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4 Health Effects of Chronic Exposure to Radiation From Mobile Communication

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CONTENTS

4.1 INTRODUCTION

Microwaves (MW, 300 MHz–300 GHz) or radio frequency (RF) radiation (3 kHz–300 GHz) induce a variety of biological and health effects which are commonly classified into thermal and nonthermal effects. Thermal effects are defined as those induced by elevation of temperature in the MW-exposed tissue. Thermal effects of acute exposure to MW are well characterized by the specific absorption rate (SAR, W/kg). Along with thermal MW effects, various biological responses to nonthermal (NT) MW, which are observed at the SAR values well below any measurable elevation of temperature, have been described by many research groups all over the world (1–6). Among many other variables, effects of NT MW strongly depend on frequency, modulation, polarization, and duration of exposure (7,8). It is generally accepted that all these parameters may be of importance for the effects of MW (4).

The SAR based safety limits adopted by the International Commission on Non-Ionizing Radiation Protection (ICNIRP), 2 W/kg, protecting from thermal MW effects only (9). In contrast to the ICNIRP, the Russian safety standards, which are based on nonthermal effects, do not use SAR values but instead limit the duration of exposure and power flux density (PD) (10).

Mobile phones emit a variety of MW signals (hundreds and even thousands, depending on location and type of mobile communication), which are different in carrier frequencies or frequency bands and modulations. The emitting signals, for example, GSM frequency channels, can be changed even within the same exposure session/talk. While one MW frequency/frequency band/modulation can induce detrimental effects, another one can be inactive (8). The studies with real mobile phones, given that the electromagnetic field (EMF) emitted by a phone is measured, represent the most valuable type of studies for assessment of various health effects including cancer risks from mobile telephony. Exposure to commercial or test mobile phones is close by all physical factors (carrier frequency, type of modulation, pulsed-field variables, near/far field, et cetera) to real exposure of the human brain and thus may provide valuable data for health risk assessment. At chronic exposures with longer duration, exposure to mobile phone may reproduce a number of real signals even during the same exposure session and thus provide a better possibility to assess detrimental effects from mobile telephony than experiments with fixed frequencies/frequency bands/modulations, which evaluate only a minor part of real signals. In addition, mobile phones emit not only MW, but also static and extremely low frequency (ELF) magnetic fields (11–16), which have also been shown to produce detrimental health effects and to interfere with MW effects (4,8,17).

There were many studies performed recently with chronic exposure to NT MW. While some studies with mobile phones did not provide measurements of EMF, only refereeing the SAR values from the manuals, EMF fields were measured in other studies. Most of these studies consistently showed detrimental health effects, and thus confirmed studies with long-term animals' MW exposure previously performed in Russia/The Soviet Union (18). This chapter represents an overview of recent studies on NT MW effects (SAR $\leq$ 2 W/kg) where EMF fields were measured.

4.2 ANIMAL *IN VIVO* STUDIES

4.2.1 Central Nervous System

Kesari et al. exposed 35-day old Wistar rats to MW from mobile phones for 2 h per day for a duration of 45 days, SAR being 0.9 W/Kg (19). A significant decrease in the levels of glutathione peroxidase and superoxide dismutase, and an increase in catalase activity were found in the exposed rats as compared to sham exposure. Moreover, protein kinase was significantly decreased in the hippocampus and whole brain of the exposed rats. Also, a significant decrease in the level of pineal melatonin and a significant increase in creatine kinase and caspase 3 were observed in the exposed group's whole brains as compared with the sham exposure. Finally, MW exposure significantly increased the level of reactive oxygen species (ROS). The authors concluded that a reduction or an increase in antioxidative enzyme activities, protein kinase C, melatonin, caspase 3, and creatine kinase are related to overproduction of ROS in animals under chronic exposure to mobile phone radiation.

Haghani et al. elucidated the possible effects of prenatal exposure of female Wistar rats to EMF from mobile phones (pulsed 900 MHz, SAR varying 0.5–0.9 W/kg, 6 h per day during gestation period) on the cerebellum of male and female offspring (20). Cerebellum-related behavioral dysfunctions were analyzed in offspring using motor learning and cerebellum-dependent functional tasks. Whole cell patch clamp recordings were used for electrophysiological evaluations. The results failed to show any behavioral abnormalities in rats chronically exposed to EMF from mobile phones. However, whole cell patch clamp recordings revealed decreased neuronal excitability of Purkinje cells in rats exposed to EMF. The changes were observed in after-hyperpolarization amplitude, spike frequency, half width, and first spike latency. The results showed that prenatal EMF exposure led to altered electrophysiological properties of Purkinje neurons. However, these changes might not be severe enough to alter the cerebellum-dependent functional tasks.

Ikinci et al. investigated changes in the spinal cords of Sprague-Dawley male rat pups exposed for 1 h daily between postnatal days 21 and 46 to the 900 MHz EMF (whole body SAR 0.01 W/kg) (21). At the end of exposure, the spinal cords in the upper thoracic region were collected for biochemical, light microscopic (LM), and transmission electron microscopic (TEM) examination. EMF exposure significantly increased malondialdehyde and glutathione levels as compared to control and sham exposed rats. LM revealed atrophy in the spinal cord, vacuolization, myelin thickening, and irregularities in the perikarya of the exposed rats. Marked loss of myelin sheath integrity and invagination into the axon and broad vacuoles in axoplasm was induced by EMF exposure as revealed by TEM. The authors concluded that biochemical alterations and pathological changes may occur in the spinal cords of male rats following chronic exposure to 900 MHz EMF.

Aslan et al. investigated possible pathological changes in the cerebellum of adolescent rats chronically exposed to 900 MHz EMF (13.4 V/m, the whole body SAR of 0.01 W/kg) 1 h daily for 25 days from postnatal days 21 through 46 (22). The cerebellums of animals were removed on postnatal day 47, then sectioned and stained with cresyl violet for histopathological and stereological analyses. Significantly fewer

Purkinje cells were found in the EMF exposed animals than in control and sham exposed rats. Histopathological evaluation revealed alteration of normal Purkinje cell arrangement and pathological changes including intense staining of neuron cytoplasm in the EMF exposed rats. The findings suggested that exposure to 900 MHz EMF for 1 h/day during adolescence can disrupt cerebellar morphology and reduce the number of Purkinje cells in the brain of adolescent rats.

Kerimoglu et al. exposed Sprague-Dawley male rats to MW (900 MHz, 8.4 V/m, 0.187 W/m2, whole body SAR 0.0067 W/kg, 1 h daily, days 21–59 throughout the adolescent period) and studied the 60-day old rat hippocampus (23). The left hemispheres were analyzed biochemically and the right hemispheres were subjected to stereological and histopathological evaluation. Histopathological examination revealed increased numbers of pyknotic neurons with black or dark blue cytoplasm in the brain of MW exposed rats. Fewer pyramidal neurons were found after MW exposure by stereological analysis. MW exposure increased malondialdehyde and glutathione levels, but decreased catalase levels in the brain. The data indicated that oxidative stress-related morphological damage and pyramidal neuron loss may be induced in the rat hippocampus following exposure to MW under given conditions throughout the adolescent period.

Deshmukh et al. investigated the effects of MW exposure at three different frequencies (900, 1800, and 2450 MHz, SAR being 5.953×10^{-4}, 5.835×10^{-4} and 6.672×10^{-4} W/kg, respectively) for 90 days on cognitive function, heat shock protein 70 (HSP70) level, and DNA damage in brain of Fischer rats (24). Cognitive functions were tested for using elevated plus maze and Morris water maze, HSP70 levels were estimated by enzyme-linked immunosorbent assay (ELISA), and DNA damage was assessed using alkaline comet assay. MW exposures at all frequencies led to decline in cognitive function and increased HSP70 level and DNA damage in the brain. The MW effects were significantly higher at 2450 MHz than at 900 MHz as measured with HSP70, tail length, the head and tail DNA content, the Olive tail moment, and the tail extent moment of the comets. The findings suggested that MW may lead to hazardous effects on the brain in dependence on frequency.

Gokcek-Sarac et al. studied effects of chronic exposure of young male albino Wistar rats to RF electromagnetic radiation (RF-EMR) at 900 and 2100 MHz (modulation frequency 217 Hz and pulse width 0.577 msec, 2 h/day, 5 days a week, for one week and ten weeks), on the hippocampal enzymes such as protein kinase A (PKA), Ca^{2+}/calmodulin-dependent protein kinase II alpha (CaMKIIalpha), cAMP response element-binding protein (CREB), and p44/42 mitogen-activated protein kinase (MAPK) from the N-methyl-D-aspartate receptor (NMDAR) related signaling pathways (25). The electric field strengths over the rat's head positioned 3.5 and 10 cm away from the antenna were 35.5 and 35.2 V/m for 900 and 2100 MHz RF-EMR, respectively. The average whole body SAR was 5.284 and 128 mW/kg for 900 and 2100 MHz, respectively. The average brain SAR was 0.66 and 0.27 W/kg for 900 and 2100 MHz, respectively. The hippocampal level/activity of selected enzymes was significantly higher after 10 week exposure as compared to 1-week exposures to RF-EMR at both 900 and 2100 MHz. Hippocampal level/activity of selected enzymes was significantly higher at 2100 MHz than at 900 MHz. The data indicated that chronic exposure of Wistar rats at different conditions had different effects on the protein expression of the hippocampus in dependence on duration of exposure.

Sharma et al. evaluated the effects of prolonged exposure of 2-week aged Swiss albino mice to MW (10 GHz, 0.25 mW/cm^2, 0.1790 W/kg, 2 h/day for 15 consecutive days) on developing mice brain (26). Various biochemical, behavioral, and histopathological parameters were analyzed in the exposed and sham exposed animals, which were autopsied either immediately after the completion of exposure or were allowed to attain 6 weeks of age for the follow-up study. Body weight showed significant changes immediately after exposure, whereas nonsignificant changes were observed in mice attaining 6 weeks of age. Brain weight, lipid peroxidation, glutathione, protein, catalase, and superoxide dismutase were found significantly altered in mice whole brain both immediately after exposure and in mice attaining 6 weeks of age. MW exposure affected spatial memory as measured using the Morris water maze test and histopathological parameters observed in the CA1 region of the hippocampus, cerebral cortex, and ansiform lobule of the cerebellum. The findings indicated that the brain of 2-week aged mice was sensitive to MW exposure as observed immediately after exposure and during follow-up study up to 6 weeks of age.

