11 FERTILITY, REPRODUCTION AND CHILDHOOD DEVELOPMENT

11.1 Epidemiological studies

Regarding adverse effects of radiofrequency (RF) electromagnetic fields on reproductive health, the previous EHC monograph differentiated between exposure to VDUs (Visual Display Units) and other sources of RF exposures at the workplace (WHO, 1993). In the present EHC monograph, a frequency range from 100 kHz to 300 GHz is considered. Since VDUs operate at frequencies between 15 and 35 kHz, epidemiological studies investigating these devices are not included. However, these findings have already been covered by the most recent EHC monograph on extremely-low frequency fields (WHO, 2007). With regard to other occupational RF exposures, only a limited number of studies were available at that time. These studies had included job groups considered as highly exposed such as military radar workers, technicians, RF welders and physiotherapists. The outcomes of interest comprised sperm quality as well as pregnancy outcomes like congenital malformations or prenatal mortality and the incidence of Down's syndrome in the offspring of exposed fathers. Depending on the respective outcome, either contradictory study results or the lack of data precluded the authors of the previous EHC monograph from drawing firm conclusions. However, there were some suggestions of an increase in adverse pregnancy outcomes among physiotherapists working with shortwave diathermy. Therefore, the EHC authors recommended that some occupational groups, such as physiotherapists and industrial workers should be studied further.

The systematic literature search identified 55 relevant epidemiological studies regarding RF exposures and reproductive health that were published between January 1992 and June 2013. Based on full text evaluation, 17 of these papers were excluded according to our exclusion criteria, leaving 38 studies for the final analysis. Ten of these studies are only summarised in the respective paragraph but not tabulated because of major methodological shortcomings or missing information.

11.1.1 Male fertility

11.1.1.1 Mobile phone use and sperm quality

Between 1992 and 2012, potential effects of mobile phone use on several parameters of sperm quality were investigated in five epidemiological studies. All of these studies are of cross-sectional design and have major methodological weaknesses, making their informative value highly questionable. In general, the cross-sectional design does not allow assessing whether the investigated exposure actually preceded the health outcome. Moreover, selection bias is a major concern because the results can be heavily biased if either the selection or the willingness of subjects to participate was related to both exposure and outcome. This is especially of concern if the response rates are low, e.g. around 50% of all eligible subjects, or if convenience samples are used. Valid conclusions can only be drawn from cross-sectional studies if the participants were selected randomly and can be regarded as a representative sample of the underlying population. Additionally, participation rates have to be reported and the comparability of exposed and unexposed subjects regarding other risk factors should be evaluated. Furthermore, potential confounders have to be considered.

Since all available studies regarding mobile phone use and sperm quality (n=5) provided insufficient information about their participant selection procedures or were based on samples of questionable representativity their results are not tabulated. These studies are described below.

A Hungarian cross-sectional study was conducted in order to investigate the effects of mobile phone exposure in men of fertile ages presenting at a university clinic because of infertility problems (Fejes et al., 2005). A group of 611 men consecutively attending the clinic between 1 November 2002 and 31 March 2004 were examined. Patients with other factors potentially causing subfertility like organic testicular alterations, chronic disease, genital tract infections, hormonal changes or smoking (>10 cigarettes/day) were excluded. Since 240 patients did not meet the inclusion criteria, 371 men (61% of initially examined) contributed to the analyses regarding sperm concentration and percentage of motile sperm. Besides total motility, also the percentages of rapid progressive, slowly progressive and non-progressive motile or immotile sperm were assessed. After 3 weeks, a second sperm sample was taken and for each participant "the better findings" were analysed. The participants were asked about their habitual mobile phone use including duration of possession (in months), duration of standby position closer than 50 cm to the body (in hours) and duration of daily use (in minutes). The correlation between mobile phone use and sperm characteristics was evaluated using Pearson correlation coefficients. Regarding total sperm motility, no correlation with either duration or intensity of mobile phone use was observed. However, there was a negative correlation between the proportion of rapidly progressive sperm and both the duration of mobile phone possession (r=–0.12, p=0.02) and daily use (r=–0.19, p<0.01). The proportion of slowly progressive sperm increased with duration of mobile phone possession and daily use (r=0.12, p=0.02 and r=0.28, p<0.01, respectively). No association was observed between these measures of mobile phone use and other outcome variables including sperm volume, sperm concentration and percentage of immotile sperm. Also, the duration of daily standby within 50 cm was not correlated with any of the sperm characteristics. An additional analysis compared participants with less than 15 minutes of daily mobile phone use (n=195) with those who used their mobile phone more than 60 minutes per day (n=58). A higher proportion of rapid progressive motile sperm was found for low users (48.7 vs. 40.6%, p=0.01). Four other sperm quality parameters did not differ significantly between these groups: sperm concentration, proportion of slowly progressive motile sperm, proportion of non-progressive motile sperm and motility. [It is unclear how the cut-off points for these comparisons were selected and no results for intermediate groups are presented. Throughout the study, the effects of age or other potential confounders like sedentary lifestyle were not taken into account. Moreover, the use of Pearson correlation coefficients requires the assumption of normally distributed data. It is not reported in the paper if this was the case. The correlations may be strongly influenced by outliers.]

The primary aim of a socio-scientific cross-sectional study from Australia was to investigate the influence of image contents on semen quality (Kilgallon & Simmons, 2005). This hypothesis was based on increasing evidence from animal trials that males are able to adjust their ejaculate expenditure according to the risk of sperm competition. As the authors state, it has repeatedly been reported by the artificial insemination industry that increased sperm counts can be obtained from male animals allowed to view conspecific mating activity prior to ejaculate delivery. Likewise, in the human fertility industry, viewing sexually explicit images or videos prior to ejaculation has been reported to increase the total number of sperm and the percentage of motile sperm. As potential confounders for this objective, the authors also collected information on mobile phone use and a wide variety of other lifestyle factors such as smoking and alcohol consumption. The study included 52 men between 18 and 35 years of age who were recruited from the campus of the University of Western Australia. Sperm quality of men who carried their mobile phone in their hip pocket or on their belt was compared with the sperm quality of men who carried their mobile phone elsewhere on the body. The analysis revealed that men who carried a mobile phone in their hip pocket or on their belt had a lower mean percentage of motile sperm than men belonging to the comparison group (49.3 +/- 8.2% vs. 55.4 +/- 7.4%, p<0.0001). A similar result was observed regarding sperm concentration. Men who carried a mobile phone in their hip pocket or on their belt had a lower mean number of sperm cells per ml than controls (65.6 +/- 1.2 vs. 75.7 +/- 1.3 million/ml, p=0.0013). The generalised linear models were adjusted for several factors including age, height, frequency of ejaculation, cigarette smoking, alcohol consumption, caffeine intake, self-rated stress and occupation. [The selection procedure for recruiting participants is insufficiently described in the paper. In addition, numbers of exposed and unexposed individuals are missing and no further details about mobile phone habits are given, e.g. years of use or minutes of daily use with and without hands-free kits.]

Another cross-sectional study was conducted among men attending two outpatient infertility clinics in Poland from June 2004 to May 2006 (Wdowiak, Wdowiak & Wiktor, 2007). After exclusion of patients with diseases of the reproductive organs, with hormonal disorders or pathological body mass index values, the study sample consisted of 304 men. All participants answered a questionnaire concerning place of residence, occupation and lifestyle factors including cigarette smoking and mobile phone use. Sperm samples were analysed with regard to standard quality parameters including volume, concentration, motility and morphology. The participants were divided into three exposure groups: 99 patients without mobile phone use, 157 patients who had been using mobile phones sporadically for 1 to 2 years and 48 men with regular mobile phone use for more than 2 years. Comparisons regarding age, smoking habits, place of residence and occupation revealed no statistically significant differences between the 3 exposure groups (all p-values >0.05). In the unadjusted analyses, sperm motility and sperm morphology differed significantly between all user groups (p-values <0.001): Among the non-users, 65.7% had at least 50% of rapidly or slowly progressive sperm. Among sporadic mobile phone users, this percentage was 51.6%, among regular users it was 35.4%. Also, a higher proportion of non-users had more than 30% sperm cells of normal morphology (55.6%) compared to sporadic users (27.4%) and regular users (16.7%). In contrast, the sperm concentration did not differ significantly between the three study groups. [It is unclear how the participants were selected among men attending the outpatient clinics (randomly, consecutively?) and there was no adjustment of potential confounders in the analyses. Also, the number of excluded patients, participation rates and the age distribution are not presented. No details about self-reported mobile phone use were collected, e.g. frequency or duration of calls or use of hands-free devices. Moreover, the definitions of "sporadic" and "regular" mobile phone use are not described. It is also unclear if the observed differences were statistically significant (only overall p-values given).]

Another clinic-based cross-sectional study comprised 361 men attending an infertility clinic in Cleveland, Ohio, from September 2004 to October 2005 (Agarwal et al., 2008). The mean age of the participants was 31.81 +/- 6.12 years. Subjects with a history of smoking, chewing tobacco, alcohol consumption, orchitis, varicocele, tuberculosis, diabetes mellitus or hypertension were excluded. The same applied to patients who had suffered from viral or bacterial infection during the past 4 weeks, presented with a history of cardiac, neural or nephrotic disease or had a family history of any genetic disease. The sperm analysis comprised eight parameters: volume, liquefaction time, pH, viscosity, sperm count, motility, viability and percentage of spermatozoa with normal morphology. According to their daily talking time on a mobile phone, the participants were divided into four exposure groups: no mobile phone use (n=40), <2 h/day (n=107), 2 to 4 h/day (n=100) and >4 h/day (n=114). The technicians analysing the semen samples were blinded with regard to the participants' mobile phone use. The mean values of the eight sperm parameters were compared among the four exposure groups by a multivariate analysis of covariance (only adjusted for age). The effect of age on the outcome variables was evaluated but was not found to be statistically significant. For four semen parameters a continuous decrease with increasing duration of daily mobile phone use was observed: sperm count, motility, viability and normal morphology. [It is not clear from the paper if these differences between the exposure groups were statistically significant. Use of mobile phones for >4h/day is quite rare, especially for early years 2004-2005, and it is unclear why so many persons in this study reported such a heavy use. Residual confounding is of concern because only the effect of age was considered in the analysis but no other potential confounders were evaluated, such as distress, physical activity, smoking, or occupational exposures. Moreover, it is unclear if the participants were selected randomly.]

In a cross-sectional study from Austria, 2110 men consecutively attending an infertility clinic between 1993 and October 2007 were assessed (Gutschi et al., 2011). Patients with a history of smoking or alcohol consumption were excluded; the same applied to men suffering from a systemic disease, orchitis or varicocele. After dividing all participants into 991 mobile phone users and 1119 non-users, a multivariate analysis of variance was performed. Statistically significant differences were observed for sperm motility and one out of two parameters related to sperm morphology: The proportion of rapidly progressive spermatozoa was found to be lower among mobile phone users compared to non-users (23.9 vs. 25.1%, p<0.01) and the proportion of pathological spermatozoa was indicated as 68% among mobile phone users compared to 58% among non-users (p<0.0001). Regarding sperm count, no statistically significant difference existed between the two groups. [A limitation of this study is the crude exposure classification without information about duration or intensity of mobile phone use. Moreover, it is not stated in the paper if the mean age of the participants in both groups was comparable and if age was taken into account in the statistical analysis. Also, no other potential confounding factors were considered and the participation rate is unknown.]

11.1.1.2 Far-field RF exposure and sperm quality or male fertility

In a cross-sectional study conducted by the U.S. Army and the National Institute for Occupational Safety and Health (NIOSH), semen parameters of artillery soldiers potentially exposed to microwaves were assessed (Weyandt et al., 1996). The study was originally targeted on adverse reproductive effects of exposure to airborne lead aerosols among artillery soldiers. From the questionnaire data it turned out that many soldiers in the initial control group had potentially experienced microwave exposure emitted from radar equipment. Therefore, a third group of soldiers without potential lead or microwave exposures, but with similar environmental conditions, was selected as a comparison group. Assessments included exposures to lead, microwaves, and other physical or chemical interactions that could potentially interfere with sperm production or maturation. All exposure data were self-reported. The final analysis regarding microwave exposure was based on 20 radar equipment operators and 31 control individuals. Exposed and control group differed in terms of ethnicity (60% Caucasians in the exposed group, 71% in the control group) and with regard to self-perceived fertility problems (10% of exposed). Potential confounders like age, race, self-perceived fertility problems and duration of abstinence were taken into account using analysis of covariance. Fifteen measures of semen quality were a priori defined as primary outcome variables (see table). Statistically significant differences between radar equipment operators and control soldiers were observed for two of these parameters: sperm concentration (13 vs. 35 million/ml, p=0.0085) and total sperm count per ejaculate (33 vs. 78 million, p=0.027). After authors had applied a Bonferroni adjustment for multiple comparisons, none of these comparisons achieved the stricter level of statistical significance (alpha=0.0033). [Limitations of this study include the crude, self-reported exposure estimate, the small sample size and the disregard of the participants' medical history. It is unclear if potential influences of tobacco or alcohol consumption were considered in the analyses. Moreover, the participation rate and the age of the participants are not reported.]

