	13.9	35.5
$3\lambda/8$	0°	0.69 (1.06 g)	0.16 (1.00 g)	7.0	29.4

TABLE IX
COMPARISON OF SAR DISTRIBUTIONS FOR MODELS OF AN ADULT MALE AND 10-YEAR AND 5-YEAR-OLD CHILDREN. FREQUENCY = 835 MHz. TIME-AVERAGED RADIATED POWER = 600 mW. A $\lambda/4$ ANTENNA ABOVE A HANDSET IS TAKEN FOR THE CALCULATIONS

	Adult male	10-year-old child	5-year-old child
Peak 1-voxel SAR (W/kg)	10.86	16.82	31.73
Peak 1-g SAR* (W/kg)	2.93 (1.00 g)	3.21 (1.02 g)	4.49 (1.00 g)
Peak 1-g SAR for brain* (W/kg)	1.13 (1.09 g)	1.42 (1.00 g)	1.56 (1.00 g)
Power absorbed by head and neck	45.0%	42.6%	39.5%
Power absorbed by "hand"	9.2%	10.7%	5.5%
Peak 1-voxel SAR for brain (W/kg)	1.62	3.02	4.62
CSF average (mW/kg)	72.7	187.2	283.2
Brain average (mW/kg)	72.3	160.3	239.8
Humour average (mW/kg)	31.8	78.2	117.3
Lens average (mW/kg)	11.3	33.6	52.5
Sclera average (mW/kg)	17.8	48.7	73.7

* $5 \times 5 \times 4$ cells; $0.987 \times 0.987 \times 1.200$ cm; 1.170 cm^3 for the adult male
$7 \times 7 \times 4$ cells; $1.057 \times 1.057 \times 0.939$ cm; 1.049 cm^3 for the 10-year-old child
$8 \times 8 \times 5$ cells; $1.039 \times 1.039 \times 0.950$ cm; 1.026 cm^3 for the 5-year-old child

the individual subvolumes to obtain 1-g SAR's. Furthermore, we have considered only those subvolumes where at least 80 percent of the cells are occupied by the tissues and no more than 20 percent of the cells are in air. As expected, there is a great deal of variability in the 1-g SAR's that are obtained. In keeping with the ANSI/IEEE safety guidelines, weights equal to or in excess of 1 g are considered to obtain the spatial-peak SAR's that are given in Table III.

TABLE X
COMPARISON OF SAR DISTRIBUTIONS FOR MODELS OF AN ADULT MALE AND 10-YEAR and 5-YEAR-OLD CHILDREN. FREQUENCY = 1900 MHz. TIME-AVERAGED RADIATED POWER = 125 mW. A $\lambda/4$ ANTENNA ABOVE A HANDSET IS TAKEN FOR THE CALCULATIONS

	Adult male	10-year-old child	5-year-old child
Peak 1-voxel SAR (W/kg)	3.90	4.90	6.20
Peak 1-g SAR* (W/kg)	1.11 (1.03 g)	0.90 (1.02 g)	0.97 (1.07 g)
Peak 1-g SAR for brain* (W/kg)	0.20 (1.00 g)	0.25 (1.07 g)	0.31 (1.00 g)
Power absorbed by head and neck	35.6%	34.4%	32.2%
Power absorbed by "hand"	13.8%	9.4%	6.8%
Peak 1-voxel SAR for brain (W/kg)	0.29	0.42	0.61
CSF average (mW/kg)	8.0	20.6	33.4
Brain average (mW/kg)	7.6	19.6	32.9
Humour average (mW/kg)	3.2	17.4	39.2
Lens average (mW/kg)	1.5	7.6	17.8
Sclera average (mW/kg)	1.8	9.9	20.5

* $5 \times 5 \times 4$ cells; $0.987 \times 0.987 \times 1.200$ cm; 1.170 cm^3 for the adult male
$7 \times 7 \times 4$ cells; $1.057 \times 1.057 \times 0.939$ cm; 1.049 cm^3 for the 10-year-old child
$8 \times 8 \times 5$ cells; $1.039 \times 1.039 \times 0.950$ cm; 1.026 cm^3 for the 5-year-old child

In Table III it is interesting to note that even though the peak 1-g SAR's for the superficial tissues are highly variable (by almost 2:1), the corresponding values for the internal tissues such as the brain are nearly identical regardless of the subvolumes that are considered. The reason for the highly variable peak 1-g SAR's for the superficial tissues is that various subvolumes of, say, 0.8–1.2 cm^3 in the shape of a cube may each give a weight of about 1 g, depending on the amount of air in such subvolumes. For our case, larger subvolumes such as $5 \times 5 \times 4$ and $6 \times 6 \times 3$ cells with volumes of 1.17 and 1.26 cm^3, respectively, involve more of air and the ear tissues and still have weights of at least 1 g, whereas the smaller subvolumes of $5 \times 5 \times 3$ cells with a total volume of 0.88 cm^3 must have more of the nonear head tissues in order to get weights of 1 or more grams of weight. Since the subvolumes to consider for peak 1-g SAR's have not been clearly defined in the ANSI/IEEE safety guidelines, the variability in the peak 1-g SAR's given in Table III is hard to resolve and is clearly troublesome. All three peak 1-g values have, therefore, been given in Table III. For each of the cases, the weights and percentage of tissues by volume are given within parentheses of the peak 1-g SAR's.

This problem of lack of definition of the subvolume to consider was brought to the attention of the Dosimetry Working Group[2] of Wireless Technology Research. At its meeting in Duarte, California, on October 30, 1995, the working group decided to recommend to ANSI/IEEE that the tissue subvolume to consider should not extend beyond the most exterior surfaces of the body (e.g., the upper, lower, and side boundaries of the ear) but may include the air that is contained therein (e.g., the air in the crevices of the ear). Also, the weight of the subvolume may not be smaller than 1.0 g, but preferably as close to it as possible. For the SAR data given in Table III, this corresponds to case 2 with a peak 1-g SAR of 1.11 W/kg for the $\lambda/4$ antenna and 0.69 W/kg for the $3\lambda/8$ monopole antenna above the handset.

[2] The Dosimetry Working Group of Wireless Technology Research consists of the following individuals: A. W. Guy (Chairman), C. K. Chou, C. Gabriel, O. P. Gandhi, N. Kuster, R. Petersen, P. Polson, V. Santomaa, Q. Balzano, and A. Taflove.

V. TEST RUNS—COMPARISON WITH CALCULATIONS OF DIMBYLOW AND MANN [6]

Even though all of our calculations have been done for plastic-coated handsets and antennas, we have made a limited number of runs using the same configurations as previously used by Dimbylow and Mann [6]. The objective of these runs was to verify that the SAR distributions obtained at 900 MHz and 1800 MHz were fairly similar to those obtained by another research group which had used a very different model of the head and neck. For these test runs we used the tissue properties given in Table II, which were taken from [6] as far as possible, and likewise assumed the handset dimensions of $2.4 \times 6 \times 15$ cm. Unlike the cubical cell sizes of 2 mm used by Dimbylow and Mann [6], we have taken a voxel size of $1.974 \times 1.974 \times 3$ mm for our calculations. The summaries of the results obtained for the four test cases without the hand are given in Tables IV and V for 900 and 1800 MHz, respectively. Also given as footnotes are the data calculated by Dimbylow and Mann [6] for comparison. Since the exact weights of the $1 \times 1 \times 1$ cm subvolume were not prescribed in [6], we have considered the various subvolumes 1, 2, and 3 that were previously considered for the data given in Table III. Also, even though the exact placements of the assumed handset vis à vis the ear were not exactly prescribed in [6], it is interesting to note that the peak 1-g SAR's calculated for our model are fairly similar to Dimbylow's [6] both at 900 and 1800 MHz. For our calculations we have assumed the feed points to be in the cross-sectional plane 6 mm below the top of the ear.

TABLE XI
COMPARISON OF SAR DISTRIBUTIONS FOR MODELS OF AN ADULT MALE AND 10-YEAR AND 5-YEAR-OLD CHILDREN. FREQUENCY = 835 MHz. TIME-AVERAGED RADIATED POWER = 600 mW. A $3\lambda/8$ ANTENNA ABOVE A HANDSET IS TAKEN FOR THE CALCULATIONS

	Adult male	10-year-old child	5-year-old child
Peak 1-voxel SAR (W/kg)	5.97	7.65	12.75
Peak 1-g SAR* (W/kg)	1.60 (1.00 g)	1.49 (1.00 g)	1.88 (1.00 g)
Peak 1-g SAR for brain* (W/kg)	0.65 (1.05 g)	0.78 (1.00 g)	0.85 (1.00 g)
Power absorbed by head and neck	33.7%	28.8%	25.5%
Power absorbed by "hand"	5.6%	4.3%	2.8%
Peak 1-voxel SAR for brain (W/kg)	0.93	1.40	2.01
CSF average (mW/kg)	79.8	170.6	244.5
Brain average (mW/kg)	63.9	125.5	183.0
Humour average (mW/kg)	21.4	46.5	69.8
Lens average (mW/kg)	7.9	20.6	31.2
Sclera average (mW/kg)	12.0	29.3	43.3

* $5 \times 5 \times 4$ cells; $0.987 \times 0.987 \times 1.200$ cm; 1.170 cm^3 for the adult male
$7 \times 7 \times 4$ cells; $1.057 \times 1.057 \times 0.939$ cm; 1.049 cm^3 for the 10-year-old child
$8 \times 8 \times 5$ cells; $1.039 \times 1.039 \times 0.950$ cm; 1.026 cm^3 for the 5-year-old child

TABLE XII
COMPARISON OF SAR DISTRIBUTIONS FOR THE FULL MODEL AND TRUNCATED HALF AND ONE-THIRD MODELS OF THE HEAD AND NECK OF AN ADULT MALE. A $\lambda/4$ ANTENNA ABOVE A HANDSET IS TAKEN FOR THE CALCULATIONS AT 1900 MHz. RADIATED POWER = 125 mW

	Full model	Truncated half model	Truncated One-Third Model
Peak 1-voxel SAR (W/kg)	3.90	3.96	3.96
Peak 1-g SAR (W/kg)	1.11 (1.03 g)	1.11 (1.03 g)	1.11 (1.03 g)
Peak 1-g SAR for brain (W/kg)	0.20 (1.00 g)	0.19 (1.05 g)	0.19 (1.00 g)
Power absorbed by head and neck	35.6%	34.5%	32.4%
Power absorbed by "hand"	13.8%	14.3%	13.3%
Peak 1-voxel SAR for brain (W/kg)	0.29	0.29	0.29
CSF average (mW/kg)	8.0	7.1'	4.8'
Brain average (mW/kg)	7.6	7.3'	6.1'
Humour average (mW/kg)	3.2	3.2'	2.4'
Lens average (mW/kg)	1.5	1.5'	1.5'
Sclera average (mW/kg)	1.8	1.7'	1.4'

' Average over the total mass of tissue in the full model.

VI. EFFECT OF TISSUE PROPERTIES ON SAR DISTRIBUTIONS

As given in Table I with both the old and the new values of dielectric properties, considerably higher values of ϵ_r and σ have recently been reported for fat, bone, and cartilage by Gabriel [12]. The ear is composed mainly of cartilage that is covered by the skin. In Table VI we compare the salient features of the SAR distributions at 835 MHz that are obtained using both the new and old dielectric properties for these tissues. For this and all further tables we give the SAR's that are calculated using the procedure suggested by the Dosimetry Working Group of WTR [see Section IV].

Since some measurement systems for SAR evaluations use an homogeneous phantom model, also shown for comparison in Table VI are the SAR's obtained for the homogeneous model with properties identical to that of the brain at 835 MHz [see Table II]. It is interesting to note that the homogeneous model overestimates the peak 1-g SAR by 42 percent as compared to that obtained using the anatomically based model.