Tang et al. exposed male Sprague-Dawley rats to continuous wave EMF at 900 MHz, 1 mW/cm^2, SAR varying between 0.016 (whole body) and 2 W/kg (locally in the head), for 14 or 28 days, 3 h daily (27). The Morris water maze test was used to examine spatial memory performance. Morphological changes were investigated in the hippocampus and cortex, and the Evans Blue assay was used to assess blood brain barrier (BBB). Immunostaining was performed to identify heme oxygenase-1 (HO-1)-positive neurons and albumin extravasation detection. Western blot was used to determine HO-1 expression, expression of phosphorylated extracellular signal–regulated kinase (ERK) and upstream mediator mkp-1. EMF exposure did not affect the behavior of the rats at 14 days but impaired their performance at 28 days. BBB permeability increased 14 days after exposure to EMF and to a higher level after 28 days. Albumin uptake occurred more frequently in the cortex and hippocampal regions of brain in EMF exposed 28-d group than in the sham irradiated rats and EMF exposed 14-d group. Significant difference was found in HO-1 staining between the exposed rats and the sham exposed rats, as well as between the EMF 28-d group and the EMF 14-d group. Up-regulation of mkp-1 protein was observed at 28 days of exposure to EMF but not at 14 days. Dephosphorylation of ERK was detected in the rats at 28 days of exposure to EMF, and no difference between the nonexposed group and EMF 14-d group was observed. Taken together, the results demonstrated that chronic exposure to 900 MHz EMF for 28 days can significantly impair spatial memory and damage BBB permeability in rat by activating the mkp-1/ERK pathway.

Mugunthan et al. have investigated the effect of chronic exposure to radiations emitted from a 2G mobile phone (900–1800 MHz, SAR 1.6 W/kg, 48 minutes per day for a period of 30–180 days) in the hippocampus of mice (28). Random serial brain sections were analyzed for histomorphometric changes. The mean density of neurons in the hippocampus regions CA1, CA2 and dentate gyrus dorsal blade (DGDB) was significantly lower in the 2G exposed groups. However, the 2G exposed mice showed significantly higher density of neurons in CA3 and ventral blade/inferior limb (DGVB) regions. The mean nuclear diameter of neurons in the hippocampus region of CA1, CA2, CA3, DGDB, and DGVB showed lower nuclear diameter in 2G exposed mice. The authors concluded that chronic exposure to 900–1800 MHz

frequency radiations emitted from 2G mobile phone could affect neuron density and decrease nuclear diameter in the hippocampus neurons of mice.

Finally, the emerging data have shown that chronic exposure to real signals from mobile communications under specific conditions can affect brain cells and important functions that may be related to various health effects including carcinogenesis.

4.2.2 Cognitive Functions

Zhao et al. analyzed the effects of chronic exposure of Wistar rats to MW (average power densities of 2.5, 5, and 10 mW/cm^2, SAR of 1.05, 2.1, and 4.2 W/kg, respectively, 6 min daily for 1 month) on hippocampal structure and function (29). Learning and memory abilities were assessed by the Morris water maze. High performance liquid chromatography was used to detect neurotransmitter concentrations in the hippocampus and hippocampal structures were subjected to histopathological analysis. MW exposure significantly decreased learning and memory activity as analyzed 7, 14, and 30 days in all three MW exposure groups. Neurotransmitter concentrations of four amino acids (glutamate, aspartic acid, glycine, and gamma-aminobutyric acid) in the hippocampus were increased in the 2.5 and 5 mW/cm^2 groups and decreased in the 10 mW/cm^2 group. There was evidence of neuronal degeneration and enlarged perivascular spaces in the hippocampus of exposed animals. Mitochondria became swollen and cristae were disordered after MW exposure. The rough endoplasmic reticulum exhibited sacculated distension and there was a decrease in the quantity of synaptic vesicles. These findings suggested that the hippocampus can be injured by long-term microwave exposure followed by impairment of cognitive function due to neurotransmitter disruption.

Given the suggested link between EMF exposure, iron overload in the brain, and neurodegenerative disorders including Parkinson's and Alzheimer's diseases, Maaroufi et al. investigated co-exposure to MW (900 MHz, SAR 0.05–0.18 W/kg, 1 h/daily) and iron overload (daily injection of 3 mg FeSO4 per kg body weight) during 21 consecutive days in Long-Evans rats (30). The co-exposed rats were tested in various spatial learning tasks (navigation task in the Morris water maze, working memory task in the radial arm maze, and object exploration task involving spatial and nonspatial processing). Biogenic monoamines and metabolites (dopamine, serotonin) and oxidative stress were measured. Rats exposed to MW were impaired in the object exploration task but not in the navigation and working memory tasks. They also showed alterations of monoamine content in several brain areas including the cerebellum and striatum, but mainly in the hippocampus. Rats that received combined treatment did not show greater behavioral and neurochemical deficits than MW-exposed rats. No oxidative stress was detected after treatments. These data indicated that MW affected the brain and cognitive processes but no synergistic effects were found between MW and iron overload in the brain.

Deshmukh et al. investigated the effects of chronic low-intensity MW exposure on cognitive function, heat shock protein 70 (HSP70), and DNA damage in rat brain (31). Male Fischer rats were exposed to MW for 180 days at 3 different mobile phone frequencies of 900, 1800, and 2450 MHz, SAR ranging 5.835×10^{-4}–6.672×10^{-4} W/kg. The rats were tested for cognitive function at the end of the exposure. The brain was analyzed for HSP70 by enzyme-linked immunotarget assay

and DNA damage using alkaline comet assay. The results showed declined cognitive function, elevated HSP70 level, and DNA damage in the brain of MW-exposed animals. The results indicated that chronic low-intensity microwave exposure in the frequency range of 900–2450 MHz may cause hazardous effects on the brain.

Schneider and Stangassinger exposed male and female rats to EMF at a frequency of 900 MHz at GSM modulation or 1.966 GHz (Universal Mobile Telecommunications System [UMTS]) at 0.4 W/kg and analyzed memory performance of adult EMF-exposed and sham exposed female rats (at 6 months of age) and male rats (at 3 and 6 months of age) using a social discrimination procedure (32). The animals were exposed chronically for their entire lives to the far field linear polarized quasi-plane wave EMF. Differences in sniffing duration to the familiar and novel target rats were used to assess memory performance. EMF-exposed females exhibited no differences in sniffing duration compared with sham exposed controls. In contrast, the sniffing durations of EMF-exposed males at 3 months of age were significantly affected. At 6 months of age, GSM- but not UMTS-exposed male adults showed a memory performance deficit. This study showed that lifelong exposure to GSM EMF impairs social memory performance in adult male rats while lifelong exposure to UMTS EMF, with the same SAR, seems to display an age or exposure duration (3 months vs. 6 months) related adverse effect on the social memory retention.

Narayanan et al. investigated the effects of chronic EMF exposure from a mobile phone on spatial cognition and hippocampal architecture in prepubescent rats (33). Four weeks old male Wistar rats were exposed to EMF (GSM 900 MHz; SAR 1.15 W/kg with peak power density of 146.60 $\mu W/cm^2$ at 3 cm from mobile phone) for 1 h/day, 28 days. Spatial cognition was evaluated by Morris water maze test. Hippocampal morphology was studied in hippocampal sections by H&E staining, cresyl violet staining, and Golgi-Cox staining. CA3 pyramidal neuron morphology and surviving neuron count in CA3 region were studied using H&E and cresyl violet stained sections. Dendritic arborization pattern of CA3 pyramidal neuron was investigated by concentric circle method. Progressive learning abilities were found to be decreased in EMF exposed rats. Memory retention test performed 24 h after the last training revealed minor spatial memory deficit in the EMF-exposed group. However, EMF-exposed rats exhibited poor spatial memory retention when tested 48 h after the final trial. EMF exposure affected the viable cell count in the dorsal hippocampal CA3 region and the dendritic arborization pattern of both apical and basal dendritic trees. Structural changes found in the hippocampus of EMF-exposed rats could be one of the possible reasons for altered cognition.

Junior et al. investigated potential effects of mobile phone radiation on the central nervous system (CNS) using behavioral tests (open field and object recognition) in male Wistar rats (60 days old), which were exposed to EMR from a Global System for Mobile (GSM) cell phone (1.8 GHz, 2 V/m, 25-second long phone calls, every 2 minutes, for 3 days) (34). The exposed animals did not present anxiety patterns or working memory impairment, but stress behavior actions were observed upon exposure.

In some studies with chronic exposure to a specific RF signal generated by a signal generator (not by a mobile phone) neither neurodegenerative effects (35) nor effects on behavior and memory of exposed animals (36) were found.

In conclusion, most studies indicated that long-term chronic exposure to signals of mobile communications has a negative impact on cognition.

4.2.3 Immune Functions

Szmigielski reviewed studies on the impacts of weak RF/MW fields, including cell phone radiation, on various immune functions, both *in vitro* and *in vivo* (37). The bulk of available evidence clearly indicated that various shifts in the number and/or activity of immunocompetent cells are possible, while the results were inconsistent. In particular, a number of lymphocyte functions have been found to be either enhanced or weakened based on exposure to similar MW intensities although other important variables of experiments were different. The author concluded that, in general, short-term exposure to weak MW radiation may temporarily stimulate certain humoral or cellular immune functions, while chronic irradiation inhibits the same functions.