As a follow-up to this cross-sectional study the same authors subsequently examined a larger group of soldiers with potential exposures to microwaves (Schrader et al., 1998). Participants were selected among soldiers stationed at Fort Hood, Texas. The exposure groups were defined according to the job classification and self-reported exposure information: 33 men were exposed to radar as part of their duty assignment in the Signal Corps while 103 unexposed soldiers served as the control group. Sperm samples were collected during one week in July 1993. For statistical analysis, the primary study variables were defined as: sperm concentration, sperm/ejaculate, semen volume, percentage of spermatozoa with normal morphology, percentage of motile sperm, percentage of viable sperm (both vital stain and hypoosmotic swelling), curvilinear velocity, straight-line velocity, linearity of motion as well as sperm head length, width, area and perimeter. If confounding factors like age, race, smoking, alcohol consumption or duration of sexual abstinence were identified as statistically significant predictors, they were included in the analysis of covariance models. The comparisons between radar operators and unexposed soldiers revealed no statistically significant differences with regard to any of the primary parameters of sperm quality. As explanation for the failure to confirm their previous findings the authors suggested that these Signal Corps soldiers were exposed to much lower levels of radar emissions than the previous group of Army Intelligence soldiers. [Strengths of this study are a somewhat larger sample size and the consideration of potential confounding factors including alcohol or tobacco consumption. However, the exposure assessment was still based on self-reports and did not include important characteristics like exposure duration, power levels or proximity of radar equipment at the workplace. Also, the actual number of soldiers initially invited or attending the study is unknown.]

Another cross-sectional study conducted by the National Institute for Occupational Safety and Health (NIOSH) in 1988 aimed to determine whether men who worked with RF sealers or dielectric heaters experienced adverse reproductive effects (Grajewski et al., 2000). The exposed group was recruited among employees of 4 water mattress manufacturers in Maryland (USA) where most personnel were considered to be exposed to RF heaters. A comparison group was selected from workers at a nearby communications equipment facility, e.g. inspectors, technicians and assemblers in quality assurance and fiber-optic assembly departments with minimal exposure to physical and chemical agents. The participants were required to have worked full-time for at least 3 months at the companies. Data on work history and medical conditions as well as on demographic, lifestyle and reproductive health was collected by questionnaire. Subjects with diseases or exposure histories possibly affecting the relationship between RF exposure and reproductive outcomes were excluded. For each water mattress company, the mean RF exposure was calculated based on measurements. Geometric means of the time-weighted averages (TWA) of the E-fields ranged from 35 to 95 V/m; for the H-field the means varied between 0.14 and 0.25 A/m. The arithmetic means of the TWA induced foot currents ranged from 70 to 130 mA. The statistical analyses comprised 33 variables of semen quality. Potential confounders like solvent exposure, tobacco and alcohol consumption were considered using least squares linear regression and multivariate analysis of variance. After several exclusions, the statistical analyses were based on 12 RF-exposed and 34 unexposed participants (17% and 27% of originally eligible, respectively). Exposed RF heater operators were primarily Pakistani and black (92%), whereas 85% of the comparison group were white. The analyses revealed no significant differences in sperm concentration, sperm count, semen volume, or osmolality between exposed and unexposed groups. Moreover, the participants were not found to differ with regard to mean sperm motility or sperm velocity variables. However, samples from exposed men showed a significantly higher percentage of viability (75 vs. 65.9%, $p=0.01$). Regarding sperm morphology, a slightly higher proportion of double-headed sperm was observed in the unexposed group ($p=0.07$). [The authors themselves state that withdrawal of the largest water mattress company resulted in insufficient statistical power for some of the analyses despite a 63% response rate among RF heater operators at the other companies. A strength of this study is the objective exposure measurements performed at the companies, even if not always available on an individual level. Some potential confounders were considered in the analysis but residual confounding is still of concern, particularly regarding the different ethnic composition of the two groups.]

A series of studies were performed among employees of the Royal Norwegian Navy in response to concerns about health effects of radiofrequency fields, including reproductive effects. In the 1990s, congenital anomalies were reported among children whose fathers worked aboard a missile torpedo boat, the KNM Kvikk, which prompted the Norwegian Navy to commission research into the work environment and health among their personnel. These studies were conducted by the University of Bergen.

A cross-sectional study among male employees of the Royal Norwegian Navy evaluated self-reported information about work close to RF emitting equipment, one-year infertility, number of children and sex ratio of the offspring (Baste, Riise & Moen, 2008). The study population comprised all military personnel employed in September 2002 (n=2497) and former employees who had worked for the Royal Norwegian Navy for at least 16 months during the period from 1950 to September 2002 (n=15,259). Response rates were 62% (n=1550) among current employees and 63% among former employees (n=9666). After exclusion of men who had either been employed for less than 1 year or had only worked as a civilian in the Navy, a total of 10'497 men were included (59% of originally eligible). The study questionnaire contained 3 options of exposure to RF fields: work closer than 10 m to RF aerials, closer than 3 m to communication equipment or closer than 5 m to radar. Potential RF exposures outside the Navy were also taken into account. Moreover, exposures to organic solvents, lead, paint, welding or torch-cutting were considered as potential confounders. The exposure categories were labelled 'not at all', 'low', 'some', 'high' and 'very high'. Infertility was determined by the question: 'Have you and your partner ever tried to become pregnant without success for more than 1 year?'. In addition, the participants stated whether they had biological children and, if yes, how many and of which gender. After excluding participants with invalid answers and those with doubtful information concerning fertility, the final analyses were based on about 8000 men. Smoking habits, alcohol consumption and exposure to organic solvents, welding or lead were included in logistic or linear regression models. The main analyses were stratified by age groups of <29, 30 to 39, 40 to 49 and >/=50 years. In total, 22% of the participants reported that they had been working closer than 10 m from high-frequency aerials to a 'high' or 'very high' degree; 19% had worked closer than 3 m from communication equipment and 21% had worked closer than 5 m from radar. Infertility was reported by a total of 1231 participants (14.7%). The adjusted analyses revealed significantly higher odds ratios of infertility in men who reported having been exposed to one of the 3 RF sources to a 'high' or 'very high' degree. Linear associations were observed among all age groups except for those below 29 years of age and exposed to communication equipment. Significant linear associations were also shown between self-reported RF exposure and the prevalence of involuntary childlessness. However, RF exposure was not significantly associated with whether the participants had biological children or with the mean number of children. [The lack of objective data regarding both RF exposure and outcomes may have led to recall bias potentially causing an overestimation of the true association. In addition, duty on board of ships may have confounded the association because this type of work is also related with long journeys away from home. Potential infertility problems of the female partner were not evaluated. Moreover, the point in time and the duration of RF exposure is unknown and it is unclear how many individuals were exposed to more than one of the RF emitting sources.]

Another analysis within this cross-sectional study was restricted to male military employees who served in the Royal Norwegian Navy at the end of 2002 and had completed their compulsory military service (Møllerløkken & Moen, 2008). Infertility was evaluated by the previously applied question: 'Have you and your partner ever tried to become pregnant without success for more than 1 year?'. In addition, information on adverse pregnancy outcomes was collected. Participants were also asked about the work categories they had passed through during their employment. A list of 18 work categories was pre-defined and a group of experts classified them according to potential electromagnetic field exposures. In total, 1487 men were included in the analyses (response rate: 63%). Men working in the job categories 'tele/communication' and 'radar/sonar' were classified as having 'high' or 'very high' RF exposures by both the experts and the participants themselves. In these two groups, statistically significant more men reported infertility than in the unexposed control group. A logistic regression analysis adjusted for age, ever smoked, military education, and physical exercise at work resulted in infertility risks of 1.72 (95% CI 1.04–2.85) for the 'tele/communication' group and 2.28 (95% CI 1.27–4.09) for the 'radar/sonar' group. For the 'electronics' group, no significant increase in infertility was observed (odds ratio not presented). Moreover, the number of biological children and paternal age at birth of the first child did not differ between exposed and unexposed job groups. [The exposure assessment was not primarily restricted to RF fields. Additionally, the definition of infertility is very crude and may have produced biased results.]

Studies with insufficient information for assessment of inclusion criteria

Two studies did not provide enough information to allow assessment of the study quality or whether inclusion criteria were fulfilled. These are only briefly described below, and results are not tabulated.

In a cross-sectional study from Northern China, 289 male soldiers working at radar stations were compared to 148 male soldiers in a field army, considered to be unexposed to RF fields (Yan et al., 2007b). Microwave exposure was measured at the workplace and information on demography, life style and health outcomes was collected by questionnaires. Analyses were made with chi-square test, and were not adjusted for confounders. The authors reported higher rates of sexual dysfunction among exposed soldiers (43.6% vs. 24.4%) and lower natural pregnancy rates within one year of marriage (53.5% vs. 81.1%). [The procedure used to recruit study subjects was not described, and it is impossible to assess whether the two studied groups constitute representative samples, or which the underlying population is. Moreover, there was no adjustment for potential confounders and no risk estimates were calculated. Additionally, the definition of "sexual dysfunction" was not reported.]

Another cross-sectional study from Northern China included three groups of male soldiers with different levels of measured radar exposure (Ding et al., 2004). High levels of exposure were found among 103 soldiers, 198 soldiers were exposed to low levels and 197 soldiers had no occupational RF exposure. Analyses were made with chi-square test, with no control of potential confounders. The analyses revealed differences between these groups regarding sperm dysmorphia and sub-clinical sperm injury without adverse reproductive effects. A dose-response relationship with increasing sperm dysmorphia at higher levels of exposure was reported. [The size of the underlying population is unclear and neither recruitment procedures nor participation rates were reported. Lack of adjustment for potential confounders is another limitation.]

Table 11.1.1. Epidemiological studies on occupational exposure to RF far-field sources and sperm quality or male fertility

Specific outcome	Country Time period	Study design, sample size, age, response rate	Exposure details, assessment, categories	No. of exposed and unexposed subjects	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
Sperm quality	USA 1990	Cross-sectional; male artillery soldiers, 20 radar operators, 31 controls; mean age and participation rate not given	Microwave exposure from radar equipment in Army Intelligence, self-reported Controls Radar operators Controls Radar operators	 31 20 31 20	Adjusted mean of sperm concentration (p=0.0085): 35 million ml^{-1} 13 million ml^{-1} Adjusted mean of total sperm count (p=0.027): 78 million 33 million No differences for percentages of normal forms, of motile sperm, of cells stained or cells swollen; curvilinear velocity; length, width, area, perimeter and width/length ratio of sperm cell head; percentage of hamster egg cells penetrated	Selection procedure and participation rate unknown; no details of microwave exposure reported; observed differences lost statistical significance after Bonferroni adjustment for multiple comparisons (type 1 error (alpha)=0.0033)	Weyandt et al. (1996)
Sperm quality	USA 1993	Cross-sectional; male soldiers at Ford Hood, Texas; 33 radar equipment operators, 103 controls, participation rate not given	Microwave exposure from radar equipment in Signal Corps, self-reported Controls Radar operators	 103 33	No differences for 14 semen parameters: sperm concentration, total sperm count, semen volume, percentage of spermatozoa with normal morphology, percentage of motile sperm, percentage of viable sperm (both vital stain and hypoosmotic swelling), curvilinear velocity, straight-line velocity, linearity of motion, sperm head length, width, area and perimeter	Selection procedure and participation rate unknown; no details of microwave exposure reported	Schrader et al. (1998)
Sperm quality	USA 1988	Cross-sectional; male RF heater operators, mean age: 32.3 +/- 7.5 years; control workers, mean age: 34.5 +/- 9.3 years; participation rates: 63% of exposed, 34% of unexposed	Work with RF sealers and dielectric heaters (12 to 57 MHz); mean E-field: 35 to 95 V m^{-1}; mean H-field: 0.14 to 0.25 A m^{-1}; induced foot currents: 70 to 130 mA Control workers RF heater operators	 34 12	No differences for sperm count, sperm concentration and 30 other parameters of sperm motility, velocity and morphology Percentage of viable sperm (by stain exclusion, p=0.01): 75 +/- 0.6% 65.9 +/- 2.3%	Small sample size	Grajewski et al. (2000)

Table 11.1.1. Epidemiological studies on occupational exposure to RF far-field sources and sperm quality or male fertility

Specific outcome	Country Time period	Study design, sample size, age, response rate	Exposure details, assessment, categories	No. of exposed and unexposed subjects	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
Male infertility, self-reported	Norway 1950-2002	Cross-sectional, current (n=2497) and former (n=15'259) male employees of the Norwegian Navy; 10'497 respondents; participation rate: 59%, mean age: 49 years	Work closer than 10 m from RF aerials, self-reported: Not at all To a low degree To some degree To a high degree To a very high degree Age-stratified analyses: Work closer than 10 m from RF aerials, closer than 3 m from communication equipment or closer than 5 m from radar	 2341 2684 2373 1237 903	Self-reported infertility (all age groups combined): 1 1.39 (1.15-1.68) 1.52 (1.25-1.84) 1.93 (1.55-2.40) 1.86 (1.46-2.37) Linear trends of infertility with increasing RF exposure in all 4 age groups and among all 3 exposure sources (p<0.05), except the subgroup of men <29 years exposed to communication equipment No differences regarding numbers of biological children among all exposure groups	Self-reported exposure and outcome; exposure details unknown. Logistic regression analyses, adjusted for smoking habits, alcohol consumption, organic solvents or paint, welding, torch-cutting or working with hull and lead	Baste et al. (2008)
Male infertility, self-reported	Norway 2002	Cross-sectional, current male employees of the Norwegian Navy; 1487 men, mean age: 36 years, age range: 20 to 62 years; response rate: 63%	Work categories, expert judgement: Unexposed Tele/communication group Radar/sonar group	No. reporting infertility: 106 (8.7% of this category) 24 (14.8%) 17 (17.5%)	Self-reported infertility: 1 1.72 (1.04–2.85) 2.28 (1.27–4.09) No differences regarding numbers of biological children between the exposure groups	Exposure details unknown. Logistic regression analyses adjusted for age, ever smoked, military education and physical exercise at work	Møllerløkken & Moen (2008)

11.1.2 Pregnancy outcomes

A variety of pregnancy outcomes have been investigated with regard to RF exposure. Some studies were conducted among female physiotherapists exposed to diathermy devices during pregnancy, whereas other analyses were focused on paternal occupational RF exposure, especially among male employees of the Royal Norwegian Navy.