For each of the calculations given in Table VI, we have considered a quarter-wave monopole antenna above a handset of dimensions $2.96 \times 5.73 \times 15.5$ cm ($14\delta_x \times 28\delta_y \times 51\delta_z$ for the metal covered with 1-mm thick plastic on all sides) and the model of the adult male. The telephone is held against the

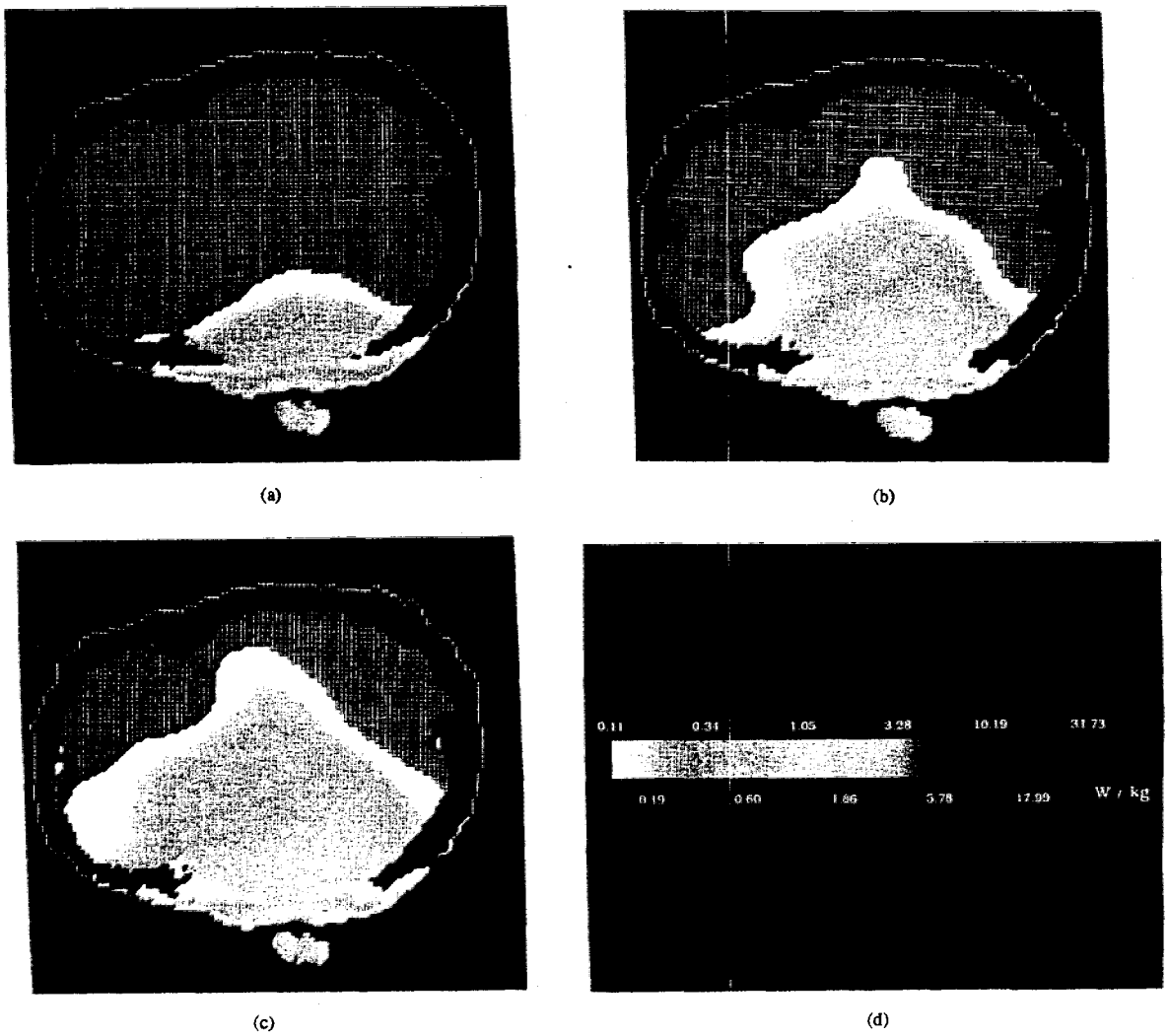


Fig. 2. The SAR distributions for layer no. 34 for models of an adult male and 10-year and 5-year-old children (a)–(c). (d) Scale. This layer contains the feed point and is 2 cells lower than the cross-sectional plane passing through the top of the ear for each of the models. Frequency = 835 MHz. Radiated power = 600 mW.

left side of the head. The driving point of the monopole is located at the top of the handset, in the center of the 5.73-cm side furthest from the ear on the edge of the 2.96-cm side. The thin monopole antenna is embedded in a covering sheath of dielectric material $\epsilon_r = 4.0$ which, in the FDTD formulation, is modeled by a 2×2 cell square stack of dielectric cells of cross-sectional dimensions 3.95×3.95 mm. New dielectric properties of the various tissues given in Table I are used for the results given in column 1 for these and all further cases considered in this paper.

Even though very similar fractional powers absorbed by the whole head are obtained for all three models, the peak 1-voxel SAR's are considerably higher for the models using the newer higher conductivities for the cartilage. Furthermore, the homogeneous model grossly overestimates the SAR and is also incapable of providing tissue-relevant SAR distributions.

VII. Effect of Antenna Length and Tilt on the SAR Distributions

We have examined the effect of antenna length and its tilt on the power absorbed and the SAR distribution for the various regions of the head and neck. For these studies, two different lengths of the antenna $\lambda/4$ and $3\lambda/8$ and two different orientations of the handset, 0° and 30° relative to vertical, were used for irradiation frequencies of 835 and 1900 MHz. The salient features of the results are given in Tables VII and VIII, respectively. For each of the cases, the handset dimensions are the same as in Section VI ($2.96 \times 5.37 \times 15.5$ cm) and the antennas placed on the back side of the handset similar to Section VI are assumed to be covered by a dielectric sleeve as described in the previous section. It is interesting to note that the powers absorbed by the head and neck and peak 1-g SAR's

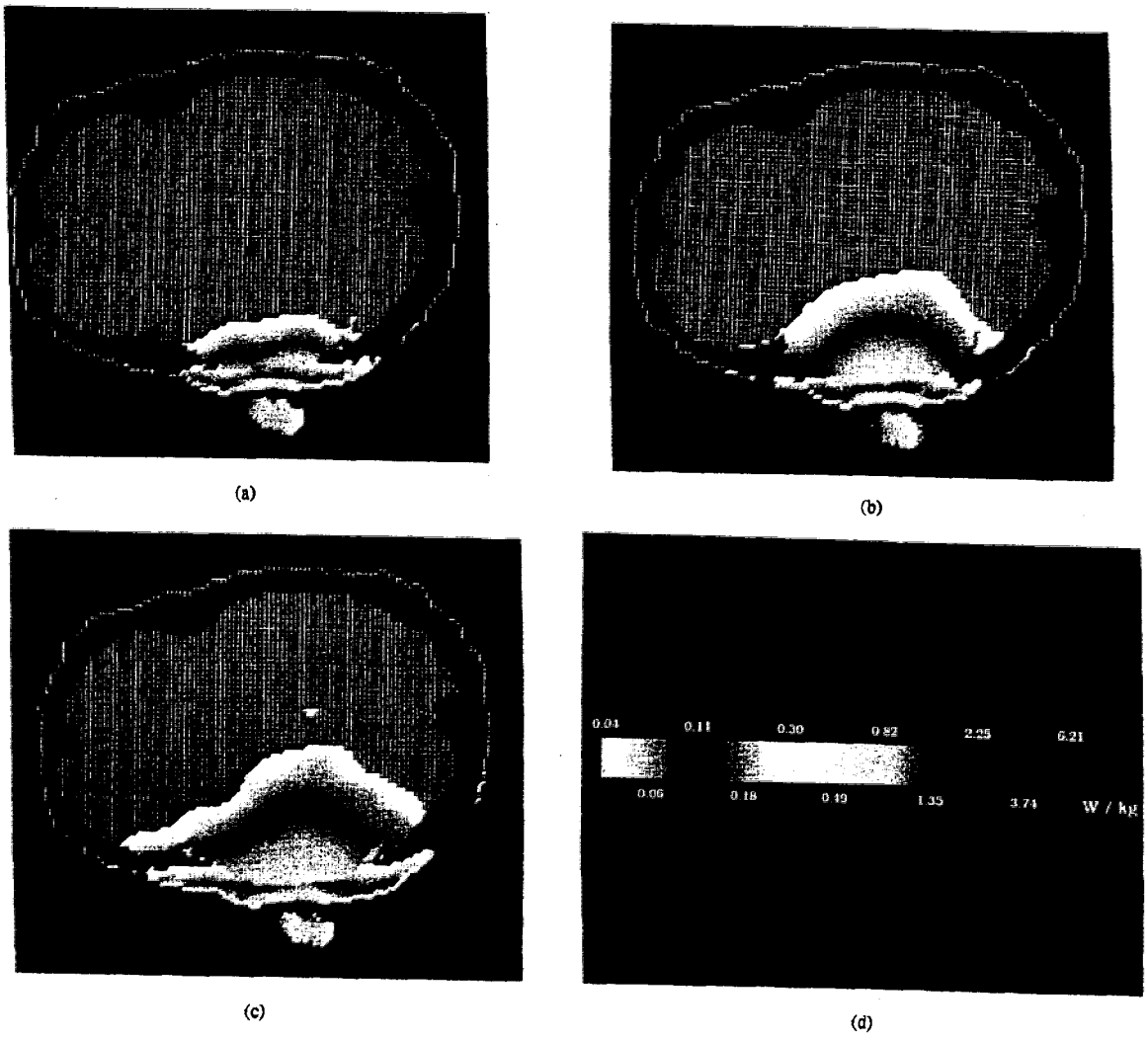


Fig. 3. The SAR distributions for layer no. 34 for models of an adult male and 10-year and 5-year-old children (a)–(c). (d) Scale. This layer is 2 cells lower than the cross-sectional plane passing through the top of the ear for each of the models. Frequency = 1900 MHz. Radiated power = 125 mW.

are lower for $3\lambda/8$ antennas vis à vis $\lambda/4$ antennas both at 835 MHz and 1900 MHz (Tables VII and VIII). This may be due to the fact that $3\lambda/8$ antennas are 50 percent longer than $\lambda/4$ antennas at each of the frequencies. The peak current region for a $3\lambda/8$ antenna is $\lambda/8$ above the feed point, whereas for a $\lambda/4$ antenna it is at the base of the antenna, and, hence, very close to the ear. For the longer $3\lambda/8$ antennas both at 835 and 1900 MHz, the peak current regions are, therefore, somewhat removed from the ear and the head, which results in lower absorbed powers and SAR's than the $\lambda/4$ antenna. Similar arguments can also be given for the calculated lower SAR's for 30° tilted $\lambda/4$ antenna vis à vis the vertically held antenna at 835 MHz (Table VII), since the considerably longer antennas are physically further away from the head, which results in lower SAR's for the tilted antenna, while a similar effect does not occur at the higher frequency of 1900 MHz (Table VIII) because of the smaller length of the antenna.

VIII. Effect of Head Size on SAR Distribution: Comparison for Adult and 10- and 5-Year-Old Children

As previously described in Section III, we have developed smaller models of the head, neck, and "hand" by reducing the voxel size 1.974 × 1.974 × 3.0 mm of the MRI-based model to new voxel sizes of 1.51 × 1.51 × 2.3469 mm and 1.2989 × 1.2989 × 1.9048 mm in order to obtain dimensions characteristic of 10- and 5-year-old children, respectively. In Tables IX and X, we give the salient features of the SAR distributions obtained for quarter-wave monopole antennas mounted as discussed earlier at irradiation frequencies of 835 and 1900 MHz, respectively. It is interesting to note that even though the peak 1-g SAR's are fairly similar for the three models at 1900 MHz, the 1-g SAR's are considerably higher for the smaller head sizes at 835 MHz (Table IX).

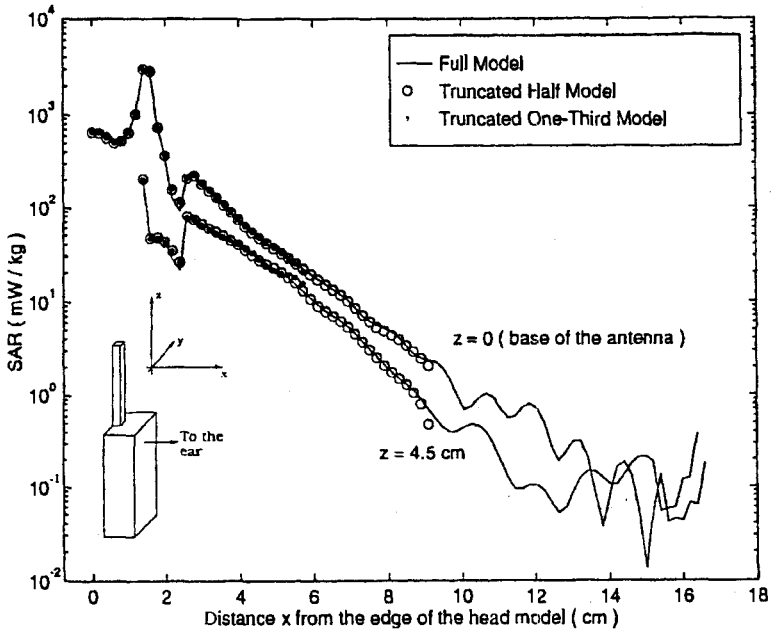


Fig. 4. Comparison of the SAR distributions for the full model and the truncated half and one-third models of the human head along the axis for $z = 0$ and $z = 4.5$ cm for a $\lambda/4$ monopole above the handset. Frequency = 1900 MHz. Radiated power = 125 mW.