Ohtani et al. studied the effects of RF exposure (2.14 GHz wideband code division multiple-access (W-CDMA) signal, whole body SAR of 0.2 W/kg, for 20 h/day, 7 days/week) for a total of 9 weeks spanning in utero development, lactation, and the juvenile period on the immune system in Sprague-Dawley rats (38). Flow cytometry revealed no RF-induced changes in the numbers of CD4/CD8 T cells, activated T cells or regulatory T cells among peripheral blood cells, splenocytes, and thymocytes. Expression levels of 16 genes that regulate the immunological Th1/Th2 paradigm were analyzed using real time polymerase chain reaction (PCR) in the spleen and thymus. The Il5 gene was significantly upregulated in spleen and thymus, while Il4 and Il23a genes were significantly upregulated in thymus tissues only. ELISA showed no changes in serum IL-4 protein concentration. These data indicate no effects on immune-like T cell populations and T cell activation, while significant transcriptional effects of chronic RF exposure under given conditions were observed.

Kulaber et al. investigated changes in the thymic tissue of male Sprague-Dawley rats chronically exposed to MW (900 MHz, 8.86 V/m, 0.208 W/m2, 0.0067 W/kg) for 1 h every day between postnatal days 22 and 59 (39). On day 60, sections of thymus were assessed histologically and biochemically. MW exposure increased malondialdehyde (MDA) levels. Extravascular erythrocytes were observed in the medullary/corticomedullary regions in the sections of exposed rats. The findings indicated that MW exposure for 1 h/day on postnatal days 22–59 can increase tissue MDA and induce histopathological changes in the thymic tissue of male rats.

While the number of studies is still limited, available data indicate that chronic MW exposure may affect the immune system.

4.2.4 Sperm, Reproductive System, Fertility

Kesari and Behari chronically exposed Wistar rats to radiation from mobile phones (GSM 900 MHz, 0.9 W/kg, 2 h/day) for 45 days and analyzed the effects on sperm cells (40). EMF exposure significantly decreased the level of testosterone and increased caspase-3 activity, which is a marker of apoptosis. Distortions in sperm head and the mid-piece of sperm mitochondrial sheath were also observed by Transmission Electron Microscopy (TEM). A progeny from EMF-exposed rats showed a significant decrease in number and weight as compared with that of sham exposed animals.

Kumar et al. investigated the effect of 10 GHz chronic exposure (2 h per day for 45 days, power density 0.21 mW/cm^2, SAR 0.014 W/kg) on male Wistar rats'

reproductive systems (41). Chromosomal aberrations (CA) and micronuclei were determined in blood samples of exposed and sham exposed animals. Spermatozoa were analyzed for Caspase-3, DNA damage, testosterone, and by electron microscopy. Scanning electron microscopy revealed shrinkage of the lumen of the seminiferous tubules. Apoptotic bodies and increased caspase 3 were found in exposed animals. A flow cytometry examination showed formation of micronuclei body in lymphocytes of the exposed group. While no CAs were detected, comet assay revealed DNA strand breaks. Testosterone level was found to be significantly decreased along with a shrinkage of testicular size. This study has shown that chronic exposure at 10 GHz, 0.21 mW/cm^2, and SAR of 0.014 W/kg has potentially deleterious effects on blood and fertility of exposed male Wistar rats.

Tas et al. investigated the effects of long-term (3 h per day, 7 d a week, for one year) mobile phone exposure at 900 MHz (point, 1 g and 10 g SAR levels of testis and prostate were 0.0623 W/kg, 0.0445 W/kg and 0.0373 W/kg, respectively) on reproductive organs of Wistar Albino male rats (42). Epididymal sperm concentration, progressive sperm motility, abnormal sperm rate, all genital organs weights, and testis histopathology were evaluated. No effect of RF exposure was observed on sperm motility and concentration. Although histological examination showed similarities in the seminiferous tubules diameters in exposed and sham exposed animals, RF exposure decreased tunica albuginea thickness and the Johnsen testicular biopsy score. The authors concluded that long-term exposure to 900 MHz RF radiation alters some reproductive parameters. Of note, at least some of the reported effects might be dismissed by applying the adjustment for multiple comparisons.

Qin et al. investigated whether chronic exposure to RF (1800 MHz, PD 205 μw/cm^2, SAR 0.0405 W/kg) for 2 h/day for 32 days at different zeitgeber time (ZT) points (ZT0, ZT4, ZT8, ZT12, ZT16, and ZT20) affects circadian rhythms of reproductive functional markers in adult male Sprague-Dawley rats (43). Testicular and epididymis tissues were collected and assessed for testosterone levels, daily sperm production and sperm motility, testis marker enzymes gamma-glutamyl transpeptidase (gamma-GT) and acid phosphatase (ACP), cytochrome P450 side-chain cleavage (p450cc) mRNA expression, and steroidogenic acute regulatory protein (StAR) mRNA expression. These measurements revealed pronounced circadian rhythms in sham exposed animals. RF exposure disrupted the circadian rhythms decreasing testosterone levels, lowering daily sperm production and sperm motility, down-regulating activity of gamma-glutamyl transpeptidase (gamma-GT) and ACP, and altering mRNA expression of cytochrome P450 and StAR. The most significant changes were observed in rats exposed to RF at ZT0. The findings indicated potential adverse effects of RF exposure on male reproductive functional markers in terms of daily overall levels and circadian rhythmicity.

The effect of prolonged MW exposure (2G, 900–1900 MHz, 48 minutes per day for a period up to 180 days) cell phone on rats' testis was evaluated (44). Body weight was found to be significantly reduced after 30, 60, and 120 days of exposure, mean testis weight was significantly reduced 30, 60, 90, 150, and 180 days of exposure, and the mean testis volume was significantly reduced in groups with 30, 60, and 90 days of exposure compared to sham exposed mice. In histological analysis, the mean density of seminiferous tubules was significantly lower in all exposure groups except for 30 days of exposure, the mean seminiferous tubule diameter was significantly

reduced in all exposure group except for 60 days of exposure, and the numbers of Sertoli cells/tubule and Leydig cells was significantly reduced in all exposure groups compared to the sham exposure groups. For Johnson testicular biopsy score count and testosterone level, all exposure groups were pooled and a significantly reduced serum testosterone level and mild histological changes compared to sham exposed animals were found. The authors concluded that chronic exposure of mice to the 2G 900–1900 MHz mobile phone radiation might have detrimental effects on testes histology and function with possible consequences for fertility.

Kumar et al. chronically exposed male albino rats to EMF from a 3G cell phone (the frequency of the cell phone was fixed at 1910.5 MHz and kept in 'talk mode,' SAR varied from 0.28 to 0.0226 W/kg) for 60 days, two hours each day (6 days a week) and analyzed testicular functions (45). Significant decrease in sperm count, increase in the lipid peroxidation damage in sperm cells, reduction in seminiferous tubules and testicular weight, and DNA damage were revealed in rats following EMF exposure. The results demonstrated that exposure to the mobile phone radiation can negatively affect sperm functions via mechanisms that involve oxidative stress. The results suggest that mobile phone exposure adversely affects male fertility.

Liu et al. investigated whether chronic exposure of rats to MW (900 MHz, 0.66 $\pm$ 0.01 W/kg, 2 h/daily) for 50 days can trigger ROS, sperm cell apoptosis and affect semen morphology, concentration, and microstructure (46). The sperm count, morphology, apoptosis, ROS, and total antioxidant capacity (TAC), representing the sum of enzymatic and nonenzymatic antioxidants, were measured. Western blotting and reverse transcriptase PCR were used to determine the expression levels of apoptosis-related proteins and genes, including bcl-2, bax, cytochrome c, and capase-3. MW exposure increased ROS concentration and number of apoptotic sperm cells by 46.21% and 91.42%, respectively, while the TAC was decreased by 28.01%. MW exposure also significantly decreased the protein and mRNA expression of bcl-2 and increased that of bax, cytochrome c, and capase-3. The data indicated that MW exposure altered expression levels of apoptosis-related genes and triggered sperm apoptosis through induction of ROS and bcl-2, bax, cytochrome c, and caspase-3 signaling pathways.

Odaci and Ozyilmaz exposed Sprague-Dawley male rats to a 900 MHz EMF (whole body SAR 0.025 W/kg, 1 h daily, 30 days) and investigated EMF effects on the rat testicles (47). The levels of malondialdehyde, superoxide dismutase, catalase, and glutathione along with apoptotic index measured with terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay and histopathological damage scores were analyzed. EMF exposed rats exhibited vacuoles in seminiferous tubules basal membrane and edema in the intertubular space. Both seminiferous tubule diameters and germinal epithelium thickness were smaller, while apoptotic index was higher in the EMF exposed animals. The levels of malondialdehyde, superoxide dismutase, and catalase were increased in the EMF exposed rats as compared to the sham exposure group although glutathione was decreased. The authors concluded that chronic exposure to the mobile phone frequency of 900 MHz caused pathological alterations in rat testicular morphology and biochemistry.

Mugunthan et al. evaluated and compared effects of chronic exposure to 900–1800 MHz radiation emitted from 2G cell phone and 1900–2200 MHz from 3G

cell phones on the testis of mice (48). Mice were intermittently exposed to 2G and 3G radiation, 48 minutes per day (2 min per each 30 min 8.00 a.m. – 8.00 p.m.) for a period of 30–180 days. The highest SAR value for this standard handset was 1.69 W/Kg (10 g). Measurements were performed at the end of 30, 60, 90, 120, 150, and 180 days of exposure. There was significant reduction of animal weight at first, second, and fourth months following chronic exposure to 2G and 3G cell phone radiation. The mean testis weight and volume of 2G and 3G radiation exposed mice were significantly reduced in the first three months. The comparison between 2G and 3G exposed groups showed no significant changes in mean body weight, mean testis weight, and mean testis volume. 2G and 3G chronic exposure decreased density of seminiferous tubules, mean seminiferous tubule diameter, and mean number of Sertoli and Leydig cells. Few changes were observed by microscopic analysis in the 2G and 3G exposed mice. Chronically exposed mice had significantly lower serum testosterone at the end of first, second, third, fourth, and sixth months of 2G and 3G exposures while no difference was observed between the 2G and 3G exposed groups. The authors concluded that chronic exposure to radiation from 2G and 3G cell phones could cause changes in the seminiferous epithelium, reduction of serum testosterone level, and reduction in the number of Sertoli cells and Leydig cells.

To conclude, most *in vivo* studies with animals indicated that NT MW induce detrimental effects in sperm, which can affect fertility and may occur through induction of ROS and ROS-dependent molecular pathways.