11.1.2.1 Maternal near-field exposure and pregnancy outcomes

A nested case-control study within a cross-sectional survey was conducted in order to assess whether the occupational use of shortwave (27.12 MHz) or microwave (915 or 2450 MHz) diathermy equipment was associated with the risk of miscarriage among physical therapists (Ouellet-Hellstrom & Stewart, 1993). The survey population consisted of 42 403 current and former members of the American Physical Therapy Association. In 1989, they were asked to answer a postal questionnaire on work history and use of various therapeutic treatment modalities 6 months prior to the pregnancy and during the first trimester of pregnancy. Treatment modalities included infrared radiation, whirlpool, electrical stimulation, ultrasound, microwave diathermy, shortwave diathermy and the use of chemicals. The therapists also answered questions on infertility, use of oral contraceptives, smoking during pregnancy and pregnancy outcomes. The overall response rate was 55.4% based on 19 114 complete questionnaires out of 34 497 that were delivered to the appropriate households. All analyses were restricted to respondents who reported at least one pregnancy or having tried to become pregnant (n=11 598, 60.7%). Of these, 6684 therapists (57.6%) had ever used microwave or shortwave diathermy at some time during employment and were considered for the case-control study. Pregnancies were considered "exposed" only if the therapist had been working 6 months prior to and during the first trimester of the pregnancy and if she reported having used diathermy in that specific job. Among a total of 14 989 pregnancies, 1791 miscarriages and 12 949 potential control pregnancies were identified. One control pregnancy was matched to each of the 1753 case pregnancies with complete information. Matching variables were mother's age at the time of conception and the number of years elapsed between conception and the date the questionnaire was completed. A mother could contribute more than one pregnancy as a case and could be used as a control for another case pregnancy. Conditional logistic regression models were adjusted for mother's age at conception, years elapsed between conception and interview, number of prior fetal losses, genitourinary conditions, use of transcutaneous nerve stimulation and use of a whirlpool for microwave exposure. Other potential confounders like the use of electric blankets, water beds or heated mattress pads were not found to be significantly associated with the risk of miscarriage. Having used microwave diathermy was reported for 11.9% (n=209) of 1753 case pregnancies and 9.5% (n=167) of 1753 control pregnancies. The fully adjusted conditional regression model revealed a statistically significant association between occupational exposure to microwave diathermy and the risk of miscarriage (OR: 1.34, 95% CI 1.04-1.59). Based on crude analyses, an exposure-response relationship with increasing number of exposures per month was observed ($p<0.005$). Restricting the analysis to mothers with no prior fetal loss resulted in a non-significantly increased odds ratio of 1.22 (95% CI 0.92-1.63). Use of shortwave diathermy was reported by 28.5% (n=499) of case mothers and 26.9% (n=472) of control mothers. Based on an unconditional regression analysis, no association between shortwave diathermy exposure and the risk of miscarriage was observed (OR: 1.07, 95% CI 0.91-1.24). [Weaknesses of this study include the low participation rate of the underlying population and the lack of objective information on exposure and outcome. Therefore, recall bias is of concern. Another uncertainty arises from the fact that over 78% of the therapists who reported using microwave diathermy and 64% among therapists using shortwave diathermy also used at least four other treatment modalities. Since these other modalities included electrical stimulation and chemicals they could also constitute risk factors for miscarriages. Moreover, the actual level of occupational RF exposure among physical therapists caused by setting up the microwave treatment for a patient is unclear. However, the differential findings regarding microwave and shortwave diathermy might indicate a real association.]

A cross-sectional study was conducted among female physiotherapists in Switzerland (Guberan et al., 1994). The aim of this survey was to reassess a deficit of male births that had been previously observed in a Danish study (Larsen, Olsen & Svane, 1991). A self-administered questionnaire was mailed to all 2846 female members of the Swiss Federation of Physiotherapists in November 1992. The questions included gender and birth weight of all children, whether born alive or dead, but excluding abortions. Additionally, the participants stated whether they had been exposed to shortwave or microwave diathermy during the first month of pregnancy. Further information included the duration of exposure, the typical distance from the diathermy equipment and the type of electrodes. The questionnaire was returned by 2263 physiotherapists (79.5%), of which 1030 had one or more children. The analyses comprised 1781 pregnancies and the gender ratio was calculated as number of males per number of females x 100. Measurements of one shortwave diathermy device (27.12 MHz, 600 W peak power) resulted in power density values ranging from below 1 W/m^2 for a circuplode at a distance of 1 m up to

2000 W/m^2 for a plate electrode at a distance of 30 cm. The gender ratio among the offspring of shortwave exposed physiotherapists was 107 (95% CI 89-127) and 101 (95% CI 90-113) for unexposed women. Regarding microwave diathermy, a gender ratio of 85 (95% CI 61-118) was estimated for exposed physiotherapists and of 106 (95% CI 96-117) for unexposed. These differences were statistically nonsignificant and all confidence intervals included the expected population value of 105 that had been consistently observed in the general Swiss population during the last century. Furthermore, the gender ratio was neither related to the type of electrode nor to the duration of exposure per week. There was also no association between maternal shortwave exposure and the prevalence of low birth weight among the offspring (≤2500 g). [In this study, the exposure assessment was crude and based on self-reports. Potential confounders like maternal age were not taken into account and no multivariate analyses were conducted.]

Associations between the use of shortwave diathermy and pregnancy outcomes were further investigated in a case-control study from Israel (Lerman, Jacubovich & Green, 2001). Female members of the Union of Israeli Physiotherapists who had ever been pregnant were asked to complete a postal questionnaire and underwent telephone interviews about their reproductive history and the use of shortwave diathermy, ultrasound and heavy lifting during pregnancy. Four types of adverse pregnancy outcomes were assessed: spontaneous abortion (<28th week of pregnancy), congenital malformation, premature birth (<36th week of pregnancy) and low birth weight (<2500 g). A mother could contribute more than one pregnancy as a case, but normal pregnancies of mothers who had other pregnancies that ended in an abnormal delivery were excluded. The duration of exposure to shortwaves and ultrasound per week was estimated on a 3-level scale: no exposure, <10 hours/week, >10 hours/week. Several conditions during pregnancy were considered as potential confounders including febrile diseases, alcohol consumption, drug use, smoking, maternal age, previous abortions and number of pregnancies. The final study population consisted of 434 women contributing 933 pregnancies. Among the 300 “case pregnancies”, 175 were spontaneous abortions, 45 were children with congenital malformations, 47 were premature births and 33 children with low birth weight. The remaining 633 pregnancies of women without adverse reproductive outcome served as the control group. With regard to shortwave exposure, the analyses revealed no associations with spontaneous abortions and prematurity. In the univariate analysis, a significant association was found for congenital malformations (OR: 2.24, 95% CI 1.27-4.83) that decreased and lost statistical significance after controlling for potential confounders (OR: 1.33, 95% CI 0.68-2.75). In contrast, the risk of having a child with low birth weight was significantly elevated among exposed women in the univariate analysis (OR: 2.99, 95% CI 1.32-6.79) as well as the multivariate analysis (OR: 2.75, 95% CI 1.07-7.04). The univariate results indicated an exposure-response relationship for both outcomes. [The authors controlled for several important potential confounders in the multivariate analyses. However, the demographic characteristics of cases and controls are not presented and the response rate is unknown. Another limitation is the self-reported information on both exposure and pregnancy outcome.]

Studies with insufficient information for assessment of inclusion criteria

The three studies described below did not provide sufficient information about procedures used for selection of individuals for participation in the studies, and their results are therefore not included in the tables.

Two hospital-based case-control studies carried out by a research group from Beijing evaluated adverse effects of maternal mobile phone use on different pregnancy outcomes. The first study comprised 200 women with clinically diagnosed early spontaneous abortions identified during the period 2004-2006. and 200 age-matched control women with normal new-borns from the same hospital (Liu et al., 2007). All participants answered questions regarding a wide variety of individual and environmental risk factors including several sources of RF and ELF electromagnetic fields. Self-reported mobile phone use during pregnancy was dichotomized in the categories "often" and "not often". Frequent mobile phone use was defined as using a mobile phone at least once per week and for a minimum of 30 minutes each day the phone was used. Multivariate logistic regression analyses adjusted for potential confounders resulted in several statistically significant associations between environmental exposures and the risk of early spontaneous abortions. For frequent maternal mobile phone use, an odds ratio of 4.63 (95% CI 1.63-13.17) was estimated. [A strength of this study is the consideration of potential confounders, although a weakness is that the confounders included in the model are not specified. Also, some other important information is missing in the paper, e.g. recruitment procedure for cases and controls, participation rates, and the numbers of exposed and unexposed subjects. The wide confidence interval of the risk estimate indicates a rather small number of exposed or unexposed participants. Another limitation arises from the fact that recall bias could have distorted the participants' answers and could have led to an overestimation of the association.]

In the second study from Beijing, 138 pregnant women with clinically diagnosed embryo growth ceasing, identified during 2003-2005, were compared to 138 age-matched control women without this diagnosis (Han et al., 2010). Among several other exposures, the participants reported their use of mobile phones and other electronic devices during the first trimester of pregnancy. Frequent use was defined as using a mobile phone at least once per week and for a minimum of 30 minutes each day the phone was used. Conditional logistic regression analysis was adjusted for potential confounders and revealed an highly increased risk of embryo growth ceasing among mothers who reported a frequent use of mobile phones compared to mothers with less frequent use (OR: 6.02, 95% CI 1.92-18.91, based on 126 exposed cases and 93 exposed controls, while only 12 cases and 45 controls were unexposed). [This study suffers from the same limitations as the previous one. In addition, it is unclear if there was some overlap between the two studies since they took place at the same hospital and during a similar time period].

Another case-control study from China took place at a paediatric Rehabilitation Centre and comprised 202 children with cerebral palsy and 404 control children aged 1 to 12 years (Xu et al., 2010). The control children did not suffer from cerebral palsy or any other nervous system disease. However, the selection procedure is unclear in the paper. Information about maternal environmental exposures during pregnancy was collected by questionnaires. Among the exposures of interest were air pollution, dietary factors, use of household chemicals and electronic devices including mobile phones. The authors differentiated between GSM phones (referred to as “high radiation”) and CDMA or other phones (indicated as “low radiation”). A multivariate analysis resulted in an association between maternal use of GSM phones during pregnancy and the risk of cerebral palsy in the offspring (OR: 2.20, 95%-CI 1.54-3.15). Significant associations were also observed for air pollution and watching TV. [In this paper, no information about the amount of mobile phone use was reported and it is unclear if the study participants actually knew the specific system of their mobile phone. In addition, the regression model was not adjusted for important risk factors like gestational age, birth weight and maternal age. It is unclear if persons were randomly selected, or if a source population was defined. Therefore, the study is not included in the table.]