Also, the peak 1-voxel SAR's are higher and a larger in-depth penetration of absorbed energy or higher SAR's are obtained for the smaller models both at 835 and 1900 MHz. The fact that there is a larger in-depth penetration of SAR's for the models of 10- and 5-year-old children as compared to those for the model of the adult is illustrated in Figs. 2 and 3 for 835 and 1900 MHz, respectively. Because of a larger depth of penetration of EM field at 835 MHz into the heads of the small subjects, increased SAR's are obtained for smaller models at this frequency. A similar trend of increasing 1-g SAR's for the smaller models at 835 MHz has also been observed for a longer $3\lambda/8$ antenna for which the SAR distributions are given in Table XI. The higher 1-voxel SAR's for the smaller models in Tables IX–XI are likely due to the thinner ears, which results in the antennas being somewhat closer to the region of highest SAR's that are observed generally at the points of contact of the ear pressed against the scalp of the head.

IX. Use of Truncated Head Models for Efficient Computations

With ever-increasing frequencies being considered for wireless communications, it is obvious that even finer-resolution anatomically based models than those being used at the present time will be needed in the future. Since even present models require a lot of computer memory (150–170 Mbytes), the required higher-resolution models will be extremely difficult to use unless more efficient FDTD formulations are developed. We have recently developed a technique to reduce the size of the problem to half or less, recognizing that the distal side of the head is relatively shielded from the EM fields of personal mobile devices. Because of the minuscule coupling, we may place another identical source (a mobile telephone) symmetrically on the opposite side leaving the problem unaltered, provided this dummy source is assumed to be devoid of RF power. This latter assumption can be implemented by exciting the dummy source identically and in phase or out of phase from the actual source for two consecutive simulations and superimposing the EM fields obtained for these even- and odd-mode calculations, respectively. The even-mode simulation can be done by putting a perfect magnetic conductor at the plane of symmetry of the problem and an odd-mode simulation can be done by putting a perfect electric conductor at the same plane of symmetry. Using this approach, only half-problem simulation may be done at a time with a considerable saving of computer memory. To check the validity of this approach, several test cases, including spheres, layered, spheres, etc., were considered for an assumed radiation frequency of 1900 MHz. Excellent agreements of the SAR distributions were obtained for the truncated half and one-third models with those for the full models.

Fig. 4 shows the SAR distributions obtained for an MRI-based model of the human head for which the $\lambda/4$ monopole above a box cellular telephone described earlier in Sections II and VI is placed against the left ear, which is assumed to be squished against the head. The SAR distributions are shown for the model of the head and for truncated half and one-third models for two axes in the x-direction corresponding to $z = 0$, i.e., the plane containing the base of the antenna and $z = 4.5$ cm above this plane. The peak SAR of 3.000 mW/kg for the $z = 0$ line in the plane containing the driving point is due to focusing of induced currents passing at the points of contact between the squished ear and the head. Salient features of the data obtained for this case are given in Table XII. It is

interesting to note that nearly identical SAR's are obtained for the electromagnetically coupled region in proximity to the telephones for each of the models. Because of the truncation of the models, somewhat lower SAR's are obtained for the more distal tissues for which the SAR's are fairly small anyway. The difference in the peak and 1-g average SAR's calculated using the full and the truncated models is less than 1.5 percent.

X. Concluding Remarks

The previously tested finite-difference time-domain method has been used with a new MRI-based millimeter-resolution model of the human to study electromagnetic energy absorption in the head and neck due to mobile telephones at 835 and 1900 MHz. We have used dimensions of the handsets that are characteristic of the newer telephones to obtain SAR distributions due to two different lengths of the monopole antennas of lengths $\lambda/4$ and $3\lambda/8$. As expected, the longer antennas give SAR's that are considerably smaller than those for $\lambda/4$ antennas. A limited number of test runs using the antennas and handset dimensions previously used by Dimbylow and Mann [6] give 1-g SAR's that are very similar (within 10 percent) to those obtained by these authors. This is most interesting since considerably different anatomically based models of the human head and neck have been used. We have also examined the effect of using the widely different tissue properties that have been reported for fat, bone, and cartilage. As expected, the new higher conductivities and dielectric constants recently reported for these tissues give peak 1-voxel and 1-g SAR's that are higher than those obtained with the previously reported lower electrical properties. Use of a homogeneous brain-equivalent model is shown to grossly overestimate peak SAR's for 1-voxel as well as for 1-g of tissue. To represent typical usage, we have studied the effect of tilting the telephone relative to the head at an angle of 30°. Because of the longer antenna at 835 MHz, this results in a reduction of SAR's relative to the untilted configuration, since the antenna is now further away from the head for much of its length. This effect is inconsequential at 1900 MHz, where the antenna length is fairly small.

A highlight of this paper has been to calculate SAR distributions using reduced-scale models of the head and neck and "hand" to correspond to the dimensions that are characteristic of 10 and 5-year-old children. Because of the deeper penetration of EM energy in smaller models, considerably higher internal tissue SAR's are obtained both at 835 and 1900 MHz. Also, higher 1-g SAR's are obtained at 835 MHz for both $\lambda/4$ and $3\lambda/8$ antennas. Lastly, we have shown it possible to use truncated one-half and one-third models of the head and neck and obtain SAR distributions that are nearly identical to those for full models. Use of truncated models allows considerable savings in computer memory and computation time for SAR distributions.

Acknowledgment

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EXHIBIT K

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

SOME PRESENT PROBLEMS AND A PROPOSED EXPERIMENTAL PHANTOM FOR SAR COMPLIANCE TESTING OF CELLULAR TELEPHONES AT 835 AND 1900 MHz

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ABSTRACT

We compare the peak 1- and 10-g SARs for two different anatomically-based models with the corresponding 6 mm thick plastic ear models recommended for SAR compliance testing both in U.S. and Europe. The SARs obtained with the insulating plastic ear models are two or more times smaller than realistic anatomic models. To alleviate this problem, we propose a 2 mm thin shell phantom with lossy ear that gives SARs within ±15% of those of anatomic models. Also, the SARs for smaller (-9.1%) models are higher than for larger (+11.1%) scaled versions of the two models.

I. INTRODUCTION

We have previously reported that the peak 1-g SARs for scaled models of children are higher than the corresponding value for full-scale models of the human head [1]. In the same paper, we have also shown that there is a deeper penetration of absorbed energy in smaller models of the head for electromagnetic fields of mobile telephones both at 835 and 1900 MHz. The explanation for both of these observations are the scaled thinner ear and skull and smaller overall dimensions of the brain for children as compared to that for the adult. To examine this issue further, we have taken two different and distinct anatomically-based heterogeneous models of the human head and neck and have scaled them up or down for the voxel size by 11.11% and -9.1% i.e. by approximately ± 10% along each of the three axes, respectively. These variations are certainly within the range of the head sizes encountered for men and women [2]. Three different scaled models for each of the adult heads are thus considered for SAR distributions. Used for the SAR calculations is the finite-difference time-domain (FDTD) method which is extremely popular and has been highly tested for dosimetry of cellular telephones (see e.g. refs. 1, 3). Using the six models thus created, the following issues are examined.

1. Effect of the head size on the peak 1-g SAR both at 835 and 1900 MHz. For these calculations, a number of handset sizes and monopole or helix antennas are considered.
2. Comparison of the peak 1- and 10-g SARs with those obtained using the corresponding 6 mm thick plastic ear models. This study is done since plastic ear models are recommended for SAR compliance testing both in Europe and the U.S. [4, 5].
3. To alleviate the problem of lower SARs with the 6 mm thick plastic spacer (in the shape of pinna) phantoms, we propose a smoothened ear model of the human head.

II. TWO MODELS OF THE HEAD

For the present studies, we have used two different anatomically-based models of the human head and neck. Model 1 – the so-called Utah model was obtained from the magnetic resonance imaging (MRI) scans of a male volunteer. This model described in detail in [1, 3] has a pixel resolution of 2 x 2 mm for the cross sections and 3 mm spacing between the various slices or cross sections. As described in these papers, this model has been segmented into 31 tissues of which 15 tissues are involved for the model of the head and neck considered for the present calculations. To create a 2 x 2 x 2 mm resolution model, we subdivided each of the 2 x 2 x 3 mm resolution voxels of the Utah model into 12 smaller cells of 1 mm resolution along each of the three axes and then combined 2 x 2 x 2 smaller cells into new voxels of dimension 2 mm along each of the axis. The tissue classifications for the new voxels of dimension 2 x 2 x 2 mm was decided by the majority tissue in the subvolume of the voxel i.e. the tissue for five out of eight cells forming the 2 x 2 x 2 mm resolution model. A second tissue-classified model used for the present calculations is based on the scans of the "Visible Man" model, which was kindly provided by John Ziriax and Patrick Mason of Brooks AFB, Texas. This model with 1 mm resolution is classified into 24 tissues. As for the Utah model, here too, we combined 2 x 2 x 2 cells to form the 2 x 2 x 2 mm resolution model of the head and neck.

A visualization of the two heterogeneous models used for the calculations is given in Fig. 1.

(a) The Utah model (b) The "Visible Man" model

Fig. 1. A visualization of the two anatomically-based 30°-tilted models of the head used for SAR calculations.

III. VARIATION OF SAR WITH HEAD SIZE

A thrust of this study is to evaluate coupling of electromagnetic fields from cellular telephones to the various sizes of the human head. Toward this end, we have created two additional sizes of the head for each of the two models, described in Section II by considering the cell size from 2 mm to 2.222 mm for the larger models and down to 1.818 mm, respectively. This results in scaling the dimensions of the two head models up by 11.11% and down by 9.1% i.e. by approximately ± 10% along each of the three axes, respectively. The peak 1-g SAR values determined for a variety of antennas (monopoles and helices), various handset dimensions and larger, average, or smaller scaled versions of the two anatomic models are given in Table 1. Because of the possible revision of the IEEE Safety Standard to focus on the peak 1-g SAR for body tissues instead of all tissue, the data given in Table 1 give only the peak 1-g SARs for body tissues and the brain. The salient features of the results are as follows:

1. The peak 1-g SARs for both the body tissue and the brain increases monotonically with the reducing head size (and pinna thickness) for both of the head models and for all handset dimensions and the antennas i.e. monopoles as well as helices.
2. The peak 1-g SARs for body tissues for smaller models may be up to 50 to 60 percent higher at 1900 MHz and 10-20% higher at 835 MHz as compared to that for the larger head models. This is understandable since the shielding effect of the pinna is larger at the higher frequency of 1900 MHz.
3. Similar to the results previously reported for head models of adult and the children [1], there is a deeper penetration of absorbed energy for the smaller head models as compared to that for the larger head models [6].

IV. COMPARISON WITH SAR FOR PLASTIC EAR MODELS

A 6 mm plastic spacer homogeneous model with brain-simulant properties is presently used by industry and has also been proposed to obtain a "conservative" determination of the peak 1-g SAR of body tissues for SAR compliance testing of cellular telephones [5]. An identical 6 mm "plastic ear" homogenous model has also been proposed to determine peak 10-g all-tissue SAR for compliance testing against the ICNIRP Guidelines [4]. For our calculations, smooth ear models corresponding to the two anatomic models of Fig. 1a, b is used. For example, the model thus developed for the Utah model of the human head shown in Fig. 1a is given in Fig. 2. A dielectric constant $\varepsilon_r = 2.56$ is assumed for the plastic in the shape of the smoothened ear and the 2 mm thick container, while homogeneous dielectric properties representative of the head tissues ($\varepsilon_r = 41.5$, $\sigma = 0.9$ S/m at 835 MHz and $\varepsilon_r = 40.0$, $\sigma = 1.4$ S/m at 1900 MHz) are assumed for the rest of the model [5].

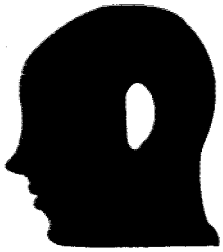

Fig. 2. A proposed 6 mm thick smooth lossy ear phantom to obtain peak 1- and 10-g SARs within ±10-15% of those obtained for anatomically-realistic models. This model with the lossy ear replaced by a 6 mm thick plastic ear ($\varepsilon_r = 2.56$) gives SARs that are a factor of 2 or more lower as given in Tables 2, 3.