4.2.5 Other Tissues

Esmekaya et al. investigated whether chronic exposure to 900 MHz pulse-modulated RF fields (rectangular pulses with repetition frequency 217 Hz and pulse width 0.576 ms, the whole body average SAR 1.20 W/kg, 20 min/day for three weeks) induce oxidative damage in lung, heart, and liver tissues of Wistar albino rats (49). They assessed oxidative damage by investigating lipid peroxidation (malondialdehyde, MDA), nitric oxide (NOx), and glutathione (GSH) levels, which are the indicators of tissue toxicity. MDA and NOx levels were increased significantly in liver, lung, testis, and heart tissues of the exposed group compared to sham exposed animals. Conversely, GSH levels were significantly lower in exposed rat tissues. The authors concluded that pulse-modulated RF radiation causes oxidative injury in liver, lung, testis, and heart tissues mediated by lipid peroxidation, increased level of NOx, and suppression of antioxidant defense mechanism.

Tsybulin et al. elucidated the effects of MW emitted by a commercial model of GSM 900 MHz cell phone on embryo development in quails (*Coturnix coturnix japonica*) (50). Fresh fertilized eggs were irradiated during the first 38 h or 14 days of incubation by a cell phone in a connecting mode activated continuously through a computer system. Each connection attempt lasted about 45 s. Exposure during 38 h/14 days comprised of about 3000/26,900 calls. Maximum incident PD on the egg's surface was 0.2 $\mu W/cm^2$. The irradiation led to a significant increase in numbers of differentiated somites in 38-hour exposed embryos and to a significant increase in total survival of embryos from exposed eggs after 14 days exposure. The level of thiobarbituric acid (TBA) reactive substances was significantly higher in brains and

livers of hatchlings from the exposed embryos. An especially conspicuous increase was detected in brains, where the TBA levels were higher by 3.5 fold in comparison with the unexposed samples. Consequently, it pointed to the increased lipid peroxidation of hatchling's tissues from exposed embryos, which is closely connected to levels of ROS. Thus, the observed effects of radiation from the commercial GSM 900 MHz cell phone on the developing quail embryos can be accounted for by the enhancement of metabolism provoked via peroxidation mechanisms due to radiation-induced ROS.

Ozorak et al. studied the effects of chronic exposures to EMF at 900 MHz, 1800 MHz, and 2.45 GHz (pulsed at 217 Hz, mean whole body SAR 0.18 $\pm$ 0.07 W/kg, 60 min/day, 5 days per week) on oxidative stress and trace element levels in the kidney and testis in rats growing from pregnancy to 6 weeks of age (51). EMF exposure decreased the level of lipid peroxidation in the kidney and testis and the copper, zinc, reduced glutathione (GSH), glutathione peroxidase (GSH-Px), and total antioxidant status (TAS) values in the kidney, while iron concentrations in the kidney as well as vitamin A and vitamin E concentrations in the testis increased at the 4th week of exposure. Iron, vitamin A, and beta carotene concentrations increased in the kidney of EMF exposed animals, while the GSH and TAS levels decreased after five weeks of exposure. Iron concentrations in the kidney and the extent of lipid peroxidation increased in the EMF groups in the kidney and testis after six weeks of exposure, while copper, TAS, and GSH concentrations decreased at this time. EMF exposure did not induce any changes in the kidney's concentrations of chromium, magnesium, and manganese. The authors concluded that chronic exposure to EMF caused oxidative damage by increasing the extent of lipid peroxidation and the iron level, while decreasing total antioxidant status, copper, and GSH values.

Eser et al. studied the histopathological and biochemical changes in the frontal cortex, brain stem, and cerebellum of Spraque-Dawley rats exposed to MW at 900, 1800, and 2450 MHz (average SAR 1.04 W/kg) 1 h daily for 2 months (52). MW exposures induced degenerative changes, shrunken cytoplasm, and extensively dark pyknotic nuclei in the frontal cortex and brain stem, which were more profound at 2400 MHz. The levels of Total Oxidative Capacity and Oxidative Stress Index were significantly increased in the frontal cortex, brain stem, and cerebellum of MW exposed animals. The frontal cortex was more affected at 900 MHz. MW exposures significantly increased the IL-1beta level in the brain stem, while exposure at 900 MHz was statistically significantly most efficient. MW exposures induced caspase-3 immunoreactivity in the frontal cortex and brain stem, although the frequency of 2450 MHz was most efficient. The data indicated that chronic MW exposure caused histopathological changes in the frontal cortex, brain stem, and cerebellum and impaired the oxidative stress and inflammatory cytokine system in dependence on frequency.

Tsybulin et al. assessed the effects of low intensity radiation from a GSM (Global System for Mobile communication) 900 MHz cellular phone on early embryogenesis in dependence on the duration of exposure (53). Embryos of Japanese Quails were exposed in ovo to GSM 900 MHz cellular phone radiation (890–915 MHz carrier frequency, nonmodulated by any voice signal while maintaining a pulse modulation which is equivalent to an amplitude modulation simultaneously by 217 Hz and

harmonics, average power density 0.25 μW/cm^2, SAR 3 μW/kg) during the initial 38 h of brooding or alternatively during 158 h (120 h before brooding plus initial 38 h of brooding) interruptedly: 48 s on followed by 12 sec off intervals. A number of differentiated somites and DNA damage were assessed microscopically and by alkaline comet assay, respectively. Exposure significantly altered the number of differentiated somites. In embryos exposed during 38 h, the number of differentiated somites increased, while in embryos irradiated during 158 h, this number decreased. The lower duration of exposure led to a decrease in the level of DNA strand breaks in cells of 38-h embryos, while the higher duration of exposure significantly increased DNA damage as compared to the control. The authors concluded that effects of the GSM 900 MHz cellular phone radiation on early embryogenesis can be either stimulating or deleterious depending on the duration of exposure.

Ozgur et al. investigated effects of prenatal and/or postnatal chronic exposure to 1800 MHz RF radiation (pulsed with frequency of 217 Hz and a duty cycle of 1:8 (pulse width 0.576 ms), corresponding to the dominant modulation component of the GSM, 0.1 W output power) on the blood chemistry and lipid peroxidation levels of New Zealand female and male infant rabbits (54). Thirty-six females and 36 males were divided into four groups which were composed of nine infants each: (i) Group 1 was sham exposure; (ii) Group 2 was exposed to RF, 15 min daily for 7 days in the prenatal period (between 15th and 22nd days of the gestational period) (prenatal exposure group); (iii) Group 3 was exposed to RF 15 min/day (14 days for male, whereas 7 days for female) after they reached 1-month of age (postnatal exposure group); (iv) Group 4 was exposed to RF for 15 min daily during 7 days in the prenatal period (between 15th and 22nd days of the gestational period) and 15 min/day (14 days for male, whereas 7 days for female) after they reached 1-month of age (prenatal and postnatal exposure group). RF exposure affected serum lipid peroxidation level in both female and male rabbits and changed several biochemical parameters in blood (creatinine, uric acid, g-glutamyl transpeptidase (GGT), alanine transaminase (ALT), Albumin (ALB), and malondialdehyde (MDA) in males; urea, GGT, aspartate aminotransferase (AST), ALT, total protein (TP), MDA in females). Thus, the blood biochemistry of male and female infants was differently affected by RF exposure. The authors concluded that the whole body 1800 MHz GSM-like RF exposure may lead to oxidative stress and changes in some blood chemistry parameters.

Mugunthan et al. evaluated histological effects of chronic exposure to MW emitted from 2G (900–1900 MHz) cell phone on kidneys of mice (55). 21 days old mice were exposed to 2G MW, 48 minutes per day for a period up to 180 days. Animals were sacrificed at the end of 30, 60, 90, 120, 150, and 180 days of exposure and both kidneys were harvested and processed for histomorphometric study. MW exposure significantly reduced weight of kidney in mice exposed at the age of 21–51 days while kidney weight was significantly increased in the fifth month. In dependence on age and exposure time: (i) glomerulus showed dilated capillaries and increased urinary space; (ii) proximal convoluted tubule showed wider lumen with reduced cell size; (iii) brush border interrupted at places and vacuolated cytoplasm and pyknotic nuclei; and (iv) wider lumen with decreased cell size and marked basal striations were found in the distal convoluted tubule. The authors concluded that chronic exposure

to radiation from 2G cell phone could cause microscopic changes in glomerulus, proximal, and distal convoluted tubules of the kidney.

Çiftçi et al. determined the effects of prenatal and postnatal exposure (2 h/day during the periods of pregnancy, 21 days, and lactation, 21 days) to Wi-Fi radiation (2.45 GHz, pulsed with 217 Hz, SAR 0.009 ± 0.002 W/kg per head) on tooth and surrounding tissue development as well as the element levels in growing Wistar albino rats (56). The offspring of these dams were also exposed to radiation up to decapitation. On the 7th, 14th, and 21st days after birth, EMR-exposed and sham exposed male offspring rats were decapitated and the jaws were taken for histological and immunohistochemical examination. Caspase-3 was used in the immunohistochemical examination for apoptotic activity. On the last day of the experiment, the rats' incisors were also analyzed. RF exposure induced no apoptotic activity. However, iron and strontium concentrations were increased in the Wi-Fi-exposed group, whereas boron, copper, and zinc concentrations were decreased. There were no statistically significant differences in calcium, cadmium, potassium, magnesium, sodium or phosphorus values between the groups. Histological and immunohistochemical examinations revealed no effects of exposure to 2.45 GHz radiation on the development of teeth and surrounding tissues. Given that Zn, B, and Cu can act as antioxidants by decreasing ROS while the increased Fe levels trigger OH^- formation, the authors concluded that the revealed alterations in the elemental composition of the teeth, especially affecting such oxidative stress-related elements as copper, zinc, and iron, suggest an imbalance in the oxidative stress condition in the teeth of growing rats exposed to Wi-Fi radiation. The authors noted that the animals were exposed to Wi-Fi radiation for a period which is equivalent to approximately 10 years in humans. Thus it is clear that the exposure period of this study is of too short a duration to draw conclusions as to the effects of Wi-Fi exposure over a lifetime.