Table 11.1.2. Epidemiological studies on maternal exposure to diathermy or mobile phones and pregnancy outcomes

Specific outcome	Country Time period	Study design, sample size, age, response rate	Exposure details and assessment	Exposure categories	Number of exposed and unexposed subjects	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
Spontaneous abortion	USA 1989	Nested case-control study; female physical therapists; 1753 cases and 1753 matched controls 30–49 years (77.4% of ever exposed)	Maternal use of diathermy 6 months prior to and during the first trimester of pregnancy, self-reported Microwave diathermy: 915 or 2450 MHz 0.8–12.0 W/m^2	Microwave diathermy: Exposed vs. unexposed	No exact numbers given for adjusted analyses	Spontaneous abortion (adjusted): Total sample: 1.34 (1.04-1.59) No prior fetal loss: 1.22 (0.92-1.63)	Low coverage of source population; self-reported information on exposure and outcome.	Ouellet-Hellstrom & Stewart (1993)
			Shortwave diathermy: 27.12 MHz 0.4–165.8 W/m^2	Shortwave diathermy: Unexposed	1158 cases, 1176 controls	Spontaneous abortion (unadjusted): 1		
				Exposed	499 cases, 472 controls	1.07 (0.91-1.24)		
Gender ratio and low birth weight	Switzerland 1992-1993	Cross sectional; 2263 female physiotherapists, of which 1030 had one or more children; 1781 pregnancies; response rate: 79.5% mean age not given	Maternal exposure to microwave diathermy during the first month of pregnancy, self-reported; Maternal exposure to shortwave diathermy; 27.12 MHz, 600 W peak power; <1–2000 W/m^2	Microwave diathermy Unexposed Exposed Shortwave diathermy Unexposed Exposed Shortwave diathermy Unexposed Exposed	794 boys, 748 girls 67 boys, 79 girls 641 boys, 632 girls 262 boys, 246 girls 25 boys, 36 girls 11 boys, 14 girls	Gender ratio: 106 (96-117) 85 (61-118) Gender ratio: 101 (90-113) 107 (89-127) Low birth weight: 4.3% of boys, 6.1% of girls 4.4% of boys, 5.9% of girls	Potential confounders like maternal age not considered.	Guberan et al. (1994)
Congenital malformations, low birth weight, spontaneous abortion, prematurity	Israel Not given	Case-control; 434 female physiotherapists; 300 cases, 630 control pregnancies, response rate and mean age not given	Maternal exposure to shortwave diathermy during pregnancy; self-reported	Exposed vs. unexposed	Exposed: 28 cases, 310 controls Number of exposed cases not given for multivariate analysis Exposed: 23 cases, 310 controls, Number of exposed cases not given for multivariate analysis	Congenital malformations: univariate: 2.24 (1.27-4.83) multivariate: 1.33 (0.68-2.75) Low birth weight: univariate: 2.99 (1.32-6.79) multivariate: 2.75 (1.07-7.04)	Self-reported information on exposure and outcome; response rate and mean age unknown.	Lerman et al. (2001)

Table 11.1.2. Epidemiological studies on maternal exposure to diathermy or mobile phones and pregnancy outcomes

Specific outcome	Country Time period	Study design, sample size, age, response rate	Exposure details and assessment	Exposure categories	Number of exposed and unexposed subjects	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
					Exposed: 80 cases, 310 controls	Spontaneous abortion: univariate: 0.90 (0.64-1.27)		
					Exposed: 21 cases, 310 controls	Prematurity: univariate: 0.87 (0.48-1.59)		

[a]RF=Radiofrequency, OR=Odds ratio, CI=Confidence interval

11.1.2.2 Parental far-field RF exposure and pregnancy outcomes

In a register-based cohort study from Norway, the risk of adverse pregnancy outcomes was investigated among the offspring of men who were occupationally exposed to RF fields (Mjoen et al., 2006). Regarding birth defects, 24 categories were defined based on data of the country-wide Medical Birth Registry. Additional outcome variables comprised preterm delivery, low birth weight, perinatal mortality including stillbirths and the proportion of boys among the offspring. Information about paternal occupation was derived from two general population censuses (1980 and 1990) and was linked to the Medical Birth Registry by national identification numbers. Between 1976 and 1995 about 1.1 million births were registered. Complete information on paternal identity and occupational exposure was available for 541 593 births (approximately 49%). The levels of occupational RF exposure were classified by an expert panel based on job titles as “probably not exposed”, “possibly exposed” or “probably exposed”. Associations between paternal RF exposure and 33 adverse reproductive outcomes were analysed by logistic regression after adjustment for year and place of birth as well as father's level of education. Approximately 5% of the births were considered as “probably exposed” (n=24 885). Among them, a slightly increased odds ratio for preterm delivery of 1.08 (95% CI 1.03-1.15) was estimated. No risk increase was observed for any of the 24 specific categories or for the pooled analysis comprising all types of birth defects. The risk of total cleft lip was significantly decreased among the offspring of “probably exposed” fathers (OR: 0.63, 95% CI 0.41-0.97). Children with “possibly exposed” fathers had a statistically significant increased risk of “other birth defects” (OR: 2.40, 95% CI 1.22-4.70). No significant differences were observed regarding low birth weight, perinatal mortality and sex ratio. [The crude exposure classification was based on job titles without information about other occupational exposures. Non-differential misclassification may have biased the risk estimates towards the null. Paternal occupation was available only for about 50% of the original study population.]

An early analysis of a large cross-sectional study among male and female employees of the Royal Norwegian Navy evaluated the risk of having stillborn children or children with congenital anomalies (Mageroy et al., 2006). The study population included workers who had served aboard a missile torpedo boat (MTB) called *KNM Kvikk*. Besides RF transmitters and radar devices commonly used on MTBs, the *KNM Kvikk* was equipped with an additional 750 W transmitter for electronic warfare. In September 2002, all employees, both military and civilians with different types of work on ships and ashore were invited to answer a questionnaire. The questionnaires covered occupational history, numerous exposures including organic solvents, oil, gasoline, exhaust gas, welding and noise during work or leisure time. In addition, the respondents answered questions concerning their lifestyle. For each of their biological children, they stated whether the child had a congenital anomaly or a chromosomal anomaly and whether he or she was born premature, stillborn or died within the first week of life. With 2265 respondents out of 3878 employees, the overall response rate was 58%, somewhat higher in men (2001 respondents, 59%) than in women (250 respondents, 52%). Employees who had served aboard the *KNM Kvikk* were compared to all respondents, to people who had served aboard a ship in general, and to those who had served aboard another MTB. Among the 2265 respondents, 1365 had served aboard a ship, 441 aboard a MTB and 62 aboard the *KNM Kvikk*. In total, 1438 respondents parents reported 3122 biological children, and 83 of them had 97 children with congenital (n=77) or chromosomal (n=20) anomalies. According to a paediatric evaluation based on the information provided by the parents, 8 children with congenital anomalies were born to parents who had served aboard the *KNM Kvikk* at least one year before the child was born. Based on these 8 children, the odds ratio of having a child with a congenital anomaly was estimated to be 4.0 (95% CI 1.9–8.6). Compared with parents who had been exposed to a Navy ship or another MTB, the respective odds ratios were 3.5 (95% CI 1.6–7.7) and 3.4 (95% CI 1.4–8.6). Based on 6 cases among workers aboard the *KNM Kvikk*, the odds ratio of having a stillbirth or a child who died within one week was 4.1 (95% CI 1.7–9.9) when compared to all respondents. Comparisons with parents exposed to a Navy ship or a MTB resulted in odds ratios of 3.6 (95% CI 1.5–8.9) and 2.7 (95% CI 1.0–7.5), respectively. There were no significant differences regarding age, alcohol consumption, smoking or body mass index between those who had served aboard the *KNM Kvikk* and other respondents. However, workers aboard the *KNM Kvikk* more frequently reported exposure to vapour from oil, gasoline or diesel, to exhaust gas, noise, vibration or shaking and passive smoking than other respondents (all $p<0.05$). In addition, a higher percentage of these employees reported to work closer than 10 m to RF aerials, closer than 3 m to communication installations or closer than 5 m to radar devices (all $p<0.05$). [A limitation of this analysis is the rather low response rate of 58%. Without information about the response rates in different exposure groups, selection bias cannot be excluded. Other weaknesses are the crude exposure assessment without objective data and the small number of exposed cases, which also limits the possibility to control for relevant confounders.]

Within the previously mentioned cross-sectional analysis (Baste, Riise & Moen, 2008) the sex ratio among the offspring of all current and former male employees of the Royal Norwegian Navy as of September

2002 was also investigated. Based on a total of 18'625 children, significant linear associations were observed between self-reported RF exposure from aerials (p for trend: 0.008) or from communication equipment (p for trend: 0.031) and a lower ratio of boys to girls. This was shown both for men who had worked 'to a very high degree' either closer than 10 m to high-frequency aerials or closer than 3 m to communication equipment. For these men, the odds ratios of having male offspring were 0.84 (95% CI 0.74–0.94) and 0.87 (95% CI 0.77–0.98), respectively. A similar, but weaker and not significant trend was observed for paternal exposure to radar (p for trend: 0.062).

Another analysis within the same cross-sectional study was restricted to military men who served in the Royal Norwegian Navy at the end of 2002 and had completed their compulsory military service (Møllerløkken & Moen, 2008). Besides infertility (see above), several reproductive outcome variables were assessed based on the answers the participants provided in questionnaires. They were also asked about the work categories they had passed through during their employment. A list of 18 work categories was pre-defined and a group of experts classified these categories according to potential electromagnetic field exposure. In total, 1487 men were included in the analyses (response rate: 63%). Men working in the categories 'tele/communication' and 'radar/sonar' were classified as having 'high' or 'very high' RF exposures by both the experts and the participants themselves. In total, 1487 men were included in this analysis (response rate: 63%). The statistical analyses did not reveal any significant difference between exposed and unexposed men regarding congenital or chromosomal anomalies among their offspring, nor regarding preterm births, stillbirths or infant deaths within one year (all p-values >0.1).

Several years after the early cross-sectional analyses, a register-based cohort study within the Royal Norwegian Navy was conducted including a more sophisticated exposure assessment (Baste et al., 2012). The analyses among offspring of male employees who were exposed to RF fields aboard fast patrol boats comprised risks of congenital malformations, perinatal mortality including stillbirth, low birth weight, preterm birth, small for gestational age, pregnancy with preeclampsia and sex ratio. The cohort included all officers and enlisted personnel from 1950 to 2004. Based on a total of 28 337 servicemen, 264 065 service periods were accrued, both aboard vessels and ashore. Health information for all singleton offspring born between 1967 and 2008 was gathered by linking the cohort to the Medical Birth Registry of Norway. Transmitting patterns of RF sources and exposure levels aboard the fast patrol boats had previously been assessed by means of a measurement study (Baste, Hansson Mild & Moen, 2010). Based on these data, an RF exposure matrix with three job groups was developed: I) artillerymen and personnel who operated weapons such as torpedoes, II) bridge officers and radar operators and III) workers with tasks mainly below deck including engine room personnel and telegraph/radio operators. For each job group, an average level of RF exposure was calculated based on measurements and expressed as squared percentage of the frequency-specific limits recommended by ICNIRP. The individual RF exposure level of each participant was estimated by multiplying the group average by the number of service days in the respective job, time period, and class of the fast patrol boat. Paternal occupational exposure was analysed separately for RF exposure during the last 3 months prior to conception (“acute”) and more than 3 months before conception (“nonacute”). For both types of exposure, three comparisons were performed: a) workers aboard vessels compared to land-based personnel, b) work aboard fast patrol boats compared to work aboard other vessels during corresponding periods, c) based on individual levels of RF exposure (low, medium, high). Log-binomial regression models were adjusted for year of birth, maternal age and paternal age. Analyses of preeclampsia were adjusted for birth order. A total of 37 920 pregnancies were included. Among the fathers, 18 360 had served only ashore, 660 had been exposed to RF during the last three months prior to conception and 4456 had been exposed more than three months before conception. Compared to land-based personnel, significantly increased relative risks of low birth weight were observed among the offspring of fathers who had served aboard fast patrol boats or any other type of vessels (acute exposure: 1.29, 95% CI 1.07-1.56; nonacute exposure: 1.20, 95% CI 1.07-1.35). Since the association was observed both for paternal work aboard fast patrol boats and for work aboard other vessels, this association was not assigned to RF exposure. Compared to service aboard other vessels, “acute” paternal exposure to fast patrol boats was significantly associated with an increased risk of perinatal mortality and pregnancies complicated by preeclampsia: 2.23 (95% CI 1.08-4.62) and 1.57 (95% CI 1.03-2.41), respectively. Also the individual level of “acute” RF exposure was significantly associated with perinatal mortality among fathers with medium levels of exposure: 2.87 (95% CI 1.25-6.59), but no cases of perinatal mortality were observed in the highest exposure category. Significantly increased risks of pregnancies with preeclampsia were estimated for fathers with low-level “acute” RF exposure (2.67, 95% CI 1.50-4.75) and—based on only two cases—for highly exposed fathers (6.07, 95% CI 1.77-20.8). No increase in preeclampsia risk was observed in the medium exposure category. The proportion of male offspring was not associated with paternal work aboard fast patrol boats (RR=0.98; 95% CI 0.91-1.06), but was somewhat elevated in the highest exposure category (n=10): 1.38 (95% CI 0.99-1.93). Nonacute paternal RF exposure was not associated with any reproductive health outcome. The analyses on nonacute exposures were based on larger numbers of exposed subjects than analyses of acute exposures. [Strengths of this study are an improved exposure assessment based on measurement data and the application of several exposure indicators. Furthermore, data on pregnancy outcomes were derived from a nationwide medical birth registry. However, the comparability of the exposure groups regarding other potential risk factors for reproductive health is unclear. Fast patrol boats are known to differ from other vessels regarding several other characteristics, e.g. in the level of exposure to diesel exhaust or vibration. Moreover, lifestyle factors like tobacco smoking and alcohol consumption could differ between workers aboard vessels and land-based personnel. These potential confounders were not considered in the analyses. In addition, several of the risk estimates are based on very few exposed cases and a large number of statistical tests were performed. Repeating the regression analyses with 99% CI resulted in increased risks of preeclampsia and low birth weight but no association between RF exposure and perinatal mortality.]