In Tables 2 and 3, we compare the peak 1-g all tissue and body tissue SARs and peak 10-g any tissue SARs calculated for the average size versions of both Utah and "Visible Man" models, with the corresponding 6 mm thick smooth plastic ear average models of homogeneous brain-simulant dielectric properties suggested in [4, 5]. The calculated SARs are normalized to the maximum possible radiated power of 125 mW for the PCS telephones at 1900 MHz and 600 mW for the analog AMPS mode of 835 MHz telephones. As seen from Tables 2 and 3, the plastic ear model gives peak 1- and 10-g SARs that are lower by factors of two or more than the all-tissue SARs required for compliance testing against the present ANSI/IEEE and ICNIRP safety guidelines, respectively. This is due to a physical separation of 6 mm and absence in the plastic ear model of the high SAR region e.g. the pinna. For an anatomic model, on the other hand, the lossy ear acts as a coupler conducting EM fields into the head resulting in higher SARs.

V. A PROPOSED EXPERIMENTAL PHANTOM FOR SAR COMPLIANCE TESTING

To alleviate the problem of underestimation of SARs with the 6 mm thick plastic spacer (in the shape of pinna) phantoms, we propose a smoothened ear model of the human head such as that shown in Fig. 2. Since the SAR in the pinna region is substantial, the proposed phantom will use homogeneous lossy dielectric properties (ε_r = 41.5, σ = 0.9 S/m at 835 MHz and ε_r = 40.0, σ = 1.4 S/m at 1900 MHz) everywhere including the volume occupied by the smoothened pinna. For a 2 mm plastic shell of ε_r = 2.56 or ε_r = 4.0 assumed to contain the fluid for the desired dielectric properties, the calculated peak 10-g all-tissue SARs are within ±15% of the SARs obtained with realistic anatomic model of the head. A similar agreement for peak 1-g SARs within ±10% is also obtained for this thin shell lossy pinna phantom with the SARs for anatomic models at 1900 MHz [6], but the SARs are still considerably smaller at 835 MHz. At this lower frequency, it may be possible to use a higher conductivity fluid to get SARs to agree better with those of anatomically-realistic models.

Table 1. Comparison of the peak 1-g SARs for the various **sizes** of the two models of the head.

Handset Dimensions mm	Antenna	Model	Tissue	Peak 1-g SAR (W/kg)		
				Larger Head Model	**Average** Head Model	**Smaller** Head Model
				1900 MHz, 125 mW Radiated Power		
22x42x122	Helix 20 mm length	Utah	Body tissues	0.96	1.32	1.45
			Brain	0.22	0.31	0.45
22 x42x122	Helix 20 mm length	Visible man	Body tissues	1.16	1.22	1.61
			Brain	0.09	0.13	0.18
22x42x82	Helix 20 mm length	Utah	Body tissues	0.89	1.23	1.39
			Brain	0.22	0.33	0.48
22x42x122	Monopole 40 mm length	Visible man	Body tissues	0.95	1.00	1.21
			Brain	0.13	0.14	0.25
22x42x122	Monopole 40 mm length	Utah	Body tissues	0.76	1.02	1.13
			Brain	0.25	0.33	0.45
				835 MHz 600 mW Radiated Power		
22x42x122	Helix 20 mm length	Utah	Body tissues	3.84	3.91	4.20
			Brain	0.83	1.03	1.20
22 x42x122	Helix 20 mm length	Visible man	Body tissues	3.88	4.29	4.36
			Brain	0.37	0.49	0.56
22x42x122	Monopole 80 mm length	Utah	Body tissues	2.92	3.20	3.47
			Brain	1.04	1.24	1.38
22x42x122	Monopole 80 mm length	Visible man	Body tissues	3.01	3.29	3.43
			Brain	0.64	0.80	0.97
22x42x102	Monopole 80 mm length	Utah	Body tissues	2.65	2.81	2.86
			Brain	1.08	1.28	1.43

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Table 2. Comparison of the peak 1-g SARs for all tissues (ANSI/IEEE Guidelines) and body tissues for two anatomically-based models with the corresponding 6 mm thick smooth plastic ear models.

Handset Dimensions mm	Antenna	Model	Peak 1-g SAR (W/kg)		
			1-g all tissues, anatomically-based model	1-g body tissues, anatomically-based model	6 mm thick plastic ear, homogeneous model
			1900 MHz, 125 mW Radiated Power		
22 x42 x122	Monopole, 40 mm length	Utah	2.40	1.02	1.00
22 x42 x82	Monopole, 40 mm length	Utah	2.24	1.00	0.98
22 x42 x82	Monopole, 40 mm length	Visible man	2.55	0.95	0.80
22 x42 x122	Helix, 20 mm length	Utah	3.05	1.32	1.26
22 x42 x82	Helix, 20 mm length	Utah	2.96	1.23	1.30
22 x42 x82	Helix, 20 mm length	Visible man	3.37	1.17	0.97
			835 MHz, 600 mW Radiated Power		
22 x42 x122	Monopole, 80 mm length	Utah	9.09	3.20	2.73
22 x42 x122	Monopole, 80 mm length	Visible man	3.43	3.29	2.80
22 x42 x122	Helix, 20 mm length	Utah	13.20	3.91	3.66
22 x42 x122	Helix, 20 mm length	Visible man	4.46	4.29	3.65

Table 3. Comparison of the peak 10-g SARs for all tissues (ICNIRP Guidelines) for two anatomically-based models with the corresponding 6 mm thick smooth plastic ear models.

Handset Dimensions mm	Antenna	Model	Peak 10-g SAR (W/kg)	
			Anatomically-based model	6 mm thick plastic ear, homogeneous model
			1900 MHz, 125 mW Radiated Power	
22 x42 x122	Monopole, 40 mm length	Utah	1.14	0.62
22 x42 x82	Monopole, 40 mm length	Utah	1.09	0.61
22 x42 x82	Monopole, 40 mm length	Visible man	1.03	0.56
22 x42 x122	Helix, 20 mm length	Utah	1.44	0.77
22 x42 x82	Helix, 20 mm length	Utah	1.37	0.76
22 x42 x82	Helix, 20 mm length	Visible man	1.28	0.67
			835 MHz, 600 mW Radiated Power	
22 x42 x122	Monopole, 80 mm length	Utah	4.03	1.96
22 x42 x102	Monopole, 80 mm length	Utah	3.58	2.28
22 x42 x122	Helix, 20 mm length	Utah	5.53	2.64
22 x42 x102	Helix, 20 mm length	Utah	5.02	3.27

EXHIBIT L

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

ORIGINAL ARTICLE

Use of cellular telephones and brain tumour risk in urban and rural areas

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Aims: To investigate the association between the use of cellular or cordless telephones and the risk for brain tumours in different geographical areas, urban and rural.
Methods: Patients aged 20–80 years, living in the middle part of Sweden, and diagnosed between 1 January 1997 and 30 June 2000 were included. One control matched for sex and age in five year age groups was selected for each case. Use of different phone types was assessed by a questionnaire.
Results: The number of participating cases was 1429; there were 1470 controls. An effect of rural living was most pronounced for digital cellular telephones. Living in rural areas yielded an odds ratio (OR) of 1.4 (95% CI 0.98 to 2.0), increasing to 3.2 (95% CI 1.2 to 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 to 1.2) and 0.9 (95% CI 0.6 to 1.4), respectively. This effect was most obvious for malignant brain tumours.
Conclusion: In future studies, place of residence should be considered in assessment of exposure to microwaves from cellular telephones, although the results in this study must be interpreted with caution due to low numbers in some of the calculations.

A difference in the power output level from mobile phones between urban and rural areas has recently been shown.[1] 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. APC is used for the Global System for the Mobile Communication (GSM) network. When the Nordic Mobile Telephone System (NMT) started in Sweden in 1981, the highest power was used all the time by the mobile phones. With increasing numbers of users of the NMT, phones in this system were regulated by APC, but only if they were very close to the base station and then only in one step.

In previous epidemiological studies we found an association between use of cellular telephones and brain tumours.[2 3] However, for salivary gland tumours no association was found, although the parotid gland is located in an area with high exposure to microwaves from cellular telephones compared with other anatomical sites.[4] These and other results on this topic have been recently reviewed elsewhere[5] and will not be further discussed here.

In epidemiological studies assessment of microwave exposure is usually based on type of phone (NMT, GSM, and cordless), and years and cumulative number of hours of use. There is a variation in specific absorption rate (SAR) between the different types of cellular telephones. However, this information is not easily available since subjects can seldom remember the brand names of the cellular phones used over time. Moreover, information on SAR is usually not available from the manufacturers.

During cellular phone calls, radio frequency (RF) signals in the range of 400 to 2000 megaHertz (MHz) are used. In Sweden the analogue NMT system was introduced in 1981 operating at 450 MHz, often in a car with a fixed external antenna, but from 1984 the first portable analogue phones were available. The NMT 900 MHz system operated in Sweden between 1986 and 2000. The digital GSM system started in 1991 and is the most common phone since the end of the 1990s in Sweden. Moreover desktop cordless telephones have been used in Sweden since 1988. The analogue system in the 800–900 MHz RF range was initially used, but now digital cordless telephones that operate at 1900 MHz are available.

One interesting aspect with regard to exposure is the different output power from cellular telephones in urban and rural areas due to APC. In our previous study the results were based on 1429 cases (88%) and 1470 controls (91%) that answered the questionnaire.[2] In this further analysis of the material we grouped the place of residence for the cases and controls into urban and rural areas.

METHODS

The details of the study design have been published elsewhere[2] and only a brief summary is given here. The geographical study area was the middle part of Sweden, and encompassed patients aged 20–80 years who were diagnosed between 1 January 1997 and 30 June 2000. Histopathology and information on tumour localisation were obtained from the cancer registry and neuroradiology reports. One control for each case was drawn from the population register, matched for sex and age (five year age groups) and living in the same geographical area as the cases. The ethical committees approved the investigation.

Use of cellular and cordless phones was assessed by a questionnaire which also included lifetime work history. The answers were supplemented over the phone using a written protocol. Mean number of daily calls and minutes were asked for to calculate the cumulative use in hours for all years. Data were also collected on use in a car with a fixed external antenna or outside a car using a hands-free device with an earpiece, both taken as no exposure to microwaves. The ear

Abbreviations: APC, adaptive power control; CI, confidence interval; GSM, Global System for Mobile Communication; H, homogeneity region; MHz, megaHertz; NMT, Nordic Mobile Telephone System; OR, odds ratio; RF, radio frequency; SAR, specific absorption rate; SEI, socioeconomic index

Main messages

- Adaptive power control regulates the output power level from cellular telephones, mainly the digital system, with the highest level in areas with a long distance between base stations.
- There was a higher risk for brain tumours in users of digital cellular telephones in rural areas than in urban areas.

Policy implications

- In future studies, place of residence should be considered in assessment of exposure to microwaves from cellular telephones.

most frequently used during cellular phone calls was noted, or whether both ears were used equally.

The Swedish population register contains information on present municipality for all residents. The municipalities are classified by Statistics Sweden in 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.[6] According to this official homogeneity region classification, the two highest density categories (H1, H2) include only the largest cities of Sweden, Stockholm, Göteborg, and Malmö/Lund. H3 consists of municipalities with more than 90 000 inhabitants within a 30 km radius from the centre of that municipality. H4 includes municipalities with more than 27 000, but less than 90 000 inhabitants from the centre of that municipality and also more than 300 000 inhabitants within a 100 km radius from the same centre. H5 is identical to H4 except that there are less than 300 000 inhabitants from the centre of the municipality. Finally, H6 consists of municipalities with less than 27 000 inhabitants within a radius of 30 km from the centre. Thus, we used these official statistics for grouping of the subjects in urban or rural areas.