Olgar et al. exposed Wistar male rats to 2.1 GHz EMF (217 Hz-pulse rate, SAR 0.83 W/kg, 2 h/day, 7 days/week, 10 weeks) and investigated nitric oxide (NO), contractility and beta-adrenergic (beta-AR) responsiveness of ventricular myocytes (57). Sarcomere shortening and Ca(2+) transients were recorded in isolated myocytes loaded with Fura2-AM and electrically stimulated at 1 Hz, while L-type Ca(2+) currents (I(CaL)) were measured using whole cell patch clamping at 36 ± 1°C. Cardiac NO levels were measured in tissue samples using a colorimetric assay kit. Fractional shortening and amplitude of the matched Ca(2+) transients were not changed in the EMF exposed rats. Although the basal I(CaL) density in myocytes was similar between exposed and sham exposed groups, the isoproterenol-induced (10(−6) M) I(CaL) response was reduced in rats exposed to EMF. Moreover, EMF exposure led to a significant increase in nitric oxide levels in the rat heart. The authors concluded that long-term exposure to 2.1 GHz EMF decreases beta-AR responsiveness of ventricular myocytes through NO signaling.

Cao et al. studied whether circadian rhythms of the plasma antioxidants (Mel, GSH-Px, and superoxide dismutase [SOD]) are affected by chronic exposure of male Sprague Dawley rats to the 1.8 GHz RF (201.7 $\mu W/cm^2$ power density, 0.05653 W/kg SAR) (58). The animals were exposed to RF for 2 h/day at six specific times during the 24 h light-dark cycle (3, 7, 11, 15, 19 and 23 h Greenwich Mean Time (GMT), respectively) for 32 consecutive days. The concentrations of three antioxidants

(Mel, GSH-Px and SOD) were determined in blood samples. RF exposure shifted circadian rhythms in the synthesis of Mel and antioxidant enzymes, GSH-Px, and SOD. The Mel, GSH-Px, and SOD levels were significantly decreased when RF exposure was given at 23 and 3 h GMT. The overall results indicate that there may be adverse effects of RF exposure on antioxidant function, in terms of both the daily antioxidative levels, as well as the circadian rhythmicity.

Zhu et al. exposed adult male Institute for Cancer Research (ICR) mice to MW (continuous wave 900 MHz, 1.6 mW/cm^2, whole body average SAR 0.731 W/kg) for 4 hour/day for 15 days (59). At the end of exposure, each mouse was caged with 3 mature virgin female mice for mating. After 7 days, each male mouse was transferred to a fresh cage and mated with a second batch of 3 females. This process was repeated for a total of 4 consecutive weeks. All females were subjected to examination on the 18th day of gestation and presumptive mating. The overall observations during the 4 weeks of mating indicated that the unexposed female mice mated to MW-exposed male mice showed no significant differences in the percentage of pregnancies, total implants, live implants, and dead implants when compared with those mated with sham exposed mice. In contrast, female mice mated with GR-exposed males showed a consistent pattern of significant differences in the above indices in each and all 4 weeks of mating. These data indicated an absence of dominant lethal mutations upon exposure of the germ cells of male mice to MW under given conditions.

Kuybulu et al. investigated oxidative stress and apoptosis in kidney tissues of male Wistar rats, which were chronically exposed to MW (2.45 GHz, pulsed with 217 Hz, whole body SAR of 0.143 W/kg, 60 min/day) in pre- and postnatal periods (60). Exposure during the prenatal period increased renal tissue malondialdehyde (MDA) and total oxidant (TOS) levels and decreased total antioxidant (TAS) and superoxide dismutase (SOD) levels. Spot urine N-acetyl-beta-D-glucosaminidase (NAG)/creatinine ratio was significantly higher in animals exposed in both pre- and postnatal periods. Tubular injury was detected in most of the specimens in postnatally exposed animals. Immunohistochemical analysis showed low-intensity staining with Bax in cortex and high-intensity staining with Bcl-2 in cortical and medullar areas of prenatally exposed rats. Bcl2/Bax ratios of medullar and cortical area were higher in prenatally exposed rats than in sham exposed animals. These findings indicated that chronic MW exposure during pre- and postnatal periods may cause kidney injury.

In conclusion, available data encourage evaluation of risks for a wide spectrum of diseases before any new type of mobile communications is set up.

4.2.6 Carcinogenesis

In 2011, the International Agency for Research on Cancer (IARC) Working Group reviewed more than 40 studies in which the carcinogenicity of RF-EMF was assessed in rodents; among these studies were seven two-year oncogenicity bioassays (4,61). All these studies explored very few RF signals including the frequency of 2450 MHz and some frequencies within the frequency range of emissions from cell phones. An increased total number of malignant tumors were identified in RF-exposed animals in one of the seven chronic bioassays in animals exposed to RF-EMF for two years. Increased cancer incidences in exposed animals were noted in two of twelve studies with tumor-prone

animals and in one of eighteen studies using initiation-promotion protocols. However, four of six cocarcinogenesis studies provided evidence of increased cancer incidences after exposure to RF. Overall, the IARC Working Group concluded in 2011 that there is limited evidence in experimental animals for the carcinogenicity of RF-EMF (61).

One cocarcinogenesis lifetime study with mice suggested tumor-promoting effects of UMTS signals (62). Lerchl et al. have recently performed a replication of this study using higher numbers of animals per group and including two additional exposure levels (0 (sham), 0.04, 0.4, and 2 W/kg SAR) (63). This study confirmed and extended the originally published observations of tumor-promoting effects of life-long RF-EMF exposure. Numbers of tumors of the lungs and livers in RF-exposed animals were significantly higher than in sham exposed controls. In addition, lymphomas were also found to be significantly elevated by exposure. The same tumor-promoting effects were seen at nonthermal exposure levels (0.04, and 0.4 W/kg SAR), thus well below exposure limits for the users of mobile phones. The authors concluded that these findings may help explain the repeatedly reported increased incidences of brain tumors in heavy users of mobile phones.

A report has recently been released from The National Toxicology Program (NTP) under the National Institutes of Health (NIH) in USA on the largest ever animal 2-year study on cell phone RF radiation and cancer (64). Rats were exposed to either GSM- or code-division multiple access (CDMA)-moduleated signals at 900 MHz beginning in utero (SAR 0, 1.5, 3, 6 W/kg, 9 h per day, 10 min on/off, 7 days per week). An increased incidence of glioma in the brain and malignant schwannoma in the heart was found in rats at all SAR values and both types of signal. This effect was statistically significant in males only. A statistically significant SAR-dependent trend for GSM and CDMA exposures in males was found. Comet assay showed a statistically significant increased trend and SAR-dependent increase of DNA damage in the frontal cortex of males. Acoustic neuroma or vestibular schwannoma is a similar type of tumor as the one found in the heart, although it is benign. Thus, this animal study supported human epidemiological findings on chronic exposure to RF radiation and brain tumor risk (5,65,66). The strength of the NTP study is in its: (i) long term exposure covering *in utero* period and comparable with life span, (ii) usage of GSM/CDMA modulations and intermittent exposure that is close to exposure from mobile phones in real life, and (iii) large animal group providing high statistical power. The limitation of this study is in using only one GSM and one CDMA frequency, 900 and 1900 MHz, respectively, from multiple frequency channels used in mobile communication. The previously reviewed data showed frequency dependent effects of nonthermal RF (8). In particular, our studies showed that the mobile phone frequency channels vary in their efficiency to affect human cells (67–69). In particular, the frequency of 915 MHz was shown to affect the blood brain barrier and inhibit DNA repair in rats and human cells, respectively. The frequency of 905 MHz was much less effective in experiments with human cells. Thus, some of mobile phone frequency channels may be more or less detrimental. The usage of only two frequencies from GSM/CDMA mobile communication in the NTP study might underestimate carcinogenic effects from everyday exposures to mobile phone RF at various frequency channels. The finding that increased cancer risks was revealed in RF-exposed males only is not a limitation of this study. According to IARC, “‘the

probability that tumors will occur may depend on the species, sex, strain, genetic background, and age of the animal, and on the dose, route, timing, and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms." p. 22 (4).

4.3 HUMAN STUDIES WITH VOLUNTEERS AND EPIDEMIOLOGICAL STUDIES

4.3.1 Sperm, Reproductive System, and Fertility

Recent review included meta-analysis of 11 studies on human males of reproductive age (70). Based on this meta-analysis, mobile phone use was associated with deterioration in semen quality. The traits adversely affected were sperm concentration, sperm morphology, sperm motility, sperm viability, proportion of nonprogressive motile sperm, and slow progressive motile sperm. Direct exposure of spermatozoa to mobile phone radiation in *in vitro* studies also significantly deteriorated the sperm quality by reducing straight line velocity, fast progressive motility, hypo-osmotic swelling (HOS) test score, major axis, minor axis, total sperm motility, perimeter, area, average path velocity, curvilinear velocity, motile spermatozoa, and acrosome reacted spermatozoa. The strength of evidence for the different outcomes varied from very low to very high. The analysis shows that mobile phone use is possibly associated with a number of deleterious effects on human spermatozoa.

Al-Ali et al. evaluated association of cell phone usage with erectile function (EF) in men (71). 20 men complaining of erectile dysfunction (ED) for at least six months (Group A), and 10 healthy men with no complaints of ED (Group B) were evaluated. Anamnesis, basic laboratory investigations, and clinical examinations were performed. All men completed the German version of the Sexual Health Inventory for Men (SHIM) for evaluation of the International Index of Erectile Function (IIEF), as well as another questionnaire designed for assessing cell phone usage habits. There was no significant difference between both groups enrolled regarding age, weight, height, and total testosterone. The SHIM scores of Group A were significantly lower than that of Group B. While total time spent talking on the cell phone per week was not significantly higher in Group A over B, men with ED were found to carry their 'switched on' cell phones for a significantly longer time than those without ED. The data indicated that the total time of chronic exposure to EMF of the cell phone might be more important than the relatively short duration of intense exposure during making cellular phone calls.