Studies with insufficient information for assessment of inclusion criteria

A cross-sectional study conducted in three Cypriot villages (two exposed, one unexposed) investigated health effects of residential RF exposures caused by military antennas and other transmitters (Preece et al., 2007). Since this study covered a wide variety of health outcomes including diverse illnesses, well-being and mortality it has already been described in more detail in previous chapters of this report. Information on reproductive health was collected by means of a separate questionnaire distributed to all female residents aged 18 to 50 years. The frequencies of miscarriages, terminations of pregnancy, infant deaths, stillbirths, children with low birth weight and preterm births were not found to differ significantly between residents of the two exposed villages and the control village. [The paper provides no information about the number of women who answered the questionnaire. The individual levels of exposure are unknown. Therefore, the results of this study are not included in the table, and results are given little or no weight in the overall assessment.]

Table 11.1.3. Epidemiological studies on parental occupational far-field RF exposure and pregnancy outcomes

Specific outcome	Country Time period	Study design, sample size, age, response rate	Exposure details and methods of assessment	Exposure categories	Number of exposed and unexposed or number of cases and controls	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
Birth defects (24 categories), preterm delivery, low birth weight, perinatal mortality including stillbirths, proportion of boys	Norway 1976-1995	Register-based cohort; general male population; 541 593 births out of 1 106 665 (48.9%)	Paternal occupational RF exposure, expert judgement based on job titles	Probably not exposed Probably exposed Probably not exposed Probably exposed Probably not exposed Possibly exposed	Cases: 19 789 1417 499 21 18 16	Preterm delivery: 1 1.08 (1.03–1.15) Total cleft lip: 1 0.63 (0.41-0.97) Other birth defects: 1 2.40 (1.22–4.70) No differences for the pooled category of any birth defect, low birth weight, perinatal mortality and sex ratio.	Crude exposure classification based on job titles.	Mjoen et al. (2006)
Congenital anomalies, stillbirth or death of the child within one week after birth	Norway 2002	Cross-sectional; Norwegian Navy; 2265 military employees and civilians, among them 250 women; overall response rate: 58%	Paternal or maternal self-reported exposure during work aboard a missile torpedo boat (*KNM Kvikk*), at least one year before the child was born	Workers aboard the *KNM Kvikk* vs. other naval employees	8 exposed, 74 unexposed children 6 exposed, 53 unexposed children	Congenital anomaly: 4.0 (1.9–8.6) Stillbirth or child's death within one week: 4.1 (1.7–9.9)	Self-reported exposure; low number of exposed children	Mageroy et al. (2006)
Gender ratio of offspring	Norway 1950-2002	Cross-sectional, current (n=2497) and former (n=15'259) male employees of the Norwegian Navy; 10'497 respondents; participation rate: 59%, mean age: 49 years; 18'625 children	Paternal exposure, self-reported; work close to RF aerials, communication equipment or radar;	Children of men who worked closer than 10 m to RF aerials to a very high degree Children of men who worked closer than 3 m to communication equipment to a very high degree Children of men who worked closer than 5 m to radar	1457 1286 1559	Male offspring: 0.84 (0.74–0.94) p for trend: 0.008 Male offspring: 0.87 (0.77–0.98) p for trend: 0.031 Male offspring: 0.87 (0.79–0.97) p for trend: 0.062	Self-reported exposure and outcome	Baste et al. (2008)

Table 11.1.3. Epidemiological studies on parental occupational far-field RF exposure and pregnancy outcomes

Specific outcome	Country Time period	Study design, sample size, age, response rate	Exposure details and methods of assessment	Exposure categories	Number of exposed and unexposed or number of cases and controls	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
Congenital anomalies, chromosomal errors, preterm births, stillbirths or infant deaths within one year	Norway 2002	Cross-sectional; 1487 current male employees of the Norwegian Navy; mean age: 36 years; age range: 20 to 62 years; response rate: 63%	Paternal exposure based on work categories, expert judgement	Exposed work categories: tele/communication, radar/sonar and electronics workers	Depending on the respective outcome, range: 2 to 98	No differences regarding congenital anomalies, chromosomal errors, preterm births, stillbirths or infant deaths within one year (all p>0.1)	Exposure details unknown	Møllerløkken & Moen (2008)

Congenital malformations, perinatal mortality including stillbirth, low birth weight, preterm birth, small for gestational age, pregnancy with preeclampsia, sex ratio	Norway 1950-2004	Register-based cohort; Norwegian Navy 28 337 male officers and enlisted personnel range of mean age among exposure groups: 26.4–31.7 years 37 920 pregnancies; coverage rate not reported	Paternal exposure aboard fast patrol boats RF sources: antennas (2.1–8 MHz, 10–250 W), navigation radar (9.4 GHz, 25 kW), weapon control radar (9.1 GHz, 25 kW)	“Acute” exposure to fast patrol boats vs. service aboard other vessels:		Gender Boys	Improved exposure assessment; objective data on exposure and outcome; insufficient control for potential confounders.	Baste et al. (2012)
				Unexposed	1464	1.0		
				Exposed	387	0.98 (0.91-1.06)		
						Perinatal mortality:		
				Unexposed	17	1		
				Exposed	12	2.23 (1.08-4.62)		
						Preeclampsia:		
				Unexposed	67	1		
				Exposed	29	1.57 (1.03-2.41)		
						No associations: congenital malformations, low birth weight, preterm birth, small for gestational age, sex ratio.		
				Calculated individual dose of 'acute' RF exposure:		Gender Boys:		
				low	120	1.02 (0.90-1.16)		
				medium	214	0.96 (0.87-1.06)		
				high	10	1.38 (0.99-1.93)		
						Perinatal mortality:		
				Low	3	1.82 (0.54-6.13)		
				medium	8	2.87 (1.25-6.59)		
				high	0	-		
						Preeclampsia:		
				low	13	2.67 (1.50-4.75)		
				medium	13	1.12 (0.62-2.00)		
				high	2	6.07 (1.77-20.8)		
				'Nonacute' fast patrol boat exposure vs. service aboard other vessels		No associations with any outcome.		

[a]RF=Radiofrequency, OR=Odds ratio, CI=Confidence interval

11.1.3 Reproductive Hormones

11.1.3.1 Mobile phone use and reproductive hormones

In the Austrian cross-sectional study also mentioned in section 11.1.1, a sample of 2110 consecutive men attending an infertility clinic were recruited between 1993 and October 2007 (Gutschi et al., 2011). Patients with a history of smoking or alcohol consumption were excluded; the same applied to men suffering from a systemic disease, orchitis or varicocele. Besides sperm quality, also blood levels of testosterone, follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin were evaluated. After dividing all participants into 991 mobile phone users and 1119 non-users, a multivariate analysis of variance was performed. Regarding FSH and prolactin, the analyses revealed no statistically significant differences between the two groups. However, testosterone levels of mobile phone users were found to be slightly higher and LH levels were slightly lower than among controls (p-values <0.005). [A limitation of this study is the crude exposure classification without information about duration or intensity of mobile phone use. Moreover, it is not stated in the paper whether the mean age of the participants in both groups was comparable and whether age was taken into account. Also, no other potential confounding factors were considered.]

11.1.3.2 Occupational far-field RF exposure and reproductive hormones

The cross-sectional study among male artillery soldiers of the U.S. Army described above (Weyandt et al., 1996) also included analyses of some reproductive hormones. Blood levels of follicle stimulating hormone (FSH), luteinising hormone (LH), testosterone and prolactin were compared between 20 microwave exposed radar operators and 31 control soldiers. The authors report no differences with regard to endocrine, accessory sex gland or sperm cell function without presenting any measurement data or other details. [A limitation of this study is the small sample size leading to low statistical power.]

Schrader et al. conducted a follow-up analysis including a somewhat higher number of male radar operators (n=33) and unexposed soldiers (n=103) (Schrader et al., 1998). The participants were categorised according to job classification and self-reported exposure information. Levels of both serum and urinary follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were determined. In addition serum, salivary and urinary testosterone levels were measured. Statistical comparisons based on analysis of covariance models revealed no significant differences between radar operators and controls in any of these measurements (all p-values >0.08).

In the cross-sectional study among male RF heater operators employed at four water mattress manufactures in the U.S., blood levels of four hormones were also evaluated (Grajewski et al., 2000). Data on work history and medical conditions as well as on demographic, lifestyle and reproductive health was collected by questionnaire. For each water mattress company, the mean RF exposure was calculated based on measurements. Geometric means of the time-weighted averages (TWA) of the E-fields ranged from 35 to 95 V m^{-1}; for the H-field the mean values varied between 0.14 and 0.25 A m^{-1}. Arithmetic means of the TWA induced foot currents ranged from 70 to 130 mA. The statistical analysis was based on 12 exposed and 34 unexposed men. No significant differences in total testosterone, luteinising hormone (LH) and prolactin were determined. The mean level of follicle stimulating hormone (FSH) was, however, significantly higher among exposed workers than among controls (7.6 vs. 5.8 mIU mL^{-1}, p=0.05). [The authors themselves state that withdrawal of the largest water mattress company from the study resulted in insufficient study power for some of the analyses despite a 63% response rate at the other companies. However, the objective exposure measurement performed at the companies has to be considered as strength of this study. Several potential confounders were considered in the statistical analysis but some concern regarding residual confounding remains given the small sample size.]

Studies with insufficient information for assessment of inclusion criteria

A small cross-sectional study from Turkey included 43 technicians aged 20 to 59 years who were occupationally exposed to RF and microwave radiation (Daşdağ et al., 1999a). Ten of them worked at a TV transmitter station (202 to 781 MHz, 60 to 450 kW), 15 were employed at a radio-broadcasting station (ca. 1 to 100 MHz, 30 to 300 kW) and 18 worked at a radio-link station (420 MHz to 6 GHz, 1.5 to 200 W). Field strength measurements resulted in values between 65 and 85 dB microvolt. Twenty volunteers without occupational RF or microwave exposure but similar age, sex, type of work and working period (8 h/day) were selected as a comparison group. Blood samples were taken during work hours in order to assess the levels of thyroid hormones, estradiol, dehydroepiandrosterone sulfate (DHEA), testosterone, cortisol and progesterone.

Statistical comparisons using student's t-tests revealed significantly higher mean levels of estradiol and progesterone among all three groups of exposed technicians. Also, testosterone levels tended to be higher, whereas mainly non-significantly decreased levels of DHEA and cortisol were found. [The basic characteristics of the participants including age or sex distribution are not shown in the paper. Therefore, the comparability and representativity of the participants cannot be assessed. In addition, no information is available about the time of the day when the blood samples were taken and about the measurement units of the hormonal levels. Moreover, the actual exposure levels in each group are unknown and the reported measurement levels are extremely low. No potential confounders were taken into account. Therefore, the results of this study are not included in the table.]

11.1.3.3 Residential far-field RF exposure and reproductive hormones

A cross-sectional study from the U.S. investigated potential RF effects on the metabolism of estrogens and melatonin among women living near broadcasting transmitters for Denver, Colorado (Clark et al., 2007). Prior to this study, temporal and spatial characteristics of residential RF exposure in this area had been assessed by combining repeated spot measurements with geographic parameters (Burch et al., 2006). The study area was defined by an interstate road to the south, a park neighbourhood to the west and the natural topography to the north and east. Radio and TV transmitters in this area emitted approximately 9 MW of broadcast power and were positioned in three groups of antenna towers located about 0.4 to 1.2 km apart. Between September 2002 and December 2003, a population census identified 576 homes and 1375 individuals in the study area. Among them, a random sample of 280 male and female participants aged 8 years or older was recruited from 161 residences belonging to three strata with high (>40 mW/m^2), medium (5–40 mW/m^2) or low (<5 mW/m^2) RF exposures (participation rate: 64% among eligible persons contacted). Participants and nonparticipants did not differ regarding mean age or mean residential power density. A total of 127 post menarche women aged 12 to 81 years participated in the study. Each woman was studied for a 2.5-day period beginning in the evening on the initial day and ending in the morning on the final day of participation. Exposure assessment included RF spot measurements from one exterior and five interior locations of the home: bedroom, kitchen, living room, computer room or office and the room most used. A mean RF exposure value was created by averaging the five interior measurements. Besides average power density, mean distance from each residence to 15 major RF transmitters, geographic elevation of the house and percentage of transmitters visible from each home were also taken into account. The mean values of RF power density in the homes varied from not detectable to 67 mW/m^2 (mean: 8 ± 10 mW/m^2). Each participant collected one overnight urine sample after the first study night and a second overnight sample after the last study night. The primary hypothesis was that RF exposure would lead to a decrease in the excretion of 6-hydroxymelatonin sulfate (6-OHMS) and an increase in the estrogen metabolite estrone-3-glucuronide (E1G). Information on demographic characteristics, medical and reproductive history as well as on numerous lifestyle factors was gathered by self-administered questionnaires. Women reporting consumption of melatonin supplements (n=4), current intake of birth control pills (n=16), breastfeeding (n=4) or hormone replacement therapy (n=20) were excluded. The final analyses comprised 83 women, of whom 56 were premenopausal (median age: 43 years) and 27 postmenopausal (median age: 59 years). Subjects were grouped into RF exposure quartiles and adjusted mean metabolite concentrations in the upper and lower quartiles were compared using the least significant differences statistic. Among premenopausal women, no associations between RF exposure and E1G excretion were observed after adjustment for menstrual cycle stage, fruit intake, exercise and season of participation. There were also no exposure effects on 6-OHMS excretion after adjustment for education, miscarriages and smoking. Postmenopausal women in the highest quartile of house average RF power density (mean: 14 mW m^{-2}) had higher mean urinary E1G concentrations than women in the lowest quartile (mean: 0.4 mW m^{-2}) (p=0.02). Regarding mean nocturnal 6-OHMS excretion, no statistically significant association was observed after adjustment for month of participation and eye colour. [Main strengths of this study are the extensive exposure assessment and the comprehensive dataset. Limitations are the cross-sectional design of the study, uncertainties about the coverage of the underlying population and the small numbers of participants in the subgroup analyses limiting the possibility to adequately control for confounding factors.]