Unconditional logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) (Stata/SE 8.2 for Windows; StataCorp, College Station, TX). The material was divided into two groups, exposed and unexposed. The exposed cases and controls were further divided according to phone type: analogue, digital, and cordless. The unexposed group consisted of cases and controls without exposure to cellular or cordless telephones. Adjustment was made for sex, age, and socioeconomic index (SEI) code. In the analysis of dose-response effect the material was divided in two groups with median number of hours among controls as cut-off. Latency (tumour induction

Table 1 Odds ratios and 95% confidence intervals for brain tumours for the whole study area (H1–H6), and urban (H1–H3) and rural areas (H4–H6)

	>1 year latency			>5 year latency			>10 year latency		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Analogue									
H1–H6	247/218	1.3	1.04 to 1.6	160/135	1.4	1.03 to 1.8	61/44	1.6	1.1 to 2.5
H1–H3	167/148	1.3	0.995 to 1.7	110/96	1.3	0.9 to 1.8	40/31	1.5	0.9 to 2.6
H4–H6	80/70	1.3	0.9 to 2.0	50/39	1.5	0.9 to 2.4	21/13	1.9	0.9 to 3.9
⩽85 h									
H1–H6	134/115	1.3	0.995 to 1.7	69/51	1.5	1.0 to 2.2	12/13	1.0	0.5 to 2.3
H1–H3	88/73	1.4	0.97 to 1.9	48/35	1.5	0.9 to 2.4	7/10	0.8	0.3 to 2.0
H4–H6	46/42	1.2	0.8 to 2.0	21/16	1.5	0.7 to 3.0	5/3	1.9	0.4 to 8.2
>85 h									
H1–H6	113/103	1.3	0.95 to 1.8	91/84	1.3	0.9 to 1.8	49/31	1.9	1.2 to 3.1
H1–H3	79/75	1.2	0.9 to 1.8	62/61	1.2	0.8 to 1.8	33/21	1.9	1.1 to 3.5
H4–H6	34/28	1.4	0.8 to 2.5	29/23	1.5	0.8 to 2.7	16/10	1.9	0.8 to 4.3
Digital									
H1–H6	423/433	1.0	0.9 to 1.3	66/66	1.1	0.8 to 1.6	–	–	–
H1–H3	303/340	0.9	0.8 to 1.2	49/60	0.9	0.6 to 1.4	–	–	–
H4–H6	120/93	1.4	0.98 to 2.0	17/6	3.2	1.2 to 8.4	–	–	–
⩽55 h									
H1–H6	230/217	1.1	0.9 to 1.4	17/26	0.7	0.4 to 1.4	–	–	–
H1–H3	162/167	1.0	0.8 to 1.3	11/23	0.5	0.3 to 1.1	–	–	–
H4–H6	68/50	1.5	0.97 to 2.3	6/3	2.2	0.5 to 9.0	–	–	–
>55 h									
H1–H6	193/216	0.9	0.7 to 1.2	49/40	1.4	0.9 to 2.1	–	–	–
H1–H3	141/173	0.9	0.6 to 1.1	38/37	1.1	0.7 to 1.9	–	–	–
H4–H6	52/43	1.3	0.8 to 2.1	11/3	4.2	1.1 to 16	–	–	–
Cordless									
H1–H6	402/396	1.1	0.9 to 1.3	164/129	1.4	1.1 to 1.8	10/10	1.1	0.4 to 2.6
H1–H3	283/297	1.0	0.8 to 1.3	117/97	1.3	0.97 to 1.8	7/7	1.1	0.4 to 3.1
H4–H6	119/99	1.3	0.9 to 1.8	47/32	1.7	1.01 to 2.8	3/3	1.1	0.2 to 5.5
⩽183 h									
H1–H6	183/208	0.9	0.7 to 1.2	50/47	1.2	0.8 to 1.8	0/5	–	–
H1–H3	126/153	0.9	0.7 to 1.2	34/35	1.1	0.7 to 1.8	0/4	–	–
H4–H6	57/55	1.1	0.7 to 1.7	16/12	1.5	0.7 to 3.3	0/1	–	–
>183 h									
H1–H6	219/188	1.2	0.99 to 1.6	114/82	1.5	1.1 to 2.1	10/5	2.1	0.7 to 6.3
H1–H3	157/144	1.1	0.9 to 1.5	83/62	1.4	1.002 to 2.1	7/3	2.5	0.7 to 9.9
H4–H6	62/44	1.6	1.004 to 2.5	31/20	1.8	0.97 to 3.4	3/2	1.6	0.3 to 9.9

Unconditional logistic regression analysis was used, adjusted for age, sex, and socioeconomic index. Dose-response calculation was made with median number of hours for controls as cut-off. Numbers of exposed cases (Ca) and controls (Co) are given.

Table 2 Odds ratios and 95% confidence interval for malignant brain tumours for the whole study area (H1–H6), and urban (H1–H3) and rural areas (H4–H6)

	>1 year latency			>5 year latency			>10 year latency		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Analogue									
H1–H6	110/96	1.2	0.8 to 1.7	71/61	1.2	0.8 to 1.8	34/17	2.1	1.1 to 4.0
H1–H3	81/68	1.4	0.9 to 2.1	55/45	1.4	0.9 to 2.2	25/12	2.4	1.1 to 5.1
H4–H6	29/28	0.9	0.5 to 1.7	16/16	0.9	0.4 to 2.0	9/5	1.7	0.5 to 5.6
Digital									
H1–H6	204/167	1.2	0.9 to 1.6	39/24	1.7	0.95 to 2.9	–	–	–
H1–H3	151/132	1.3	0.9 to 1.8	29/23	1.4	0.8 to 2.6	–	–	–
H4–H6	53/35	1.2	0.7 to 2.2	10/1	8.4	1.02 to 69	–	–	–
Cordless									
H1–H6	179/143	1.2	0.9 to 1.7	69/46	1.6	1.02 to 2.4	3/4	0.8	0.2 to 3.6
H1–H3	126/110	1.2	0.9 to 1.8	51/35	1.6	0.99 to 2.7	2/2	1.2	0.2 to 8.7
H4–H6	53/33	1.3	0.7 to 2.3	18/11	1.4	0.6 to 3.3	1/2	0.3	0.02 to 3.6

Unconditional logistic regression analysis was used, adjusted for age, sex, and socioeconomic index. Numbers of exposed cases (Ca) and controls (Co) are given. Note that controls with missing cases were not included.

period) was analysed using three time periods, >1 year, >5 years, and >10 years since first use of a cellular or cordless telephone until tumour diagnosis. H1–H3 were classified as urban (n = 984 cases, 1035 controls) and H4–H6 as rural areas (n = 445 cases, n = 435 controls).

RESULTS

No significant difference existed for cumulative use in hours for cordless or cellular telephones depending on urban or rural area for the cases. If anything, cases in rural areas tended to have shorter cumulative use than cases living in urban areas.

In table 1 results for brain tumours and use of cellular or cordless phones are given for the different geographical areas (urban and rural) as well as overall results. The unexposed group consisted of 713 cases and 757 controls. For analogue phones an increased OR was found in both urban and rural areas. ORs were somewhat higher in rural areas when latency period was considered. For ipsilateral use of analogue phones with >1 year latency period, ORs were 1.7 (95% CI 1.1 to 2.5) for living in urban areas, and 1.6 (95% CI 0.9 to 2.8) for living in rural areas (data not shown). Regarding digital phones, OR was increased in rural areas, whereas OR for subjects living in urban areas was close to unity. With >5 year latency period, OR was significantly increased in rural areas (OR = 3.2, 95% CI 1.2 to 8.4). With >5 years latency period and >55 hours of cumulative use, OR was calculated to be 1.1 (95% CI 0.7 to 1.9) in urban areas compared with 4.2 (95% CI 1.1 to 16) in rural areas. For ipsilateral use of digital phones with >1 year latency period, ORs were 1.2 (95% CI 0.9 to 1.7) for living in urban areas, and 1.7 (95% CI 0.99 to 2.8) for living in rural areas (data not shown). For cordless telephones ORs were higher in rural areas than in urban areas, except for >10 year latency period, based on low numbers.

Table 2 gives the results for malignant brain tumour cases with corresponding controls. No effect of place of residence was found for analogue or cordless phones. Regarding digital phones, the risk was highest in rural areas using latency period >5 years (OR = 8.4, 95% CI 1.02 to 69), but based on low numbers. In a separate analysis of cases with astrocytoma (n = 415), OR was somewhat higher for urban living than for rural for use of analogue cellular telephones or cordless phones. For use of digital phones with >1 year latency period, results were: OR = 1.4 (95% CI 0.96 to 2.2) for urban living, and OR = 1.2 (95% CI 0.6 to 2.4) for rural living. The results for >5 year latency period were: OR = 1.8 (95% CI 0.9 to 3.5) (26 cases, 19 controls) and OR = 6.6 (95% CI 0.8 to 56) (8 cases, 1 control) for urban and rural living, respectively (data not shown).

Table 3 Odds ratios and 95% confidence intervals for benign brain tumours for the whole study area (H1–H6), and urban (H1–H3) and rural areas (H4–H6)

	>1 year latency			>5 year latency			>10 year latency		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Analogue									
H1–H6	137/97	1.4	1.01 to 1.9	89/58	1.5	1.01 to 2.2	27/21	1.3	0.7 to 2.4
H1–H3	86/62	1.3	0.9 to 1.9	55/39	1.3	0.8 to 2.0	15/14	1.0	0.5 to 2.2
H4–H6	51/35	1.7	1.01 to 3.0	34/19	2.2	1.1 to 4.4	12/7	2.1	0.8 to 5.9
Digital									
H1–H6	219/213	0.9	0.7 to 1.2	27/34	0.8	0.4 to 1.3	–	–	–
H1–H3	152/167	0.8	0.6 to 1.01	20/29	0.6	0.3 to 1.1	–	–	–
H4–H6	67/46	1.6	0.98 to 2.7	7/5	1.8	0.5 to 6.0	–	–	–
Cordless									
H1–H6	223/218	0.9	0.7 to 1.2	95/68	1.3	0.9 to 1.9	7/3	2.1	0.5 to 8.1
H1–H3	157/160	0.8	0.6 to 1.1	66/51	1.1	0.7 to 1.7	5/3	1.4	0.3 to 6.1
H4–H6	66/58	1.2	0.8 to 1.9	29/17	2.0	0.99 to 4.1	2/0	–	–

Unconditional logistic regression analysis was used, adjusted for age, sex, and socioeconomic index. Numbers of exposed cases (Ca) and controls (Co) are given. Note that controls with missing cases were not included.

Table 4 Odds ratios (OR) and 95% confidence intervals for brain tumours for the whole study area (H1–H6), and urban (H1–H3) and rural areas (H4–H6) for use of one phone type only

	>1 year latency			>5 year latency			>10 year latency		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Analogue only									
H1–H6	81/72	1.3	0.9 to 1.8	41/27	1.7	1.1 to 2.9	14/6	2.7	1.04 to 7.3
H1–H3	50/37	1.6	0.99 to 2.4	24/13	2.1	1.1 to 4.3	10/3	4.0	1.1 to 15
H4–H6	31/35	1.0	0.6 to 1.8	17/14	1.4	0.7 to 3.0	4/3	1.5	0.3 to 6.8
Digital only									
H1–H6	188/195	1.0	0.8 to 1.3	27/26	1.2	0.7 to 2.0	–	–	–
H1–H3	128/149	0.9	0.7 to 1.2	15/24	0.7	0.4 to 1.3	–	–	–
H4–H6	60/46	1.4	0.9 to 2.2	12/2	6.9	1.5 to 32	–	–	–
Cordless only									
H1–H6	159/169	1.0	0.8 to 1.3	56/36	1.7	1.1 to 2.6	2/2	1.0	0.1 to 7.4
H1–H3	109/121	1.0	0.7 to 1.3	38/27	1.5	0.9 to 2.5	1/2	0.5	0.1 to 5.3
H4–H6	50/48	1.1	0.7 to 1.8	18/9	2.3	0.97 to 5.3	1/0	–	–

Unconditional logistic regression analysis was used, adjusted for age, sex, and socioeconomic index. Numbers of exposed cases (Ca) and controls (Co) are given.

Table 3 shows results for benign brain tumours only. For all phone types ORs were highest in rural areas, although some of the calculations were based on low numbers. As has been shown previously, the increased risk was found for acoustic neuroma but not for meningioma.[2]

Table 4 gives results for use of either analogue, digital, or cordless telephones. Thus, subjects who had used more than one phone type were not included. Analogue phones yielded significantly increased ORs for >5 year and >10 year latency period, respectively. There was no effect of urban versus rural residence. However, the results were based on rather low numbers, especially in the category with >10 year latency period. Regarding digital phones OR was highest in rural areas, but based on low numbers. Thus, for >5 year latency period OR was calculated in rural areas to be 6.9 (95% CI 1.5 to 32). However, for cordless phones there was also a tendency for higher ORs in rural areas in the group with >5 year latency period.

DISCUSSION

In a study on acoustic neuroma the risk estimate was higher in urban areas compared with rural areas.[7] However, the results were based on low numbers and have been criticised for inclusion of cases not in agreement with the Swedish Cancer Registry, different geographical areas for cases and controls, and inconsistent numbers in tables.[8] Our study is the first with a substantial number of cases and controls where the place of residence for cases and controls has been considered in the analysis of an association between use of cellular telephones and the risk for brain tumours. The Swedish population register covers the whole population. The municipality for each person is registered. We used that information in combination with the classification of the municipalities in homogeneity regions by Statistics Sweden. Of course this study would benefit from more categories of homogeneity instead of only two summary groups. However, few subjects (95 cases, 111 controls) lived in the most sparsely populated areas, H5 and H6, making statistical analysis less meaningful in that group.