El-Helaly and Mansour studied the effects of cell phones usage on the quality of human semen from 262 male attending an andrology clinic for infertility evaluation (72). The study analyzed cell phone use, duration of daily use in minutes, and how the participants kept or handled their cell phones in relation to their bodies. Semen quality parameters of the participants did not differ significantly between cell phone users and cell phone nonusers. Also, semen quality parameters did not differ significantly according to daily use of cell phone in minutes or in years. Those who kept their cell phones in their trouser pockets had lower sperm motility compared to those who

kept their cell phone in their waist pouch, shirt pocket or in hands, but the diffidence was not statistically significant. This study failed to find any significant reduction of semen quality parameters in association with cell phone use.

Zilberlicht et al. investigated an association between characteristics of cell phone usage and semen quality in 106 men who underwent a first-time semen analysis as a part of infertility workup (73).Talking for $\geq$1 h/day and during device charging were statistically significantly associated with higher rates of abnormal semen concentration. Among men who reported holding their phones $\leq$50 cm from the groin, a nonsignificantly higher rate of abnormal sperm concentration was found (47.1% versus 11.1%). Multivariate analysis revealed that talking while charging the device and smoking were risk factors for abnormal sperm concentration. These findings suggested that certain aspects of cell phone usage may bear adverse effects on sperm concentration.

While not universal, available studies indicate that prolonged usage of mobile phone may affect human sperm and fertility.

4.3.2 Hearing

Few studies have recently evaluated the effects of chronic MW exposure on hearing (74–77). While these studies did not usually find any effects of using mobile phone up to 5 years on hearing, the latency of waves in auditory brainstem responses (ABR) was significantly prolonged in subjects using mobile phones for 10 years for a maximum of 30 min/day as compared to the control group in one study (76). The authors concluded that long term exposure to mobile phones may affect conduction in the peripheral portion of the auditory pathway. No endpoints relevant for carcinogenicity were evaluated in these studies and the number of participants enrolled to these studies was rather limited suggesting further investigations with a larger group.

4.3.3 Type 2 Diabetes Mellitus

Meo et al. studied the association of exposure to RF EMF generated by mobile phone base stations for 6 h daily, five days in a week, with glycated hemoglobin (HbA1c), which is commonly used as a marker of hyperglycemia and an independent and reliable marker for diabetes mellitus, and occurrence of type 2 diabetes mellitus (78). For this study, 159 male students aged 12–17 years were recruited from two different elementary schools (school-1 and school-2). Mobile phone base stations were about 200 m away from each school. RF EMF was measured inside both schools; 9.601 nW/cm^2 in school 1 and 1.909 nW/cm^2 in school 2. HbA1c was measured in blood samples collected from the students. The mean HbA1c for the students who were exposed to higher RF EMF was significantly higher than the mean HbA1c for the students who were exposed to lower RF EMF. Moreover, students who were exposed to higher RF EMF had a significantly higher risk of type 2 diabetes mellitus relative to their counterparts who were exposed to lower RF-EMF. These findings indicated that chronic exposure to RF-EMF of 9.601 nW/cm^2 is associated with elevated levels of HbA1c and risk of type 2 diabetes mellitus.

4.4 ACADEMIC PERFORMANCE, SLEEPINESS, MENTAL HEALTH, AND SUBJECTIVE WELL-BEING

Lepp et al. investigated the relationships between total cell phone use and texting on Satisfaction with Life (SWL), Academic Performance (GPA), and anxiety in college students (79). Both cell phone use and texting were negatively related to GPA and positively related to anxiety while GPA was positively related to SWL and anxiety was negatively related to SWL. These findings indicate that increased use may negatively impact academic performance, mental health, and subjective well-being or happiness.

Byun et al. evaluated the association between mobile phone use and symptoms of Attention Deficit Hyperactivity Disorder (ADHD) considering the modifying effect of lead exposure (80). A total of 2422 children at 27 elementary schools in 10 Korean cities were examined and followed up 2 years later. Parents filled in a questionnaire including the Korean version of the ADHD rating scale and questions about mobile phone use, as well as socio-demographic factors. The ADHD symptom risk for mobile phone use was estimated at two time points using logistic regression and combined over 2 years using the generalized estimating equation model with repeatedly measured variables of mobile phone use, blood lead, and ADHD symptoms, adjusted for covariates. Voice call use variables (number of outgoing calls per day, average time spent per voice call, and cumulative time spent for voice calls) showed increased risks for ADHD symptoms according to increasing mobile phone exposure. The ADHD symptom risk associated with mobile phone use for voice calls, but the association was limited to children exposed to relatively high lead after adjustment for several covariates. The authors concluded that simultaneous exposure to lead and RF from mobile phone use was associated with increased ADHD symptom risk.

Redmayne et al. evaluated associations between self-reported use of wireless telephone and internet technology and well-being of New Zealand adolescents (81). The participants completed questionnaires in class about their mobile phone and cordless phone use, their self-reported well-being, and possible confounders. Parental questionnaires provided data on whether they had WiFi at home and cordless phone ownership and model. The 373 enrolled participants were reported to use analogue and digital cordless phones, the latter utilizing DECT, DECT6, Wideband Digital Enhanced Cordless Telecommunication (WDECT), Digital Signal Standard (DSS), and frequency hopping spread spectrum (FHSS) modulation systems. They were categorized in four groups: (A) nonusers of cordless phone, (B) analogue phone, (C) DECT and DECT6 phones, and (D) the remainder. The frequency ranges were (1) 30–40 and 900 MHz, (2) 1.8 and 1.9 GHz, (3) 2.4 GHz, and (4) 5.8 GHz. Use of mobile phone and cordless phone $\geq$3 times weekly was associated with increased risk of headaches. Several cordless phone frequencies bands were statistically significantly related to tinnitus, feeling down/depressed, and sleepiness at school. This study revealed more statistically significant associations (36%) of mobile phone use and well-being than could be expected by chance (5%), with several of these associations being dependent on dose (number and duration of calls). The data also suggested apparent significance of some frequency bands or systems used by cordless phones.

Nathan et al. investigated an association between mobile phone use, especially at night, and sleepiness in a group of 191 US teenagers using a questionnaire

containing an Epworth Sleepiness Scale (ESS) modified for teens and questions about qualitative and quantitative use of the mobile phone (82). Multivariate regression analysis indicated that ESS score was significantly associated with being female, feeling a need to be accessible by mobile phone all of the time, and a past attempt to reduce mobile phone use. The number of daily texts or phone calls was not directly associated with ESS. The relationship between daytime sleepiness and mobile phone use was not directly related to the number of daily texts or phone calls, but may be related to the temporal pattern of mobile phone use.

Zheng et al. studied the association between mobile phone (MP) use and inattention in 7102 students in 4 middle schools (83). The mean age was 15.26 ± 1.77 years. Participants owned mobile phones at the time of the survey and had been using a mobile phone for a mean of 3.50 ± 2.48 years. Participants spent 57.36 ± 71.96 minutes on entertainment and 8.64 ± 15.48 minutes on making calls daily. Inattention was assessed as defined for the Attention Deficit component of Attention deficit/Hyperactivity disorder (ADHD) by the Diagnostic and Statistical Manual of Mental. After adjustment for confounders, inattention in adolescents was significantly associated with MP ownership, the time spent on entertainment on mobile phone per day, the position of the MP during the day, and the mode of the mobile phone at night. The strongest association between inattention and the time spent on the mobile phone was among students who spent $\geq$60 minutes per day playing on their mobile phone. This data indicated association between mobile phone use and inattention in Chinese adolescents. The authors advised that decreasing mobile phone usage to $\leq$60 minutes per day may help adolescents to stay focused and centered.

In their cross-sectional study, Zheng et al. investigated associations between mobile phone use and well-being among 746 children in the two primary schools in Chongqing, China (84). The average age of the participants in the survey was 10.6 ± 0.6 years and the average year of mobile phone usage was 1.3 ± 1.5 years. Fatigue was significantly associated with the years of mobile phone usage and the daily duration of mobile phone calls. Headache was significantly associated with the daily duration of mobile phone calls. However, only the association between fatigue and mobile phone usage remained statistically significant after adjusting for confounders. There was no significant association between MP use and other physical symptoms (dizziness, sleeping problems, feeling low, heart beating fast) in children. This study indicated that there was a consistent significant association between mobile phone use and fatigue in children.

Huss et al. evaluated association of chronic exposure to RF-EMF with reported quality of sleep in 2361 Amsterdam born children, aged 7 years (85). When children were about five years old, school and residential exposure to RF-EMF from base stations was assessed with a geospatial model (NISMap) and from indoor sources (cordless phone/WiFi) using parental self-reports. Parents also reported their children's use of mobile or cordless phones. When children were seven years old, sleep quality was evaluated with the Child Sleep Habits Questionnaire (CSHQ) filled in by parents. Of eight CSHQ subscales, sleep onset delay, sleep duration, night wakening, parasomnias, and daytime sleepiness were evaluated with logistic or negative binomial regression models, adjusting for child's age and sex and indicators of socio-economic position of the parents. The remaining three subscales (bedtime resistance, sleep anxiety, sleep

disordered breathing) were evaluated as unrelated outcomes (negative control). Sleep onset delay, night wakening, parasomnias, and daytime sleepiness were not associated with residential exposure to RF-EMF from base stations. Sleep duration scores were associated with RF-EMF levels from base stations. Higher mobile phone use was associated with less favorable sleep duration, night wakenings, and parasomnias, and also with bedtime resistance. Cordless phone use was not related to any of the sleeping scores. Based on inconsistent findings for different RF sources, which otherwise are well expected based on studies and mechanisms reviewed previously (2,3,8), the authors suggested that the revealed sleep disorders may also be potentially caused by other factors that are related to mobile phone usage such as the displacement of sleep by media use, physiological arousal when using media in the evenings or bright (blue) light from screens suppressing melatonin.