Studies with insufficient information for assessment of inclusion criteria

A small study from Egypt was conducted in order to investigate hormone profiles of mobile phone users and of people living close to mobile phone base stations (Eskander, Estefan & Abd-Rabou, 2012). Two groups of mobile phone users with different age ranges (14 to 22 years and 25 to 60 years, each n=41) were divided into three categories according to their daily RF exposure time (weak, moderate, strong). Two other groups of volunteers were selected because they lived at distances of 20 to 100 m or 100 to 500 m from a mobile phone base station (n=17 of each age group). In addition, 10 subjects living more than 500 m away from a base station served as a control group. All participants were followed over 6 years and blood samples were collected after 1 year, 3 years and 6 years. The hormonal analyses comprised blood levels of adrenocorticotrophic hormone (ACTH), cortisol, total T_3, T_4, prolactin, progesterone (only in women) and testosterone (only in men). Multiple statistical tests resulted in numerous significant, but inconsistent differences between the exposure groups regarding all hormones under investigation. [This study is regarded uninformative since it does not meet basic methodological requirements for epidemiological studies. It is completely unclear how the participants were recruited and the participation rates are unknown. Moreover, the gender distribution between and within study groups is unknown. No information is given about the medical or reproductive history of the participants or other factors influencing the hormonal levels. Distance to mobile phone base station has been demonstrated to be an inadequate exposure surrogate for epidemiological studies (Frei et al., 2010). Therefore, the results of this study are not included in the table.]

Table 11.1.4. Epidemiological studies on RF exposure and hormonal levels

Specific outcome	Country Time period	Study design Population, age, response rate	Exposure details and categories	No. of exposed and unexposed or number of cases and controls	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
Use of mobile phones							
Free testosterone, LH, FSH, prolactin (blood serum levels)	Austria 1993-2007	Cross-sectional study 2110 men attending an infertility clinic, mean age 31.6 +/- 6.6 years	Non-users Mobile phone users Non-users Mobile phone users	1119 991 1119 991	Testosterone (p<0.05): 4.8 ng/dl 5.1 +/- 1 ng/dl LH (p<0.05): 4.1 mIU/ml 3.3 +/- 2 mIU/ml FSH and Prolactin: no differences	Crude exposure estimate; no potential confounders considered	Gutschi et al. (2011)
Occupational exposure to far-field RF sources							
Blood levels of FSH, LH, testosterone and prolactin	USA 1990	Cross-sectional, male artillery soldiers, 20 radar operators, 31 controls; mean age and participation rate not given	Microwave exposure from radar equipment in Army Intelligence Controls Radar operators	31 20	No differences regarding endocrine, accessory sex gland or sperm cell function	No measurement data or other details of results reported	Weyandt et al. (1996)
Serum and urinary FSH and LH; serum, salivary and urinary testosterone	USA 1993	Cross-sectional, male soldiers, 33 radar equipment operators, 103 controls	Microwave exposure from radar equipment in Signal Corps Controls Radar operators	103 33	No differences in serum and urinary FSH and LH or serum, salivary and urinary testosterone (all p-values >0.08)		Schrader et al. (Schrader et al., 1998)
Serum levels of total testosterone, FSH, LH and prolactin	USA 1988	Cross-sectional study; 12 male RF heater operators; mean age: 32.3 +/- 7.5 years; 34 control workers, mean age: 34.5 +/- 9.3 years; participation rates: 63% among exposed, 34% among unexposed	Work at a company with RF sealers and dielectric heaters; 12 to 57 MHz, mean E-field values: 35 to 95 V m^{-1}, H-field: 0.14 to 0.25 A m^{-1}, induced foot currents: 70 to 130 mA Controls RF heater operators	34 12	No differences for total testosterone, LH and prolactin Mean FSH level (p=0.05): 5.8 mIU ml^{-1} 7.6 mIU ml^{-1} (95% CI for the ratio of exposed and unexposed means: 100.3-171.6%)	Small sample size	Grajewski et al. (2000)
Residential exposure to far-field RF sources							

Table 11.1.4. Epidemiological studies on RF exposure and hormonal levels

Specific outcome	Country Time period	Study design Population, age, response rate	Exposure details and categories	No. of exposed and unexposed or number of cases and controls	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
Estrogen and melatonin metabolism	USA 2002-2003	Cross-sectional study; overall participation rate: 64%; 83 women living close to broadcasting transmitters; age range: 12 to 81 years	15 radio and TV broadcasting transmitters, 55 to 687 MHz, approx. 9 MW of broadcast power; quartiles of house average RF power density with means: 0.04, 0.2, 0.4 and 1.4 µW/cm².	Premenopausal women (n=56) Postmenopausal women (n=27): Lowest quartile Highest quartile	No associations between RF exposure and mean urinary levels of estrogen or melatonin metabolites Estrone-3-glucuronide (E1G) (p=0.02): 8.4 ng/ml 17.2 ng/ml No association with melatonin excretion	Detailed data for premenopausal women not shown; representativity of study sample unclear	Clark et al. (2007)

RF=Radiofrequency, LH=Luteinising hormone, FSH=Follicle stimulating hormone

11.1.4 Childhood development

11.1.4.1 Maternal mobile phone use and childhood development

Based on data of the Danish National Birth Cohort it was investigated whether maternal mobile phone use during pregnancy was associated with behavioural problems in children (Divan et al., 2008). To that purpose, a telephone interview was conducted with the mothers when their children reached the age of 7 years. In 2005 and 2006, mothers of 13 159 children born in 1997 to 1999 provided answers about their mobile phone use during pregnancy, the children's mobile phone use at age 7, and the children's behaviour (response rate: 65%). Behavioural problems were assessed using the "Strength and Difficulties Questionnaire". Based on 25 items, an overall score of behavioural problems was generated as well as specific ratings representing emotional symptoms, conduct problems, hyperactivity and peer problems. The logistic regression analyses were adjusted for potential confounders including sex of the child, maternal age, smoking during pregnancy, social-occupational status and history of psychiatric disease. Mobile phone use during pregnancy without exposure of the child caused by his or her own mobile phone use was reported by 1895 mothers (14%). About 50% of the children had exposure neither before nor after birth and served as the reference group. Almost 90% of all participants were reported as "normal" regarding all types of behaviours. Abnormal scores were reported for 2 to 9%. A statistically significant association was observed between mobile phone use of the mother during pregnancy and overall behavioural problems, the adjusted odds ratio being 1.54 (95% CI 1.32-1.81). Also, the specific scores for hyperactivity conduct problems and peer problems were significantly associated with maternal mobile phone use during pregnancy (ORs between 1.21 and 1.29). Regarding emotional problems, this odds ratio was 1.12 (95% CI 0.97-1.30). Considering mobile phone use of the mother during pregnancy and phone use of the child separately yielded higher odds ratios for phone use during pregnancy. The highest odds ratio of overall behavioural problems was observed in children whose mothers had used a mobile phone during pregnancy and who had used a mobile phone themselves (1.80, 95% CI 1.45-2.23). [The results of this study were judged as unexpected by the authors themselves because of the very low fetal exposure levels arising from maternal mobile phone use. The main limitation is that exposure information was only collected at the age of 7 when behavioural problems were assessed. Thus, data on mobile phone use by the mothers during pregnancy may be uncertain and subject to recall bias. Furthermore, analyses including the child's own mobile phone use are based on cross-sectional data, and the sequence of events cannot be determined. There is a possibility that behavioural problems lead to increased mobile phone use rather than the opposite. Since mothers reporting mobile phone use during pregnancy differed from the reference group on several factors possibly related to the risk of behavioural problems, as reflected by decreased risk estimates after adjustment for potential confounders, residual confounding is a potential problem. Heritability is a strong determinant for behavioural problems. Moreover, the authors had no information about other potential confounders such as lead exposure or paternal history of psychiatric diseases. In addition, some maternal behavioural patterns could have been related to both mobile phone use and perceived or existent behavioural problems in children.]

In a subsequent study, the same authors evaluated whether their original results were due to chance or could have been caused by selecting a sample of "early technology adopters" (Divan et al., 2012). For these purposes, they included two additional years of follow-up (until 2008) within the Danish National Birth Cohort and obtained a dataset comprising 28 745 children born between 1998 and 2002. In addition, supplementary covariates were tested: father's age at birth, gestational age, parity, birth weight, postpartum stress, breast feeding, both parents' history of psychiatric, cognitive, or behavioural problems as a child, socio-economic status, maternal alcohol and drug use during pregnancy, maternal physical activity and prenatal exposure to ionising radiation and other sources of non-ionising radiation. As indicators of inattention, the number of daily hours mothers spent with their children at 6 and 18 months were taken into account as well as whether the child was in regular day-care by 18 months. Furthermore, proxies for prenatal mobile phone exposure intensity were used to evaluate possible dose-response relationships: calls per day, phone location when not in use, proportion of time the phone was turned on and use of headsets. In the new dataset, 39.5% of the children had not experienced mobile phone exposure before or after birth. The percentage of children without behavioural problems was 93%, whereas 3.1% were rated as having "abnormal" behaviour and 3.3% as borderline. The association between mobile phone use and overall behavioural problems was weaker than in the previous study but remained statistically significant. Again, the highest odds ratio was found for children whose mothers used a mobile phone during pregnancy and who used a mobile phone themselves (1.5; 95% CI 1.3-1.7). For children whose mothers used a mobile phone during pregnancy but who did not have one themselves, the adjusted odds ratio for overall behavioural problems was 1.3 (95% CI 1.1-1.5). After combining the new dataset with the original sample (n=41 541), the association persisted and the adjusted odds ratio related to mobile phone use during pregnancy was 1.4 (95% CI 1.2-1.5). Interestingly, odds ratios decreased over time indicating that early analyses may have been affected by confounding from "early technology adopters". [In this study, the initial results were replicated and a wide variety of potential confounders were taken into account. The associations were also confirmed when the analyses were stratified by the modelled covariates. However, uncertainties regarding self-reported mobile phone use collected retrospectively, cross-sectional analysis of the child's mobile phone use and associated possibility of reverse causation, and regarding the comparability of maternal perception of their children's behaviour remain. Number of hours that mothers spent with their child may not be indicative of inattention; using a mobile phone while spending time with the child may draw attention away from the child, but would still be reported as time spent with the child. Confounding from heritability is still a concern, although adjustment for both parents' psychiatric history and self-reported own behavioural problems as a child may have reduced this problem somewhat.]

A further analysis based on the Danish National Birth Cohort was targeted at the question whether maternal mobile phone use during pregnancy was associated with developmental milestone delays among the offspring in the first two years of life (Divan, Kheifets & Olsen, 2011). Information on the children's development was collected by means of two telephone interviews that took place when the infants reached the age of 6 and 18 months. At both interviews mothers were asked to answer two series of questions covering important developmental milestones regarding both motor skills and cognitive/language functions. Four summary measures of the developmental status were calculated for each child: motor development delay at 6 and 18 months, respectively, and cognitive/language development delay at 6 and 18 months, respectively. Higher scores implicated greater developmental delay. Children with scores corresponding to the highest 5% of all children for each of the four summary measures were classified as "delayed". When the children reached the age of 7 years, the mothers completed an internet-based questionnaire including detailed questions on mobile phone use during pregnancy. Associations with developmental delay among the offspring were investigated in multivariate logistic regression models after controlling for numerous potential confounders. With a response rate of about 60%, the database comprised 41 541 children who were born between 1997 and 2002 and had turned 7 years of age by January 2009. Mobile phone use during pregnancy was reported by nearly 34% of the mothers (n=13 938). Concerning the four summary measures, between 2 and 3.6% of the infants were classified as "'delayed". In each of the four groups, for about 20% of the children no outcome information was available. Overall, no statistically significantly increased risks of developmental delay were observed in children whose mothers used a mobile phone during pregnancy. At the age of 6 months, the adjusted odds ratio was 0.8 (95% CI 0.7-1.0) for cognitive/language delay and 0.9 (95% CI 0.8-1.1) for motor development delay. Regarding the age of 18 months, odds ratios additionally adjusted for corresponding developmental delays at 6 months were 1.1 (95% CI 0.9-1.3) and 0.9 (95% CI 0.8-1.0) for cognitive/language and motor development delay, respectively. No dose-response relationships were observed. Thus, the data provided no support for an association between mobile phone use of the mothers during pregnancy and developmental delay in children before the age of two. [The large and comprehensive dataset is an asset. Limitations of this study are the self-reported information on exposure and health outcome as estimated by the mothers.]