Interestingly, we found a somewhat higher risk for brain tumours for cases living in rural areas than in urban areas for use of NMT phones. ORs were also increased among urban inhabitants. This was not explained by socioeconomic factors since the results were adjusted for SEI code. However, when we analysed use of analogue phones only, ORs were highest in urban areas. Thus, no clear effect of place of residence was seen for analogue phones. This may be explained by the fact that APC was not initially used for this phone system.[1] We have no information when APC was introduced, if at all, for analogue phones during our study period.

For use of GSM phones we found a clear effect of urban versus rural areas. In fact, we only found an increased risk for rural living and this could not be explained by longer phone calls among these cases. Dose-response calculations seemed to further support the result. Analysis of digital phones as the only used phone type showed a similar pattern, with highest ORs among rural inhabitants. These results may be of importance in future studies of brain tumour risk for digital phones. Thus our results, if confirmed in other studies, indicate that the risk of microwave exposure from digital phones is lower in areas with a short distance to base stations due to APC.

When we analysed malignant brain tumours separately, ORs were found to be highest in rural areas for digital phones using >5 year latency period. These results were based on low numbers, only one control, and must thus be interpreted with caution. Of interest, however, is the fact that no clear pattern was found for analogue or cordless phones. Regarding benign tumours, ORs were highest in rural areas regardless of phone type. Since these results were mainly based on the increased risk for acoustic neuroma, one possibility is that a confounding factor associated with place of living may exist, although this is as yet unknown.

Clearly our results support the notion that exposure may differ between geographical areas. However, these results refer to Sweden and there is no information on the exact difference between different geographical areas. Furthermore, the published results only refer to the GSM network.[1] Our findings indicate that in future studies place of residence should be considered in assessment of exposure to microwaves from cellular telephones, although the results of this study must be interpreted with caution due to the low numbers in some of the calculations. From a precautionary perspective, users of cellular telephones should select phones with low SAR, since differences in SAR between phone types may be larger than output power levels depending on whether the users live in urban or rural areas.

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EXHIBIT M

TO

SUPPLEMENTAL REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF DEFENDANT CITY AND COUNTY OF SAN FRANCISCO'S OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

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Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997-2003

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Abstract. The use of cellular and cordless telephones and the risk of brain tumours is of concern since the brain is a high exposure area. We present the results of a pooled analysis of two case-control studies on benign brain tumours diagnosed during 1997-2003 including answers from 1,254 (88%) cases and 2,162 (89%) controls aged 20-80 years. For acoustic neuroma, the use of analogue cellular phones gave an odds ratio (OR) of 2.9 and a 95% confidence interval (CI) of 2.0-4.3; for digital cellular phones, OR=1.5; 95% CI=1.1-2.1; and for cordless telephones, OR=1.5, 95% CI=1.04-2.0. The highest OR was found for analogue phones with a latency period of >15 years; OR=3.8, 95% CI=1.4-10. Regarding meningioma, the results were as follows: for analogue phones, OR=1.3, 95% CI=0.99-1.7; for digital phones, OR=1.1, 95% CI=0.9-1.3; and for cordless phones, OR=1.1, 95% CI=0.9-1.4. In the multivariate analysis, a significantly increased risk of acoustic neuroma was found with the use of analogue phones.

Introduction

The use of cellular and cordless telephones is widespread and increasing in society. A potential association between cellular and cordless telephones and health effects is of concern and has been discussed in several articles during recent years (1-3). Of special concern is the risk of brain tumours since this is a part of the body with high exposure during phone calls compared with other parts.

Cellular telephones emit radio frequency signals during calls. Exposure is characterized through the specific absorption rate (SAR) expressed as watt/kg. Analogue (NMT; Nordic Mobile Telephone System) phones operating at 450 MegaHertz (MHz) were introduced in Sweden in 1981. At first, they were usually used in cars with a fixed external antenna. Portable NMT 450 phones were introduced in 1984. Analogue phones using 900 MHz (NMT 900) were used in Sweden between 1986 and 2000. The digital system (GSM; Global System for Mobile Communication) started in 1991 and has during recent years dramatically increased to become the most common phone type. This system uses dual band, 900 and 1,800 MHz, for communication. From 2003, the third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), was introduced in Sweden, operating at 1,900 MHz.

Desktop cordless phones using the analogue system in the 800-900 MHz RF have been used in Sweden since 1988. Digital cordless telephones (DECT) that operate at 1,900 MHz have been used since 1991.

Acoustic neuroma might be a 'signal' tumor for association with cellular and cordless telephones, since it is located in an area with high exposure during calls. The tumour risk would be higher on the same side of the head as the exposure to the RF-field (ipsilateral exposure).

In 1999, we published our first study on this topic with cases and controls from between 1994 and 1996 (4). The analyses were based on answers from 209 (90%) of the cases and 425 (91%) of the controls. Overall, we did not find an increased risk. However, for ipsilateral exposure, we saw a somewhat higher risk, although based on few exposed subjects (4,5). No conclusions could be drawn from that study due to the low numbers and short latency periods.

Our next case-control study was larger and the responding numbers were for 1,429 cases (88%) and 1,470 controls (91%) recruited during January 1, 1997, and June 30, 2000. We modified the questionnaire somewhat between the two studies to assess exposure as carefully as possible. For all brain tumours, we found an increased risk for analogue phones that was most pronounced in the group with a >10-year latency period (6,7). Moreover, the risk was highest for analogue and digital cellular telephones with ipsilateral exposure, especially for high-grade astrocytoma. We found no association for meningioma. Regarding acoustic neuroma, a high risk was calculated for the use of analogue phones (6-8).

In our third study, we used the same questionnaire and study methods as in the second in order to be able to pool these

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two studies for a larger amount of study material with a longer time of use for both cellular and cordless phones (9,10). This study was conducted from July 1, 2000, until December 31, 2003. The study area consisted of Uppsala/Örebro and Linköping medical regions in Sweden. This time, Stockholm and Gothenburg medical regions were not included since the WHO Interphone study on the same issue was performed during part of this time in these regions. Thus, there was no overlap of cases between any of our three studies on this topic or the Swedish part of the Interphone study (11,12).

Here, we present results for benign brain tumours in a pooled analysis of our second and third studies on this topic. All controls from the second and third studies are used as a reference entity.

Materials and methods

In previous studies, we have presented details on the study methods so only a short presentation is given here. Ethics committees approved the studies. Both men and women, aged 20-80 years at the time of diagnosis as defined according to the date of the histopathology report, were included. In total, 3,729 cases were reported in a consecutive manner from the regional cancer registries diagnosed during the inclusion period. Subjects that did not meet the study prerequisites were excluded, i.e. brain metastases or wrong reporting to the registry (n=288), wrong year for diagnosis (n=73), missing histopathology (n=5), not resident in the study area (n=14), deceased (n=745), physician refusal (n=81), not able to participate (n=84) and unknown address (n=2), in a total of 1,292 cases. The final pooled study included 2,437 cases or 65% of those initially reported. Of these, 1,429 had a benign brain tumor.

We drew one control subject matched on age and sex and residing in the study area to each case from the Swedish population registry, which covers the whole population with unique id-numbers and current addresses. Any change in residence can be traced in the registry. Thus, 2,437 controls were recruited.

Assessment of exposure. Different environmental and occupational exposures were assessed by using a 20-page questionnaire sent to the study subjects. It contained questions on complete working history, exposure to different agents, smoking habits, etc. Regarding the use of cellular telephones, we asked for the first year of use, type of phone (analogue with prefix 010, digital with prefix 07), mean minutes of daily use over the years, use in a car with external antenna or a hands-free (both calculated as unexposed) and ear most frequently used. Similar questions dealt with the use of cordless telephones.

At most, two reminders were sent if the questionnaire was not returned. Trained interviewers using a structured protocol made supplementary phone interviews, if necessary. The ear that had been most frequently used over the years was asked for. A change in the used ear might have occurred, e.g. in the case of acoustic neuroma, due to hearing loss. The interviewer checked this information but we also sent an additional letter and asked all study subjects using cellular or cordless telephones to clarify this issue in detail.

An id-code that did not reveal whether the individual was a case or a control was given to each questionnaire. Thus, interviews and coding of data for the statistical analysis were blinded to case or control status. Both clinical and pathology reports were sent to the cancer registry in Sweden. We obtained such data from cancer registries and histopathological departments in the study area. All cases were given a diagnosis based on histopathological examination. Tumor localization was obtained by data in the cancer registries or if missing or unclear from neuroradiology investigations. We obtained copies of records after informed consent from the cases.

Statistical methods. Odds ratios (OR) and 95% confidence intervals (CI) (Stata/SE 8.2 for Windows; StataCorp, College Station, TX) were calculated using unconditional logistic regression analysis. The unexposed category consisted of subjects that had not used cellular or cordless phones. The exposed cases and controls were divided according to phone type, analogue, digital and cordless. We calculated the OR and 95% CI for the use of only one of these phone types and for different combinations. Adjustment was made for sex, age, socio-economic index (SEI)-code and year of diagnosis. Thereby, the same year as for the case was used for the corresponding control. Adjustment for year of diagnosis was made in order to avoid bias in exposure since all controls, both to malignant and benign brain tumor cases, were used in the analysis. We used age as a continuous variable in the analysis. Latency or tumor induction period was analysed using three time periods, >1-5, >5-10 and >10 years from the first use of a cellular or cordless telephone until diagnosis. In the dose-response calculations, the median number of cumulative lifetime use in hours among controls was used as a cut-off. Note that overall results for all latency groups were calculated in one analysis whereas dose-response was analysed separately for each latency category.

Results

In total, 1,254 (88%) cases and 2,162 (89%) controls participated. Of these, 916 (73%) had meningioma, 243 (19%) had acoustic neuroma and 96 (8%) had other types of benign brain tumours. One case had both meningioma and acoustic neuroma and was included in calculations of OR and 95% CI for both diseases. We display the results for cumulative use in hours for the different phone types in Table I. Regarding acoustic neuroma, the highest OR was calculated for cellular and cordless telephones for subjects with >1,000 h of cumulative use of the respective phone. The same pattern was found for meningioma and the use of cordless phones.

In Table II, we give the results for the different phone types according to latency period and cumulative number of hours divided into two groups based on the median number of hours among the controls. For meningioma, a somewhat increased OR was found with a longer latency period, the highest with a >10-year latency period. For acoustic neuroma, the use of analogue phones produced OR=2.9, 95% CI=2.0-4.3; digital phones, OR=1.5, 95% CI=1.1-2.1; and cordless telephones, OR=1.5, 95% CI=1.04-2.0. The OR was higher in the group with a >5- to 10-year latency compared with a shorter time. Only one case had used a digital phone for >10 years

Table I. Odds ratio (OR) and 95% confidence interval (CI) for cumulative lifetime use in hours of analogue and digital cellular telephones, cordless telephones and any combination of the three phone types.[a]

	1-500 h			501-1000 h			>1000 h		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Benign									
Analogue	169/252	1.6	1.2-2.0	17/29	1.7	0.9-3.1	13/16	2.2	1.02-4.7
Digital	384/667	1.2	0.96-1.4	30/64	1.1	0.7-1.8	23/45	1.2	0.7-2.1
Cordless	269/502	1.1	0.9-1.3	70/97	1.5	1.1-2.1	84/102	1.6	1.2-2.2
Total, any combination	450/831	1.1	0.9-1.3	98/152	1.4	1.03-1.8	129/189	1.5	1.1-1.9
Meningioma									
Analogue	99/252	1.3	0.98-1.7	8/29	1.1	0.5-2.6	6/16	1.4	0.5-3.8
Digital	268/667	1.1	0.9-1.3	18/64	1.0	0.6-1.8	9/45	0.7	0.3-1.4
Cordless	185/502	1.0	0.8-1.3	49/97	1.5	1.003-2.2	60/102	1.6	1.1-2.2
Total, any combination	310/831	1.0	0.8-1.2	66/152	1.3	0.9-1.8	85/189	1.3	0.99-1.8
Acoustic neuroma									
Analogue	55/252	2.8	1.8-4.2	7/29	3.3	1.3-8.0	6/16	5.1	1.9-14
Digital	83/667	1.4	0.99-2.0	10/64	1.8	0.8-3.8	12/45	3.1	1.5-6.4
Cordless	60/502	1.3	0.9-1.9	15/97	1.6	0.9-3.0	21/102	2.1	1.2-3.7
Total, any combination	97/831	1.3	0.96-1.8	22/152	1.6	0.96-2.8	36/189	2.2	1.4-3.4
Other benign									
Analogue	16/252	1.5	0.8-3.0	2/29	2.0	0.4-9.5	1/16	2.1	0.3-17
Digital	34/667	1.5	0.9-2.7	2/64	0.6	0.1-2.7	2/45	1.1	0.2-4.8
Cordless	24/502	1.4	0.8-2.6	6/97	1.7	0.7-4.4	4/102	1.2	0.4-3.6
Total, any combination	43/831	1.5	0.9-2.4	10/152	1.7	0.8-3.7	9/189	1.3	0.6-2.8

[a]Number of exposed cases (Ca) and controls (Co) are given. Unconditional logistic regression analysis adjusted for age, sex, socio-economic index and year of diagnosis was used. Trend, benign: analogue, p=0.71; digital, p=0.97; cordless, p=0.02; total, p=0.02. Trend, meningioma: analogue, p=0.93; digital, p=0.50; cordless, p=0.02; total, p=0.04. Trend, acoustic neuroma: analogue, p=0.48; digital, p=0.08; cordless, p=0.17; total, p=0.07. Trend, other benign: analogue, p=0.91; digital, p=0.41; cordless, p=0.86; total, p=0.84.

and 4 cases had used a cordless telephone for >10 years. Regarding analogue phones, a latency period of >10-15 years yielded OR=2.9, 95% CI=1.4-6.0 (n=13 cases, 62 controls) and >15 years yielded OR=3.8, 95% CI=1.4-10 (n=6 cases, 22 controls). Digital cellular phones gave a significantly increased risk in the group of other benign tumours with a 10-year latency period but based on only 4 cases.