Schoeni et al. investigated association of memory performance in adolescents with the dose of RF exposure from mobile communication devices in their longitudinal epidemiological cohort study with 439 adolescents (86). Verbal and figural memory tasks at baseline and after one year were completed using a standardized, computerized cognitive test battery. Use of wireless devices was inquired by questionnaire and operator recorded mobile phone use data was obtained for a subgroup of 234 adolescents. Exposure from cordless phone base stations, WLAN access points, and other people's mobile phones were estimated by linear regression models calibrated on the personal measurement data available from 95 study participants. RF-EMF dose measures considering various factors affecting RF-EMF exposure were computed for the brain and the whole body. A substantial correlation was found between self-reported mobile phone call duration and brain dose of the whole sample. In linear exposure-response models, an interquartile increase in cumulative operator recorded mobile phone call duration was associated with a decrease in figural memory performance score by 0.15 (95% CI: 0.33, 0.03) units. For cumulative RF-EMF brain and whole body dose, corresponding decreases in figural memory scores were 0.26 (95% CI: 0.42, 0.10) and 0.40 (95% CI: 0.79, 0.01), respectively. Compared to the low exposure group (below median), significant decreases were observed in the high exposure group for brain dose (−1.16; 95% CI: −1.99, −0.34) and whole body dose (−0.86; 95% CI: −1.67, −0.05) of the whole sample and for the brain dose of the sample with operator data (−1.62; 95% CI: −2.63, −0.61). Stratified analyses according to the preferred side of mobile phone use revealed for the analyses of the figural memory test in the whole sample a stronger effect estimate for the brain dose of right side mobile phone users compared to the group of left side and no preference side users (change per interquartile range: −0.52 (95% CI: −0.82, −0.22) vs. 0.27 (95% CI: −0.35, 0.89)). For the verbal memory test, the pattern tended to be reversed with somewhat stronger effect estimates for the left side users and those without a side preference compared to the right side users. Of note, during figural memory processes, encoding elicits bilateral prefrontal activity and retrieval increases the activity in bilateral or right-sided temporal regions and in bilateral prefrontal regions. In contrary, during verbal encoding increases in prefrontal and temporal brain activity in the left hemisphere can be seen. Stronger overall effects observed for figural memory processes predominantly involving the right hemisphere compared to the verbal memory tasks mostly involving the left hemisphere were compatible

with the fact that 81.2% of the study participants reported mainly used mobile phones on the right side, but only 18.8% on the left side or with no laterality preference. No exposure-response associations were observed for sending text messages and duration of gaming, which produced tiny RF-EMF emissions. Finally, the data indicated that negative effects on memory performance over one year were associated with cumulative duration of wireless phone use and more strongly with RF-EMF dose. Within various dose measures, stronger associations were observed for brain than for whole body dose. The laterality analyses indicated stronger associations for right side users for the figural memory task whereas the reverse pattern was seen for the verbal task.

In conclusion, several studies provided evidence that that long-term chronic exposure to signals of mobile communications may affect cognitive functions.

4.5 PRENATAL EXPOSURE TO MOBILE PHONE

Studies examining prenatal exposure to mobile phone use and its effect on child neurodevelopment showed different results depending on the child's developmental stages. Adverse effects have been reported in later ages at 7 years (87,88), and 11 years (89). However, no effects were reported for earlier ages, at 14 months (90), at 6 and 18 months (91), at 3 years (92) and 5 years (93). All these studies were based on retrospective assessment of cell phone use. Birks et al. have recently assessed this association in a multi-national analysis, using data from three cohorts with prospective data on prenatal cell phone use, together with previously published data from two cohorts with retrospectively collected cell phone use data (94). They used individual participant data from 83,884 mother-child pairs in the five cohorts from Denmark (1996–2002), Korea (2006–2011), the Netherlands (2003–2004), Norway (2004–2008), and Spain (2003–2008). Cell phone use was categorized into none, low, medium, and high based on frequency of calls during pregnancy reported by the mothers. Child behavioral problems were classified in the borderline/clinical and clinical ranges using validated cut-offs in children aged 5–7 years. Overall, 38.8% of mothers, mostly from the Danish cohort, reported no cell phone use during pregnancy and these mothers were less likely to have a child with overall behavioral, hyperactivity/inattention or emotional problems. The trend of increased risk of child behavioral problems through the maternal cell phone use categories was observed for hyperactivity/inattention problems (OR for problems in the clinical range: 1.11, 95% CI 1.01, 1.22; 1.28, 95% CI 1.12, 1.48, among children of medium and high users, respectively). This association was fairly consistent across cohorts and between cohorts with retrospectively and prospectively collected cell phone use data. The authors concluded that maternal cell phone use during pregnancy may be associated with an increased risk for behavioral problems, particularly hyperactivity/inattention problems, in the offspring.

Tan et al. assessed the association between maternal lifestyle factors and risk of threatened miscarriage in their recent case-control study in the largest maternity hospital in Singapore, with over 12,000 deliveries a year (95). Cases were 154 women with threatened miscarriage in the 5th to 10th weeks of gestation; controls were 264 women without threatened miscarriage. Lifestyle variables were: current and past cigarette

smoking, current second-hand cigarette smoke exposure, computer and mobile phone use, perceived stress, past contraceptive use, past menstrual regularity, and consumption of fish oils, caffeine, and alcohol. A positive association of threatened miscarriage with second-hand smoke exposure, computer usage (>4 hours/day), caffeine consumption and mobile phone usage (>1 hour/day) was found using multivariate analysis. Mobile phone use for 1–2 hours/day had an odds ratio (OR) of 2.94 (95% CI 1.32–6.53) and use for >2 hours/day had an OR of 6.32 (95% CI 2.71–14.75) as compared to <1 hour/day. Thus, longer duration of mobile phone use was associated with higher risk. The data suggested that prolonged mobile phone use correlated with threatened miscarriage and a dose-response relationship was observed.

Mahmoudabadi et al. investigated possible association between chronic exposure to electromagnetic fields of cell phones and spontaneous abortion (96). In this case-control study, 292 women who had an unexplained spontaneous abortion at <14 weeks gestation and 308 pregnant women >14 weeks gestation were enrolled. The data about socioeconomic and obstetric characteristics, medical and reproductive history, lifestyles, and use of cell phones during pregnancy were collected. The data on cell usage included the average calling time per day, the location of the cell phones when not in use, use of hands-free equipment, use of phones for other applications, the phone SAR reported by the manufacturer, and the effective SAR determined as average duration of calling time per day x SAR. This last parameter estimated the per day dose of RF exposure from a phone. All the data pertaining to mobile phones were different between the two groups except the use of hands-free devices. Logistic regression analysis revealed a significant association between the effective SAR (per day RF dose) with the risk of spontaneous abortions after adjustment for maternal age, paternal age, history of abortions, and family relationships. These findings suggested that use of mobile phones can be related to the early spontaneous abortions.

To conclude, the available data encourage warnings against prenatal usage of mobile communication.

4.6 CARCINOGENESIS AND MOBILE PHONE USE

Several epidemiological studies had examined the association between cell phone use and tumors in the parotid glands. These studies provided contradictory results. de Siqueira et al. evaluated the available literature to determine their statistical significance using meta-analysis (97). Only three studies satisfied the criteria to be included in the meta-analysis. Using these independent samples representing 5087 subjects from retrospective case-control studies, cell phone use was revealed to be associated with greater odds (1.28, 95%-confidence interval 1.09–1.51) to develop salivary gland tumor.

West et al. reported a case series of four young women aged from 21 to 39 with multifocal invasive breast cancer that raises the concern of a possible association with exposure to electromagnetic fields from cellular phones (98). All patients regularly carried their smartphones directly against their breasts in their brassieres for up to 10 hours a day, for several years, and developed tumors in areas of their breasts immediately underlying the phones. While breast cancer occurring in women under the age of 40 is uncommon in the absence of family history or genetic predisposition

such as mutated BRCA1 and BRCA2, all patients had no family history of breast cancer, tested negative for BRCA1 and BRCA2, and had no other known breast cancer risks. Their breast imaging has shown clustering of multiple tumor foci in the breast directly under the area of phone contact. Pathology of all four cases revealed striking similarity; all tumors were hormone-positive, low-intermediate grade, having an extensive intraductal component, and all tumors have near identical morphology. The findings supported the notion that prolonged direct cellular phone contact may be associated with the development of breast carcinoma.

de Vocht analyzed the 1985–2014 incidence of selected brain cancer subtypes in England and compared to counterfactual 'synthetic control' time series were (99). More specifically, two specific hypotheses are addressed: (1) trends in histologically-defined brain cancers that have previously been linked to mobile phone exposure; malignant glioma and glioblastoma multiforme (Grade IV astrocytoma) or GBM4, and (2) malignant neoplasms of the temporal and parietal lobes, which receive the highest exposures, and for which the temporal lobe has especially been highlighted as an important location of interest. Annual 1985–2014 incidence of malignant glioma, glioblastoma multiforme, and malignant neoplasms of the temporal and parietal lobes in England were modeled based on population-level covariates using Bayesian structural time series models assuming 5, 10, and 15 year minimal latency periods. Post-latency counterfactual 'synthetic England' time series were nowcast based on covariate trends. The impact of mobile phone use was inferred from differences between measured and modelled time series. There was no evidence of an increase in malignant glioma, glioblastoma multiforme or malignant neoplasms of the parietal lobe not predicted in the 'synthetic England' time series. Malignant neoplasms of the temporal lobe, however, have increased faster than expected. A latency period of 10 years reflected the earliest latency period when this was measurable and related to mobile phone penetration rates, and indicated an additional increase of 35% (95% Credible Interval 9%:59%) during 2005–2014; corresponding to an additional 188 (95% CI 48–324) cases annually. The author concluded that a causal factor, of which mobile phone use (and possibly other wireless equipment) is in agreement with the hypothesized temporal association, is related to an increased risk of developing malignant neoplasms in the temporal lobe.

Few recent meta-analyses of available case-control studies have consistently shown that long term mobile phone use is associated with statistically significant increased risks of brain tumors while no such association is seen with shorter usage (5,6,66,100). The impact of study quality and source of finding has also been estimated.