In a fourth analysis of the Danish Birth Cohort, the same exposure proxy as in the previous papers was evaluated, this time in association with migraine as well as headache-related symptoms. For this study, data of 52 680 children whose mothers were enrolled during pregnancy between 1996 and 2002 was used (Sudan et al., 2012). When the children were 7 years old, mothers were asked whether their children were suffering from migraine. They also answered the question if their child "often complained of headaches, stomach aches, or sickness". A child was classified as having headache-related symptoms if the parents reported that this was "partly true" or "very true". Statistical analysis were adjusted for numerous confounders: mother's age, mother's history of migraines, mother's feelings of worry, burden, and stress during pregnancy, social-occupational status, child's exposure to tobacco smoke, and child's sex. Children whose mothers used a mobile phone during pregnancy and who used one themselves at the age of 7 years were 1.30-fold (95% CI 1.01-1.68) more likely to suffer from migraine and 1.32-fold (95% CI 1.23-1.40) more likely to have headache-related symptoms. These symptoms showed a statistically significant exposure-response association with number of daily mobile phone calls during pregnancy. For children who did not use a mobile phone at age 7, but whose mothers had used one during pregnancy, the risk estimates were lower. For migraine an OR=1.20 (95% CI 0.93-1.54) was observed, and for headache-related symptoms OR=1.16 (95% CI 1.08-1.23). The authors indicate that the results should be interpreted with caution because of the potential for uncontrolled confounding and exposure misclassification. [This study has the same strengths and limitations as discussed above. In addition, the question on headache related symptoms is unspecific and could have led to outcome misclassification. Reverse causality is an additional concern because children suffering from migraines or chronic headaches may be offered a mobile phone to contact their parents in case of emergency. However, risk estimates were slightly raised also for headache-related symptoms in children who were only exposed during pregnancy by maternal mobile phone use, and non-significantly for migraine.]

The relationship between mobile phone use of the mothers during pregnancy and neurodevelopment in the offspring was examined within a prospective birth cohort study from Spain (Vrijheid et al., 2010). The study population consisted of pregnant women who attended a primary health-care centre in the city of Sabadell between July 2004 and July 2006. Information on potential influencing factors including educational level, social class, maternal health and obstetric history, alcohol consumption, active and passive smoking as well as dietary habits was obtained by means of two questionnaires administered in person during the first and third trimesters of pregnancy. The second questionnaire also contained two questions on mobile phone use. Among 1099 eligible women, 657 (60%) agreed to participate. When the children had reached the age of 14 months (range: 12 to 17) they were tested by two trained psychologists using the mental development scale (163 items) and the psychomotor development scale (81 items) of the “Bayley Scales of Infant Development”. All multivariate linear regression models were adjusted for several potential confounders and were repeated using women with only one mobile phone call per day as control group instead of nonusers. This was done in order to control for differences between users and nonusers. Nonusers tended to belong to lower social and educational classes, whereas heavy mobile phone users were more likely to be younger and to report higher levels of active and passive smoking. Complete information on exposure and outcome was available for 530 mother-child pairs. Only 11% of mothers reported not using a cell phone, 31% reported one call per day, 45% between two and four calls and 13% made or received five or more calls per day. The scores of children whose mothers used a mobile phone during pregnancy tended to be higher on the mental developmental scale but to be lower on the psychomotor scale. After adjustment for maternal socioeconomic status and maternal education a statistically significant decrease of the psychomotor score was only observed among the offspring of women reporting at least 5 calls per day (-5.6 points, 95% CI -10.7 to -0.5). This association did not persist when the category of one mobile phone call per day was used as reference group (-2.0, 95% CI -6.3 to 2.2). In addition, the authors observed no evidence for a risk increase with increasing maternal mobile phone use. [The prospective design of this study is of particular value because mobile phone use was inquired during pregnancy before assessing the child’s neurodevelopment. This approach prevented from recall bias. A further strength of this study is that the developmental progress of the children was assessed by trained psychologists. However, the small sample size is a limitation.]

In a population-based birth cohort study of 2618 children from Amsterdam, teachers and mothers reported child behaviour problems using the Strength and Difficulties Questionnaire at the age of 5 years (Guxens et al., 2013). Mothers were interviewed about their use of mobile phones and cordless phones during pregnancy (number of calls) when the children were 7 years old. These data were analysed by means of logistic regression models adjusted for maternal education, age, country of birth, parity, pre-pregnancy body mass index, smoking during pregnancy, second-hand smoke at home during pregnancy, alcohol consumption during pregnancy, pregnancy-related anxiety subscales, anxiety and depression during pregnancy and history of psychopathology. Since the number of children without maternal mobile phone use during pregnancy was very small, this group was excluded in an additional analysis using the low “exposure” group (<1 call per day) as reference. Teacher-reported overall behaviour problems were increased in children whose mothers had used a mobile phone during pregnancy when compared to children whose mother had not. However, there was no “exposure”-response relationship and no difference was observed after omitting the “unexposed” from the analyses. No association was reported regarding cordless phone use. For overall behaviour problems reported by mothers, most risk estimates were below unity. Only one increased OR was observed for children belonging to the medium exposure category of maternal cordless phone use. [A strength of this study is the large and comprehensive data set. It is limited by the fact that data on mobile phone use were collected only when the children had reached the age of 7 years, two years after the assessment of behavioural problems. This may produce recall bias. Because of the small proportion of “unexposed” children, the analyses using children with low phone use by the mothers as reference category are more reliable.]

Table 11.1.5. Epidemiological studies on maternal mobile phone use and childhood development

Specific outcome	Country Time period	Study design Population, age, response rate	Exposure details and assessment	Number of exposed and unexposed children	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
Behavioural problems	Denmark 1997-1999	National birth cohort 13 159 children at age 7 years; response rate: 65%	Maternal mobile phone use during pregnancy, self-reported	1895 exposed vs. 6471 unexposed	Overall behavioural problems: 1.54 (1.32-1.81) Hyperactivity: 1.29 (1.08-1.53) Conduct problems: 1.21 (1.05-1.40) Peer problems: 1.27 (1.06-1.52) Emotional problems: 1.12 (0.97-1.30	ORs adjusted for child's gender, maternal age, smoking during pregnancy, mother's psychiatric history, socio-occupational status and postnatal mobile phone exposure.	Divan et al. (2008)
			Maternal mobile phone use during pregnancy and mobile phone use of the child at age 7 years	1421 exposed vs. 6471 unexposed	Overall behavioural problems: 1.80 (1.45-2.23)		
Developmental milestone delays	Denmark 1997-1999	National birth cohort 41 541 children at age 7 years in 2009; response rate: 60%	Maternal mobile phone use during pregnancy, self-reported	13 938 exposed vs. 24 942 unexposed	At 6 months of age: Cognitive/language developmental delay: 0.8 (0.7-1.0) Motor developmental delay: 0.9 (0.8-1.1) At 18 months of age: Cognitive/language developmental delay: 1.1 (0.9-1.3) Motor developmental delay: 0.9 (0.8-1.0)	ORs adjusted for child’s gender, combined social-occupational status, gestational age, parity and child’s year of birth. ORs at 18 months additionally adjusted for corresponding delays at 6 months of age	Divan et al. (2011)
Behavioural problems	Denmark 1998-2002	National birth cohort 28 745 children at age 7 years; response rates: 60 to 65%	Maternal mobile phone use during pregnancy, self-reported	Exact numbers not reported	Overall behavioural problems: 1.3 (1.1-1.5)	ORs adjusted for child's gender, maternal age, smoking during pregnancy, mother's psychiatric history and socio-occupational status.	Divan et al. (2012)
			Maternal mobile phone use during pregnancy and mobile phone use of the child at age 7 years	Exact numbers not reported	Overall behavioural problems: 1.5 (1.3-1.7)		
Migraine and other headache-related symptoms	Denmark 1996-2002	National birth cohort 52 680 children at age 7 years; response rate about 60%	Prenatal exposure only	9781 exposed vs. 21 507 unexposed	Migraine: 1.20 (0.93-1.54) Headache-related symptoms: 1.16 (1.08-1.23)	ORs adjusted for child’s gender, maternal history of migraines, mother's feelings of worry, burden, and stress during pregnancy, mother's age, social-occupational status, and child's exposure	Sudan et al. (2012)
			Postnatal exposure only	9781 exposed vs. 21 507 unexposed	Migraine: 1.21 (0.92-1.60) Headache-related symptoms: 1.28 (1.19-1.37)		

Table 11.1.5. Epidemiological studies on maternal mobile phone use and childhood development

Specific outcome	Country Time period	Study design Population, age, response rate	Exposure details and assessment	Number of exposed and unexposed children	Odds ratios, relative risks or other effect estimates (95% CI)	Comments	Reference
			Prenatal and postnatal mobile phone exposure	9781 exposed vs. 21 507 unexposed	Migraine: 1.30 (1.01-1.68) Headache-related symptoms: 1.32 (1.23-1.40)	to environmental tobacco smoke in the home. Exposure and outcome was self-reported at age 7	
Neurodevelopment at age 14 months	Spain 2004-2006	Birth cohort 530 mother-child pairs; response rate: 60%, participation rate: 48%	Maternal mobile phone use during pregnancy, self-reported; 0 calls 1 call/day 2-4 calls/day >5 calls/day 0 calls 1 call/day 2-4 calls/day >5 calls/day	 61 162 239 68 61 162 239 68	Psychomotor score 1.0 -3.5 (-7.8 to 0.8) -2.8 (-6.9 to 1.3) -5.6 (-10.7 to -0.5) Mental score 1.0 1.6 (-2.6 to 5.8) 2.0 (-2.1 to 6.0) 2.8 (-2.2 to 7.8)	Regression coefficients adjusted for child's age and gender, investigating psychologist, maternal socioeconomic status, maternal education, maternal IQ, smoking during pregnancy and smoking in the home.	Vrijheid et al. (2010)
Behavioural problems	Netherlands 2003-2004	Birth cohort 2618 children at age 5 years; participation rate: 31.7%	Prenatal mobile phone exposure (calls/day): None <1 1-4 ≥5 After excluding unexposed: <1 1-4 ≥5	 125 834 815 368 834 815 368	Teacher-reported behaviour problems: 1 2.12 (0.95-4.74) 1.58 (0.69-3.60) 2.04 (0.86-4.80) 1 0.75 (0.53-1.07) 0.97 (0.64-1.47)	ORs adjusted for maternal education, age, country of birth, parity, pre-pregnancy body mass index, smoking and second-hand smoke at home during pregnancy, alcohol consumption, pregnancy-related anxiety, anxiety and depression during pregnancy and history of psychopathology	Guxens et al. (2013)

CI=Confidence interval

11.2 Volunteer studies

Volunteer studies of relevance for fertility, reproduction and development include assessment of semen quality which may have a direct effect on fertility. Several hormones are essential for the reproductive health of both men and women. Studies concerning the neuroendocrine system are reviewed in Chapter 7, and those including hormones of particular relevance for reproductive health are also summarised here. Furthermore, experimental volunteer studies of potential effects of RF exposure on foetal physiology are of relevance for this chapter.

In the WHO report (WHO, 1993) no volunteer studies of relevance for fertility, reproduction or development were reported. The current literature searches resulted in 13 relevant studies; of these eight did not meet the inclusion criteria for volunteer studies; exposure conditions were not blinded to the participants or the study did not include two or more exposure levels (whereof one could be a sham), under otherwise similar conditions; these studies are listed at the end of this section. This left five studies to be included in the Monograph, of which two had uncertainties related to the inclusion criteria; these studies are not included in Table 11.2.1 summarizing the three other studies. All five included studies have assessed potential endocrine effects and are also reported in Section 7.2.

Table 11.2.1 summarizes results and provide information about study details including study design. Similar and further details are included in the following text. Comments about particularly small samples sizes are made since the smallest samples are attached with highest uncertainties provided other study details are similar. Exposure was controlled in all studies that fully met the inclusion criteria. If SAR was provided, it is specified in both the tables and text. Otherwise other exposure measures are provided.

The included studies are all mobile phone handset related and have assessed potential effects on luteinizing hormone that are related directly to reproduction and fertility, and melatonin that may have an indirect effect. Some of the studies also assessed other hormones that are reported in Section 7.2. Using signals from a GSM 900 mobile phone handset emitted by an antenna, Mann et al. (1998) exposed 22 male healthy volunteers during two successive nights (one night of exposure to GSM 900 MHz signal and one night sham) in which nocturnal profiles of some hormones were evaluated under polysomnographic control. These two experimental nights were preceded by and adaptation night, the order of exposure conditions was randomized and the study was performed single. The antenna was positioned behind the head at 40 cm from the vertex of the subject resulting in an average power density of 0.2 W/m^2 [SAR averaged over 10 g was 0.3 W/kg as reported from the same study by Wagner et al. (1998)]. Blood samples were taken every 20 minutes for nocturnal hormone profiles. The results for luteinizing hormone and melatonin did not show any statistically significant effect of exposure on night-time serum melatonin.