Regarding meningioma, the OR was somewhat higher for ipsilateral use of cellular or cordless phones than for contralateral, and was of borderline significance for digital phones (Table III). Also, for acoustic neuroma, the most pronounced effect on OR was seen for ipsilateral use. Thus, for analogue phones, ipsilateral use yielded OR=3.0, 95% CI=1.9-5.0, but contralateral and varying ipsi-/contralateral use also increased the risk. For other types of benign brain tumours, these calculations were based on rather low numbers of cases to permit clear conclusions.

In the multivariate analysis, as displayed in Table IV, no significantly increased risk was found for meningioma for the studied phone. For acoustic neuroma, we found an OR of 2.5 and 95% CI of 1.8-3.5 for the use of analogue phones. The result was similar in the latency groups of >5-10 years and >10 years. The use of digital cellular telephones or cordless telephones yielded no significantly increased risk. In the group with other types of benign brain tumours, digital cellular phones gave a significantly increased risk with a >10-year latency period but based on few exposed cases.

Table V shows our analysis of OR for the use of only one type of phone and for different combinations. For meningioma, the OR was highest for subjects that reported the use of several types of phones. A similar pattern was found for acoustic neuroma with a significantly increased OR for any combination of cellular and cordless telephones.

We analysed the association between use of cellular and cordless telephones for different age groups based on first use of the respective phone (Table VI). The OR was highest for subjects in the <20 years age group for use of both analogue or digital cellular telephones, although based on low numbers.

Table II. Number of exposed cases (Ca) with benign brain tumours and controls (Co), odds ratio (OR) and 95% confidence interval (CI) for use of cellular or cordless telephones.[a]

	>1- to 5-year latency		>5- to 10-year latency		>10-year latency		Total, >1-year latency	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
Benign (n=1254, 577 unexposed)								
Analogue	52/86	1.4 0.9-2.0	90/127	1.7 1.2-2.3	57/84	1.8 1.2-2.6	199/297	1.6 1.3-2.0
≤85 h	40/67	1.3 0.8-2.0	46/63	1.6 1.1-2.4	20/26	2.0 1.1-3.7	106/156	1.5 1.1-2.0
>85 h	12/19	1.6 0.7-3.4	44/64	1.7 1.1-2.7	37/58	1.8 1.1-2.8	93/141	1.7 1.3-2.4
Digital	323/581	1.1 0.9-1.4	101/177	1.2 0.9-1.7	13/18	1.6 0.8-3.5	437/776	1.2 0.96-1.4
≤64 h	208/349	1.2 0.9-1.5	37/70	1.1 0.7-1.7	0/0	-	245/419	1.1 0.9-1.4
>64 h	115/232	1.1 0.9-1.5	64/107	1.5 1.04-2.2	13/18	1.6 0.8-3.5	192/357	1.2 0.96-1.5
Cordless	250/437	1.1 0.9-1.4	145/219	1.4 1.1-1.7	28/45	1.4 0.8-2.3	423/701	1.2 1.01-1.4
≤195 h	137/260	1.0 0.8-1.3	43/74	1.3 0.8-1.9	3/17	0.6 0.2-2.1	183/351	1.0 0.8-1.3
>195 h	113/177	1.2 0.9-1.6	102/145	1.6 1.2-2.1	25/28	2.1 1.1-3.7	240/350	1.4 1.1-1.7
Meningioma (n=916, 455 unexposed)								
Analogue	32/86	1.2 0.8-1.8	47/127	1.2 0.8-1.8	34/84	1.6 1.02-2.5	113/297	1.3 0.99-1.7
≤85 h	25/67	1.1 0.7-1.8	28/63	1.3 0.8-2.2	12/26	1.8 0.9-3.7	65/156	1.3 0.9-1.8
>85 h	7/19	1.4 0.6-3.5	19/64	1.1 0.6-1.9	22/58	1.6 0.9-2.7	48/141	1.3 0.9-1.9
Digital	220/581	1.0 0.8-1.3	67/177	1.1 0.8-1.6	8/18	1.3 0.5-3.2	295/776	1.1 0.9-1.3
≤64 h	140/349	1.0 0.8-1.3	27/70	1.0 0.6-1.7	0/0	-	167/419	1.0 0.8-1.3
>64 h	80/232	1.1 0.8-1.6	40/107	1.4 0.9-2.1	8/18	1.3 0.5-3.2	128/357	1.2 0.9-1.5
Cordless	167/437	1.0 0.8-1.3	104/219	1.3 1.01-1.8	23/45	1.6 0.9-2.8	294/701	1.1 0.9-1.4
≤195 h	98/260	1.0 0.7-1.3	33/74	1.3 0.8-2.0	3/17	0.9 0.2-3.2	134/351	1.0 0.8-1.3
>195 h	69/177	1.0 0.7-1.4	71/145	1.5 1.1-2.1	20/28	2.2 1.2-4.2	160/350	1.3 0.99-1.6

Table II. Continued.

	>1- to 5-year latency		>5- to 10-year latency		>10-year latency		Total, >1-year latency	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
Acoustic neuroma (n=243, 88 unexposed)								
Analogue	16/86	2.3 1.2-4.1	33/127	3.4 2.1-5.5	19/84	3.1 1.7-5.7	68/297	2.9 2.0-4.3
≤85 h	11/67	2.1 1.03-4.2	13/63	2.5 1.3-4.9	7/26	3.6 1.4-9.2	31/156	2.5 1.6-4.0
>85 h	5/19	3.8 1.3-11	20/64	3.8 2.1-7.1	12/58	3.1 1.5-6.4	37/141	3.6 2.2-5.8
Digital	75/581	1.4 1.01-2.1	29/177	1.8 1.1-3.0	1/18	0.6 0.1-5.0	105/776	1.5 1.1-2.1
≤64 h	50/349	1.6 1.1-2.4	6/70	0.9 0.4-2.2	0/0	-	56/419	1.5 1.01-2.2
>64 h	25/232	1.2 0.7-2.1	23/107	2.4 1.3-4.4	1/18	0.6 0.1-5.0	49/357	1.5 0.99-2.3
Cordless	61/437	1.5 1.01-2.1	31/219	1.5 0.96-2.4	4/45	1.0 0.3-2.9	96/701	1.5 1.04-2.0
≤195 h	27/260	1.1 0.7-1.8	8/74	1.3 0.6-2.9	0/17	-	35/351	1.1 0.7-1.7
>195 h	34/177	2.0 1.3-3.2	23/145	1.8 1.04-3.0	4/28	2.0 0.6-6.1	61/350	1.9 1.3-2.8
Other benign (n=96, 34 unexposed)								
Analogue	4/86	0.9 0.3-2.8	10/127	2.2 0.997-5.0	5/84	1.6 0.5-4.5	19/297	1.6 0.8-3.0
≤85 h	4/67	1.0 0.3-3.1	5/63	3.2 1.1-9.1	2/26	1.9 0.4-9.4	11/156	1.8 0.9-3.8
>85 h	0/19	-	5/64	1.6 0.6-4.7	3/58	1.4 0.4-5.2	8/141	1.3 0.6-3.1
Digital	29/581	1.4 0.8-2.5	5/177	0.9 0.3-2.6	4/18	12 2.8-52	38/776	1.4 0.8-2.5
≤64 h	19/349	1.8 0.98-3.4	4/70	3.6 1.01-13	0/0	-	23/419	1.9 1.03-3.3
>64 h	10/232	0.9 0.4-2.0	1/107	0.2 0.03-1.8	4/18	12 2.8-52	15/357	1.0 0.5-2.0
Cordless	23/437	1.6 0.9-2.8	10/219	1.3 0.6-2.8	1/45	0.7 0.1-5.9	34/701	1.5 0.8-2.5
≤195 h	12/260	1.4 0.7-2.8	2/74	1.0 0.2-4.6	0/17	-	14/351	1.2 0.6-2.3
>195 h	11/177	2.1 0.98-4.4	8/145	1.7 0.7-4.0	1/28	2.5 0.2-26	20/350	1.8 0.9-3.3

[a]Unconditional logistic regression analysis adjusted for age, sex, SEI and year of diagnosis, was used. In the dose-response calculations, the median number of cumulative use in hours among controls in the total material was used as a cut-off.

Table III. Number of exposed cases (Ca) with benign brain tumours and controls (Co), odds ratio (OR) and 95% confidence interval (CI) for use of cellular or cordless telephones for tumour localisations in relation to ear used during phone calls.[a]

Localisation/type of telephone	All Ca/Co OR (CI)	Ipsilateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)	Ipsi-/contralateral Ca/Co OR (CI)
Benign				
Analogue phone	199/297	83/98	59/100	18/35
	1.6	1.9	1.4	1.3
	1.3-2.0	1.3-2.6	0.99-2.1	0.7-2.4
Digital phone	437/776	172/240	160/266	45/84
	1.2	1.5	1.2	1.2
	0.96-1.4	1.1-1.9	0.9-1.5	0.8-1.9
Cordless phone	423/701	167/232	138/235	42/77
	1.2	1.4	1.1	1.1
	1.01-1.4	1.1-1.8	0.9-1.5	0.7-1.7
Meningioma				
Analogue phone	113/297	42/98	33/100	10/35
	1.3	1.3	1.2	1.1
	0.99-1.7	0.9-2.0	0.7-1.8	0.5-2.3
Digital phone	295/776	114/240	112/266	28/84
	1.1	1.4	1.1	1.1
	0.9-1.3	1.01-1.8	0.8-1.5	0.7-1.8
Cordless phone	294/701	109/232	101/235	25/77
	1.1	1.3	1.1	0.9
	0.9-1.4	0.9-1.7	0.8-1.5	0.6-1.6
Acoustic neuroma				
Analogue phone	68/297	35/98	23/100	8/35
	2.9	3.0	2.4	2.3
	2.0-4.3	1.9-5.0	1.4-4.2	1.001-5.5
Digital phone	105/776	50/240	38/266	16/84
	1.5	1.7	1.3	1.7
	1.1-2.1	1.1-2.6	0.8-2.0	0.9-3.2
Cordless phone	96/701	52/232	28/235	15/77
	1.5	1.7	1.1	1.8
	1.04-2.0	1.1-2.6	0.7-1.7	0.9-3.4
Other benign				
Analogue phone	19/297	6/98	3/100	0/35
	1.6	4.3	1.4	-
	0.8-3.0	1.3-14	0.3-5.9	-
Digital phone	38/776	8/240	10/266	1/84
	1.4	1.7	2.2	0.6
	0.8-2.5	0.6-5.1	0.8-6.0	0.1-5.5
Cordless phone	34/701	6/232	9/235	2/77
	1.5	1.7	2.0	1.5
	0.8-2.5	0.5-5.1	0.7-5.5	0.3-8.0

[a]Ipsilateral, same side for tumour and phone; contralateral, opposite side for tumour and phone; and ipsi-/contralateral, both ears used equally. Unconditional logistic regression analysis adjusted for age, sex, SEI and year of diagnosis, was used. Note that tumour site was missing for some cases and the matched control was excluded as well as controls with a missing corresponding case.