Bortkiewicz et al. conducted a systematic review and meta-analysis of multiple works on the association between the use of mobile phones and brain cancer (66). The inclusion criteria were: original papers, case-control studies, published after the end of March 2014, measures of association (point estimates as odds ratio and confidence interval of the effect measured), and data on individual exposure. Twenty-four studies (26,846 cases, 50,013 controls) were included in the meta-analysis. A significantly higher risk of an intracranial tumors (all types) was noted for the time from the first regular mobile phone use over 10 years (odds ratio (OR) = 1.25, 95%

confidence interval (CI): 1.04–1.52), and for the ipsilateral location (OR = 1.29, 95% CI: 1.06–1.57). The results indicated that long-term use of mobile phones increased risk of intracranial tumors, especially in the case of ipsilateral exposure.

Prasad et al. investigated whether the methodological quality of studies and source of funding can explain the variation in results for increased brain tumor risks accumulated in epidemiologic studies (6). Twenty-two case-control studies were included for systematic review. Meta-analysis of 14 case-control studies showed practically no increase in risk of brain tumor (OR 1.03 (95% CI 0.92–1.14)). However, for mobile phone use of 10 years or longer (or >1640 h), the overall result of the meta-analysis showed a significant 1.33 times increase in risk. The summary estimate of government funded as well as phone industry funded studies showed 1.07 times increase in odds, although it was not significant. The mixed funded studies did not show any increase in risk of brain tumor. Relationship between source of funding and log OR for each study was not statistically significant ($p < 0.32$, 95% CI 0.036–0.010). Meta-regression analysis indicated that the increased risk was significantly associated with methodological study quality ($p < 0.019$, 95% CI 0.009–0.09). Studies with higher quality showed a trend toward high risk of brain tumor, while lower quality showed a trend toward lower risk/protection. This data provided evidence linking mobile phone use and risk of brain tumors especially in long-term users while lower quality studies underestimated this risk.

Garlberg and Hardell used Bradford Hill's viewpoints from 1965 on association or causation for assessment of glioma risk and use of mobile or cordless phones (65). All nine viewpoints were evaluated based on epidemiology and laboratory studies. (1) Strength: meta-analysis of case-control studies gave odds ratio (OR) = 1.90, 95% confidence interval (CI) = 1.31–2.76 with highest cumulative exposure. (2) Consistency: the risk increased with latency, meta-analysis gave in the 10+ years' latency group OR = 1.62, 95% CI = 1.20–2.19. (3) Specificity: increased risk for glioma was in the temporal lobe. Using meningioma cases as a comparison group still increased the risk. (4) Temporality: highest risk was in the 20+ years' latency group, OR = 2.01, 95% CI = 1.41–2.88, for wireless phones. (5) Biological gradient: cumulative use of wireless phones increased the risk. (6) Plausibility: animal studies showed an increased incidence of glioma and malignant schwannoma in rats exposed to RF radiation. There is increased production of ROS from RF radiation. (7) Coherence: there is a change in the natural history of glioma and increasing incidence. (8) Experiment: antioxidants reduced ROS production from RF radiation. (9) Analogy: there is an increased risk in subjects exposed to extremely low-frequency electromagnetic fields (see also present report. V.). The authors concluded that RF radiation should be regarded as a human carcinogen causing glioma.

A growth in brain cancer incidence including most exposed temporary lobe was described by the cancer registers of some countries (101,102). However, comparison of these data with increased cancer risks from mobile telephony should be done with caution due to reported incompleteness of cancer registers in different countries, which may mask increased cancer incidence (101,103,104).

4.7 DISCUSSION

4.7.1 Chronic Exposures to NT MW and Safety Guidelines

The effects of exposure to NT MW depend on many biological and physical parameters including exposure duration (2,3,8). This dependence is a key reason for variability in the NT MW effects reported in different studies. However, many studies have consistently shown that significant biological and health effects are observed under prolonged durations of exposure (7,105). This chapter reviewed recent studies on health effects of chronic exposure to NT MW.

Available studies show that chronic exposure to NT MW may result in various health effects affecting the central nervous system, memory, leaning, reproductive system, fertility, and immune functions. Chronic exposure to NT MW from mobile communication at $\geq$10 years correlated with increased cancer risk. Overall, there is strong evidence that chronic exposure to NT MW from mobile communication adversely affects health. As far as the ICNIRP safety guidelines, which were adopted by many countries, are based on acute thermal MW effects only, they do not save the population from the adverse effects from chronic exposure to NT MW. Moreover, the SAR concept, which is only relevant to thermal effects and acute exposures, is not useful for protection against adverse effects from chronic exposures to NT MW. Thus, all available data strongly suggest that power density along with duration of exposure should be applied for safety limits (7,106).

Russia was the first country in the world to develop the safety standards for RF/MW exposure, which were based on a 30-year research performed in several Soviet institutions. In these studies, different types of animals (mice, rats, rabbits, guinea pigs) were chronically exposed to NT MW at different PD, frequencies, and modulations. According to 40 Soviet studies selected by the Russian National Committee of Non-Ionizing Radiation Protection (RCNIRP) based on standard quality criteria, the unfavorable bioeffects were observed in animals under chronic MW exposures (18). The studied endpoints included histological analysis of tissues, central nervous system, arterial pressure, blood and hormonal studies, immune system, metabolism and enzymatic activity, reproductive system, teratogenic, and genetic effects. RCNIRP concluded that: (1) data on chronic MW exposure should be considered during development of guidelines; (2) application of SAR concept at nonthermal PD less than 100 $\mu W/cm^2$ is questionable; (3) the role of other parameters such as modulation and duration of exposure should be taken into account; (4) development of safety guidelines would greatly benefit from the knowledge of the biophysical mechanisms for the NT MW effects. Based on multiple data on chronic exposure to NT MW, Soviet/Russian safety standards limited exposure by duration and power density PD while the SAR concept was not applied (10).

Significant progress has recently been reached in understanding the biophysical mechanisms for the NT MW bioeffects (2). Emerging evidence suggests that these nonthermal effects occur due to oxidative stress, induced intracellular signaling cascades, transmembrane processes, conformational changes, changes in gene/protein expression, cellular metabolism, transmembrane signal transduction, and cell cycle progression (3).

4.8 COMBINED ASSESSMENT OF NONTHERMAL AND THERMAL EFFECTS UPON CHRONIC EXPOSURES TO MOBILE PHONE

This chapter considered the effects of chronic exposure to nonthermal MW (less than or equal to 2 W/kg) only. However, the French government agency L'Agence Nationales des Fréquences (ANFR) reported that despite non-thermal SAR values less than 2 W/kg are commonly indicated in the manuals from mobile phone, most of them significantly exceed these values if used in contact with head (https://data.anfr.fr/explore/dataset/das-telephonie-mobile/?disjunctive.marque&disjunctive.modele). The ANFR tested hundreds of mobile phones for SAR when the phones operated at maximum power. If phones were measured at the distance of 15 mm from the body, the SAR complied with the ICNIRP guidelines of 2 W/kg. When the same phones were measured at 5 mm from the body, most, but not all phones complied. On the other hand, many phones had SAR levels above the ICNIRP guidelines in contact with the body. These new data complicate assessment of risks from chronic exposures to mobile phone suggesting consideration of the combined nonthermal and thermal effects.

4.8.1 New Technologies, 5G

New mobile communication technologies are implemented every 5–10 years without any test for potential health risks under chronic exposures. As soon as the laboratory and epidemiological studies have collected data on potential health risks of currently used technologies (e.g. brain tumor risks associated with 1G, 2G, and 3G mobile communication), these signals are replaced by newer ones. However, given the dependence of MW effects on multiple parameters, generally established dependence of health effects on duration of chronic exposure, and latency time $\geq$10 years, the obtained data on current and past technologies are almost useless for prediction of health risks for newer developed mobile communication signals. At the moment, 5G communications, which use extremely high frequency MW or millimeter waves (MMW, wavelength 1–10 mm), is planned to be introduced in many countries. It follows from multiple studies that MMW can affect biological systems and human health, both positively and negatively, under specific conditions of exposure at very low intensities below the ICNIRP guidelines (107–109). Various biological and health effects have been described, which commonly depend on multiple physical and physiological parameters. In particular, MMW inhibited repair of DNA damage induced by ionizing radiation under specific conditions of exposure (109). On other hand, MMW exposure at individually selected frequencies has been used in ex-USSR countries for treatment of various diseases since the 1980s. For example, Sit'ko et al. described the frequency of 56.46 GHz, which was found during an ordinary search for therapeutic frequencies based on sensorial reactions of a patient with duodenal ulcer (110). A negative sensation (defined as spastic contraction of musculus quadricepts femoris) was repeatedly observed under applying MMW at this frequency. This sensory reaction allowed tracking the stomach meridian by using a static magnet at 4 mT. Exposure at the frequency

of 56.46 GHz worsened the health condition of the patient. Thus, this exposure was aborted and the patient received treatment at the resonance therapeutic frequency found by typical positive sensations reviewed by Kositsky et al. (https://www.salzburg.gv.at/gesundheit_/Documents/2001_kositsky_et_al._-_ussr_review-2.pdf). After successfully healing the duodenal ulcer at the MMW resonance therapeutic frequency, the negative response of the patient to the frequency of 56.46 GHz disappeared.

To what extent the 5G technology, the Internet of Things, will affect the biota and human health is definitely not known. However, based on the possible fundamental role of MMW in regulation of homeostasis (111,112) and almost complete absence of MMW in the atmosphere due to effective absorption suggesting lack of adaptation to this type of radiation, the health effects of chronic exposures to MMW may be more significant than for any other frequency range.

4.9 CONCLUSION

Chronic exposure to nonthermal microwaves (NT MW) may result in various health effects affecting the central nervous system, fertility, immune functions, and causing/promoting cancer. Taken together, available studies indicate that response to NT MW depends on PD and duration exposure (7). The SAR based ICNIRP safety standards, which have been widely adopted for protection against acute thermal effects of MW, are insufficient to protect the public from chronic exposures to NT MW from mobile communication. New safety standards should commonly be adopted based on data from multiple studies on chronic exposures and mechanisms for nonthermal MW effects (106). It should be anticipated that definite parts of human population, such as children, pregnant women, and hypersensitive persons, which constitute about 1%–10% of the general population in economically developed counties (113), could be especially vulnerable to chronic NT MW exposures. In general, new signals of mobile communication should be tested with chronic exposures before being put into practice.

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