Table IV. Number of exposed cases (Ca) and controls (Co), odds ratio (OR) and 95% confidence interval (CI) for the use of cellular or cordless telephones.[a]

	>1- to 5-year latency		>5- to 10-year latency		>10-year latency		Total, >1-year latency	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
Benign								
Analogue	52/86	1.2 0.9-1.8	90/127	1.5 1.1-1.9	57/84	1.5 1.04-2.1	199/297	1.5 1.2-1.8
Digital	323/581	1.0 0.9-1.2	101/177	1.1 0.8-1.5	13/18	1.4 0.7-3.0	437/776	1.0 0.9-1.2
Cordless	250/437	1.0 0.8-1.2	145/219	1.2 0.97-1.5	28/45	1.1 0.7-1.8	423/701	1.1 0.9-1.3
Meningioma								
Analogue	32/86	1.2 0.8-1.8	47/127	1.1 0.8-1.6	34/84	1.4 0.9-2.1	113/297	1.2 0.96-1.6
Digital	220/581	1.0 0.8-1.2	67/177	1.1 0.8-1.5	8/18	1.2 0.5-2.9	295/776	1.0 0.8-1.2
Cordless	167/437	0.9 0.7-1.1	104/219	1.3 0.98-1.6	23/45	1.4 0.8-2.4	294/701	1.1 0.9-1.3
Acoustic neuroma								
Analogue	16/86	1.7 0.96-3.0	33/127	2.5 1.7-3.9	19/84	2.2 1.3-3.8	68/297	2.5 1.8-3.5
Digital	75/581	1.1 0.8-1.6	29/177	1.5 0.9-2.3	1/18	0.5 0.1-3.9	105/776	1.1 0.8-1.6
Cordless	61/437	1.2 0.9-1.7	31/219	1.1 0.7-1.7	4/45	0.7 0.2-1.9	96/701	1.1 0.9-1.5
Other benign								
Analogue	4/86	0.7 0.2-2.0	10/127	1.6 0.8-3.2	5/84	1.1 0.4-2.8	19/297	1.2 0.7-2.0
Digital	29/581	1.1 0.7-1.7	5/177	0.6 0.2-1.5	4/18	9.6 2.6-36	38/776	1.1 0.7-1.7
Cordless	23/437	1.3 0.8-2.1	10/219	1.1 0.5-2.1	1/45	0.4 0.05-2.9	34/701	1.1 0.7-1.8

[a]Unconditional logistic regression multivariate analysis adjusted for age, sex, SEI and year of diagnosis, was used.

Discussion

The reporting of new cancer cases to the Swedish cancer registry is compulsory. Also certain benign diseases such as benign brain tumours are reported. As soon as the histopathological diagnosis is obtained, the respective pathological departments send a report to the local cancer registry in the five medical regions in Sweden. In addition, the treating physician makes a clinical report. Thus, a high reporting frequency is obtained with good coverage of all new cases and no selection bias as to reporting exists.

We recruited cases in a consecutive way from cancer registries in the included medical regions, and we have no indication of selection bias in this respect. Thus, it was possible to include cases soon after diagnosis. For inclusion, it was necessary to have histopathological verification of the diagnosis. If information was unclear or missing in the cancer registry, we obtained copies of records from the pathology and radiology departments. Since all diagnoses were based on histopathology, it was possible for us to analyse different types of benign brain tumours as well as tumour localisation in the brain.

According to Table I, in our pooled study, it is obvious that a fairly high number of lifetime cumulative use of cellular or cordless telephones is necessary in order to obtain a stable risk estimate.

Table V. Number of exposed cases (Ca) with benign brain tumours and controls (Co), odds ratio (OR) and 95% confidence interval (CI) for the use of cellular or cordless telephones for different combinations of phone use.[a]

	>1-year latency		
	Ca/Co	OR	CI
Benign			
NMT only	45/79	1.3	0.9-1.9
GSM only	168/312	1.1	0.9-1.4
Cordless only	152/272	1.0	0.8-1.3
NMT + GSM	111/173	1.6	1.2-2.2
NMT + cordless	113/138	2.1	1.5-2.8
GSM + cordless	228/384	1.3	1.05-1.7
NMT + GSM + cordless	70/93	2.0	1.4-2.9
Total, any combination	677/1172	1.1	0.98-1.3
Meningioma			
NMT only	26/79	1.0	0.6-1.7
GSM only	119/312	1.0	0.8-1.3
Cordless only	114/272	1.0	0.8-1.3
NMT + GSM	61/173	1.3	0.9-1.8
NMT + cordless	65/138	1.7	1.2-2.5
GSM + cordless	154/384	1.2	0.9-1.6
NMT + GSM + cordless	39/93	1.7	1.1-2.6
Total, any combination	461/1172	1.0	0.9-1.3
Acoustic neuroma			
NMT only	11/79	2.0	0.97-4.0
GSM only	33/312	1.2	0.8-1.9
Cordless only	25/272	1.0	0.6-1.6
NMT + GSM	43/173	3.3	2.0-5.3
NMT + cordless	42/138	3.9	2.4-6.3
GSM + cordless	57/384	1.6	1.04-2.4
NMT + GSM + cordless	28/93	4.1	2.3-7.1
Total, any combination	155/1172	1.5	1.1-2.0
Other benign			
NMT only	8/79	2.0	0.8-4.7
GSM only	16/312	1.5	0.7-2.8
Cordless only	13/272	1.8	0.9-3.6
NMT + GSM	8/173	1.3	0.5-3.3
NMT + cordless	7/138	1.1	0.5-2.8
GSM + cordless	18/384	1.5	0.8-3.1
NMT + GSM + cordless	4/93	1.2	0.4-3.8
Total, any combination	62/1172	1.5	0.9-2.4

[a]Unconditional logistic regression analysis adjusted for age, sex, SEI and year of diagnosis, was used.

Table VI. Odds ratio (OR) and 95% confidence interval (CI) in different age groups' first use of cellular or cordless telephones.[a]

	>1-year latency		
	Ca/Co	OR	CI
Analogue phone			
All ages	199/297	1.6	1.3-2.0
<20	7/6	3.9	1.2-12
-20-49	137/214	1.6	1.2-2.1
-50-80	55/77	1.5	1.03-2.2
Digital phone			
All ages	437/776	1.2	0.96-1.4
<20	6/9	1.7	0.6-5.3
-20-49	250/445	1.3	1.02-1.6
-50-80	181/322	1.1	0.9-1.4
Cordless phone			
All ages	423/701	1.2	1.01-1.4
<20	4/16	0.6	0.2-1.9
-20-49	255/416	1.4	1.1-1.7
-50-80	164/269	1.1	0.9-1.4

[a]Numbers of exposed cases (Ca) and controls (Co) are given. Unconditional logistic regression analysis adjusted for age, sex, SEI and year of diagnosis, was used.

In the analyses, we adjusted for sex, since all controls were used and they were frequency matched to the cases. It should be noted that meningioma more commonly occurs among females (13), so sex might be a confounder since the use of both cellular and cordless phones differs among men and women. The use is also age dependent and, generally, more common among younger persons, so adjustment was made for age in the calculations of OR and 95% CI. Another factor to take into account is the year of diagnosis for the cases and corresponding year for the controls since this pooled analysis encompassed cases and controls recruited during 1997-2003 and the use of both cellular and cordless telephones increases over the years. Finally, we also adjusted for current or last reported SEI-code since social class has been reported to be a determinant for brain tumours.

Different types of bias may limit the interpretation of results in all case-control studies. We designed the study to minimise this problem. We selected controls from the population registry to avoid selection bias in this respect. Blinding of case/control status in all data collection and coding of exposure avoided observation bias. Misclassification of exposure may occur if cases recall exposure different to controls. The questionnaire contained many questions other than use of cellular and cordless telephones in order to avoid focusing on such use. Furthermore, such a bias would occur for cases regardless of tumor type. Since our results differed for various types of benign brain tumours, it is less likely that the findings could be explained by recall bias. Also, the same methods and questionnaire were used in a study of salivary gland tumours where no association with cellular or cordless phones was found (14).

The main finding of our pooled analysis of benign brain tumours was an increased risk for acoustic neuroma. The highest risk was found for a latency period of >15 years for use of analogue cellular telephones. However, an increased risk was also found for shorter latency periods. This might be consistent with a tumour-promoting effect from microwaves. In support of this, a Danish study found significantly larger acoustic neuroma among cellular phone users than controls (15).

In the univariate analysis, we found also a significantly increased risk for using digital cellular or cordless telephones. Furthermore, the risk was highest for ipsilateral use of the different phones, which certainly is of biological relevance. For analogue phones, increased ORs were also found for contralateral as well as varying ipsi- and contralateral use. This may be explained by the fact that hearing loss is an early symptom of acoustic neuroma leading to shift of the ear for phone calls during the progress of the disease. Thus, in spite of our efforts to carefully assess the most used ear over time, some cases may have reported the most recently used. It should be noted that only one case had used a digital phone and four cases a cordless phone with >10-year latency period. In the multivariate analysis, only analogue phones yielded a significantly increased risk for acoustic neuroma. So the association with digital cellular phones and cordless phones is still an issue for study with cases of long-term use.

For meningioma, we found an increased risk for analogue phones in the group with a >10-year latency period. However, no dose-response effect was seen. No significantly increased risk was found for digital cellular telephones. The OR increased for cordless phones with latency period with a tendency for dose-response effect. We found also some effect of laterality with the highest risk for ipsilateral exposure for all phone types. In the multivariate analysis, no significantly increased risks prevailed for meningioma.

As has been discussed elsewhere (1-3,9), the main shortcoming of most published studies on the association between cellular telephones and brain tumours has been that the latency period is too short. Thus, both longer latency periods and a higher cumulative number of hours of use are necessary in order to obtain a more precise estimate of the risk. In our pooled study, 64 cases with benign brain tumor had used a cellular telephone (analogue and/or digital) for >10 years, and it should be noted that 28 cases had used a cordless phone for >10 years. Regarding different types of benign brain tumours, the results were based on lower numbers. Thus, risk estimates for longer use of cellular or cordless telephones must be interpreted with caution.

Recently, results were presented from the Interphone (WHO) study on mobile phone use and risk of acoustic neuroma (12). The study consisted of one study in Sweden, Denmark, Norway and Finland and two studies in the UK. The main outcome was a significantly increased risk of acoustic neuroma with OR=1.8, 95% CI=1.1-3.1 for analogue phone users after use for 10 years or longer. As we have discussed elsewhere, there are limitations in the design, conduct and interpretation of the Interphone study (16,17). For example, interviews and coding of data were not blinded to the case/control status of the subjects, cases were interviewed at hospitals and controls mostly at homes, controls were obtained from general practioners' practise lists in the UK and there was not a histopathological verification of diagnosis for all cases. For the Swedish part, the number of cases was not in agreement with the Swedish cancer registry (16,17). Thus, the results may have been influenced by selection, recall and observation bias. These pitfalls were avoided in our studies as far as possible, as discussed in more detail elsewhere (6).

The mechanism for a carcinogenic effect from RF fields has been discussed for several years. Some studies have shown biological effects in experimental studies whereas these findings have not been replicated in others (1-3). Of interest are findings of genotoxic effects in cell systems exposed to radio frequency electromagnetic fields (RF-EMF) in the recently presented REFLEX-study (18). They used SAR levels that varied between 0.3 and 2 W/kg and found an increase in single- and double-strand DNA breaks and micronuclei frequency. Findings of chromosomal aberrations were observed in fibroblasts (19) and an intracellular increase of free radicals in HL-60 cells. It was concluded that RF-EMF might activate several groups of genes that play a role in cell division, cell proliferation and cell differentiation. These results indicate pathophysiological mechanisms that could be a basis for the development of chronic diseases, such as cancer, in humans. Also, a recently published study in mice on radiofrequency exposure and cellular calcium homeostasis is of interest regarding carcinogenesis (20). The results suggested that carcinogenesis might be induced earlier and with different pathological forms in exposed mice than in controls. Based on these results and our findings, it must be concluded that the current allowed SAR level of 2 W/kg based on thermal effects from RF-EMF is not appropriate.

In conclusion, this pooled analysis showed an increased risk of benign brain tumours, especially acoustic neuroma. For other types of benign brain tumours, no convincing pattern of association was found. For cellular telephones, the OR was highest for subjects with a first phone use at <20 years of age. However, several of the calculations were based on low numbers. This research area needs further study with increased numbers of exposed cases and higher latency periods.

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