Radon et al. (2001) exposed eight male healthy volunteers to a GSM 900 MHz mobile phone signal (SAR = 0.025 W/kg). They evaluated the effect on salivary melatonin of the RF signal transmitted by an antenna positioned 10 cm behind the head of each participant. The experimental protocol consisted of twenty 4-hour sessions in the experimental chamber, “with the sessions being at least 2 days apart after a day session and at least 3 days apart after a night session”. Half of the experiments (ten 4-hour sessions) were conducted with EMF exposure and the others with sham exposure in random order, and the sessions were evenly distributed between day and night. The study was performed double blind. The same time of day was used for all day and night sessions, respectively, and saliva was collected every 30 minutes during and after exposures. The results did not show any significant difference in salivary melatonin concentrations between the exposure and sham exposure conditions. [The weight of this study is limited due to its small sample size.]

Wood et al. (2006) exposed 55 adult male and female volunteers to a mobile phone GSM 895 MH signal before sleep to test whether the overnight melatonin secretion would be reduced. The mobile phone was fixed so that it rested against the right cheek of the participants. The 10 g maximum SAR was measured to be 0.67 W/kg. The participants were both exposed and sham exposed for 30 minutes in a random sequence on two successive Sunday nights. Urine was collected immediately after exposure before getting into bed and in the next morning upon waking. Melatonin was estimated from its main metabolite in urine: 6-sulphatoxymelatonin (aMT6s). Total aMT6s output during the night did not differ between the two exposure conditions. The pre- and post-bedtime results considered separately were also not significantly different, although the pre-bedtime value was lower for RF versus sham exposure. When normalized to creatinine concentrations, the pre-bedtime value of aMT6s was found to be significantly lower ($p = 0.037$) after RF exposure compared to sham exposure. According to the data reported in the paper, only four participants out of 55 had clearly shown a substantial decrease in pre-bedtime normalised aMT6s in the exposed condition. The authors reported that if the four individuals were excluded from the analysis, the results would not be significant ($p = 0.45$). [Due to the small number of participants showing a substantial decrease in their normalised aMT6s in the exposed condition, while the remaining data were close to normally distributed, it cannot be excluded that the observed effect was an artefact. [It should also be noted that even though the study was designed to be double blind, there is no information suggesting that measures were taken to control for acoustic cues from the transmitting phone or to prevent the participants from sensing the heat produced by phone when operating.]

Papers with uncertainties related to inclusion criteria

Two single blind studies have been published that report no information about exposure levels or about control of the levels. In order to evaluate the possible effect of RF mobile phone exposure on 6-sulphatoxymelatonin (aMT6s), Bortkiewicz et al. (2002) exposed nine volunteers to a mobile phone GSM 900 MHz signal. Each participant was examined twice: on an exposure day and a control day (sham). Exposure lasted one hour starting from 19:00. Urine sampling was performed immediately before exposure (19:00), before bedtime (00:00) and in the next morning (07:00). The study showed that mean aMT6s levels did not differ significantly between the RF and sham conditions for any of the respective time points. Jarupat et al. (Jarupat et al., 2003) exposed eight female participants to a 1960 MHz mobile phone signal to test effects on salivary melatonin. Thirty minutes of exposure were performed each hour from 19:00 to 01:00. In this study saliva was collected at the beginning of and one hour after the series of exposures. Results showed that salivary melatonin levels were significantly reduced after exposure at 02:00. [In addition to uncertainties concerning exposure in both of these studies, no information was provided about randomization or counterbalance of order of about measures to ensure blinding as the phones were kept in the normal use position. Both studies had small sample sizes.]

Table 11.2.1 Studies accessing effects of RF EMF exposure on the reproduction and fertility

Endpoint and Participants	Exposure[a]	Response	Comment	Reference
Nocturnal hormone profiles of serum luteinizing hormone (LH) and melatonin assessed during exposure 22 male volunteers (18-37 years)	GSM mobile phone signals emitted by circularly polarized antenna 40 cm from the vertex of the head, 900 MHz Power density 0.02 mW/cm^2 (0.2 W/m^2), SAR_{10g} 0.03 W/kg (Wagner et al., 1998) 8 h: 23:00–07:00	No effect of exposure.	Single blind, randomized, cross-over. For Sleep EEG see (Wagner et al., 1998) in Section 5.2.2.3.	Mann et al. (1998)
Salivary melatonin and cortisol samples taken during and after exposure 8 male volunteers (20-30 years)	GSM mobile phone signal emitted by circular polarized antenna 10 cm behind head, 900 MHz SAR_{10g} 0.025 W/kg 4 h: 12:00–16:00 or 22:00–02:00; 10 times with RF and 10 with sham	No effect of exposure.	Double blind, randomized, counterbalanced, cross-over. Small group. For immune system see Section 10.2.	Radon et al. (2001)
Urine 6-sulphatoxymelatonin (aMT6s) samples taken after exposure before and after bedtime 55 volunteers (18–60 years; 30 males, 25 females)	GSM mobile phone in test mode against right cheek, 895 MHz SAR_{10g} 0.67 W/kg 30 min, 1 h before bedtime	No effect on total melatonin output. When melatonin metabolite was normalized to creatinine concentrations, the pre-bedtime value was less for EMF compared to sham.	Double blind, randomized, almost counterbalanced, cross-over.	Wood, Loughran & Stough (2006)

Abbreviations: EEG: electroencephalogram; GSM: Global System For Mobile Communication; LH: luteinizing hormone.

[a] SAR with relevant averaging volume (e.g. SAR_{10g}) is specified if included in the paper.

Excluded studies

(Celik & Hascalik, 2004; Davoudi, Brössner & Kuber, 2002; de Sèze, Fabbro-Peray & Miro, 1998; de Sèze et al., 1999; de Sèze et al., 2001; Djeridane, Touitou & de Sèze, 2008; Møllerløkken et al., 2012; Rezk et al., 2008)

11.3 Animal studies

[Please note that the section on animal studies has not yet been amended after review by the Core Group.]

Reproductive and developmental effects of RF radiation were reviewed by WHO (1993) Research on a wide range of species has consistently shown effects at exposure levels causing significant temperature increase in tissues, but no effects have been established at non-thermal exposure levels. The present review focuses on studies published after 1991. The review covers classical teratological endpoints such as malformations and foetal loss, postnatal effects of prenatal exposure, and effects on fertility.

Studies on avian and other non-mammalian species are also reviewed, although there are fundamental problems in extrapolating such data to mammals, and their relevance to assessment of human health risks is limited. Non-mammalian models are useful for investigating basic mechanisms and as screening tests to detect potential risks that should be studied in mammals or humans.

The present search resulted in 413 papers, of which 332 did not fulfil the specifications. Of the resulting 81 papers, 18 were in a language that could not be understood. Five papers were obtained from another source. That left 64 papers to be extracted.

11.3.1 Male fertility

Male fertility has long been recognised as susceptible to heat (AGNIR, 2003). Testicular temperature in mammals is normally clearly below that of the rest of the body, and the development of male germ cells can be adversely affected by increased temperatures. Exposure of anaesthetised rodents to RF radiation that elevate testicular or body temperatures can cause depletion of the spermatogenic epithelium and decreased fertility, but exposure of conscious animals has resulted in little or no significant effects, except after long exposures at thermally stressful levels (ICNIRP, 2009). This difference is most likely explained by the fact that anaesthetics impair the regulation of body temperature. Studies published since 1990 are reviewed below.

Akdağ et al. (1999) reported that the epididymal sperm count decreased and the percentage of abnormal sperm increased in Sprague-Dawley rats exposed for 1 hour daily in 13–52 days to 9.45 GHz CW RF EMF at a whole-body SAR of about 2 W/kg. [Testis SAR was not given; because of the high frequency, absorption of power was superficial, so temperature increase of the testis may have occurred because of high local SAR.]

Forgács et al. (2006)exposed male mice for 2 weeks, 2 h daily during work days, to a GSM 1800 MHz mobile phone signal at 0.018–0.023 W/kg. Increased testicular testosterone and increased red blood cell counts were observed in the exposed animals. No histological changes were observed, and serum chemistry was not affected.

Lee et al. (2010) exposed male Sprague-Dawley rats to a code division multiple access (CDMA) 848.5 MHz RF EMF for 12 weeks. The treatment consisted of two daily 45-min RF exposures at a whole-body SAR of 2.0 W/kg (testis SAR 1.8 W/kg), separated by a 15-min interval. The measurements included sperm counts in the cauda epididymis, malondialdehyde concentrations in the testes and epididymis, frequency of spermatogenesis stages, germ cell counts, appearance of apoptotic cells in the testes as well as p53, bcl-2, caspase 3, p21, and PARP immunoblotting of the testes. No effects were observed. The same group (Lee et al., 2012) used a similar daily exposure protocol to study the combined effects of simultaneous exposure to CDMA and wideband code division multiple access (WCDMA) RF signals. The total SAR was 4.0 W/kg (2.0 W/kg from both signals). Sperm count in the cauda epididymis, testosterone concentration in the blood serum, malondialdehyde concentrations in the testes and epididymis, frequency of spermatogenesis stages, and appearance of apoptotic cells in the testes were measured, and p53, bcl2, GADD45, cyclin G, and HSP70 in the testes were immunoblotted. Again, no effects were observed. Clear responses were found to γ-rays used as a positive control.

Kesari and Behari (2010) exposed male Wistar rats (60 d old) for 2 h/d for 45 days to 50 GHz microwaves at power density of 0.86 μW/cm^2 (8.6 mW/m^2), corresponding to an estimated SAR of 0.8 mW/kg. Changes in several indicators of oxidative stress were detected. In particular, superoxide dismutase and glutathione peroxidase levels were decreased and catalase was increased in sperm cells. Activity of histone kinase was decreased. Changes in cell cycle and increased apoptosis were also reported in the exposed group. [Changes in fertility were not directly assessed.]

Kumar et al. (2011) investigated the effect of 10-GHz CW microwave radiation on several parameters in rat sperm cells. Male Wistar rats (70 d old) were exposed for 2 h/d for 45 days at a power density of 0.21 mW/cm^2 (2.1 W/m^2), corresponding to an estimated SAR of 0.014 W/kg. Changes in sperm cell cycle, increased apoptosis, increased reactive oxygen species and decline in histone kinase activity were observed. In a study with identical design (Kumar, Behari & Sisodia, 2012), the same group reported a decrease in serum melatonin level and increased malondialdehyde and creatine kinase in sperm cells. [The changes in the parameters measured in these two studies were not large, and fertility was not directly assessed.]

Kumar et al. (2013) exposed 70-d old Wistar rats to 10 GHz microwave radiation for 2 h/d for 45 days at a power density of 0.21 mW/cm^2 (2.1 W/m^2), corresponding to an estimated SAR of 0.014 W/kg. Blood samples were collected for the estimation of in vivo chromosomal aberration damage and micronucleus formation. Diameter of the seminiferous tubules and testis weight were decreased in the exposed animals. Caspase-3 activity (indicating increased apoptosis) and DNA strand breaks were increased in spermatozoa of the exposed animals, while serum testosterone level was decreased. Possible changes in fertility were not directly assessed.

Imai et al. (2011) investigated effects on testicular function in male Sprague-Dawley rats exposed to 1950 MHz WCDMA fields at whole-body SARs of 0.08 or 0.4 W/kg for 5 hours per day, 7 days a week for 5 weeks (from the age of 5 to 10 weeks, corresponding to reproductive maturation). No testicular toxicity was evident. There were no differences in body weight gain or weights of reproductive organs. Testis and epididymis sperm counts were not decreased, but the testicular sperm count was significantly increased at 0.4 W/kg. No changes in sperm motility or morphology were observed, and the histological appearance of seminiferous tubules was normal.

Studies not included in the analysis

Several studies have been conducted using a mobile phone for exposing the animals to RF electromagnetic fields. Exposure levels in these studies are either not known or poorly characterized, and it is therefore difficult to interpret the findings. Daşdağ et al. (1999b) reported that the seminiferous tubule diameter in rat testes was decreased after one month of 3-min daily exposures to 890-915 MHz fields from a GSM phone. The authors report a SAR value of 0.14 W/kg, but it is unclear how that value was determined. In a subsequent study, longer (20 min) daily exposures to pulsed 890-915 MHz fields from GSM phones had no effect on lipid composition, malondialdehyde concentration, p53 immune reactivity, sperm count, morphology or histological structure of testes in rats (Daşdağ et al., 2003). The SAR levels given (0.51 W/kg whole body average; 3.1 W/kg peak SAR averaged over 1 g) are maximum levels during the 20 min exposure; the true emission level was varying due to adaptive power control of the mobile phones used for exposure. Kesari et al. (2011) exposed six male rats per group 2h/d for 45 days to 900 MHz mobile phones placed on top of the animal cages. Exposure level is not known. Changes in sperm cell cycle, increased micronuclei in blood, increased ROS level and changes in antioxidant enzyme activities were reported. In a similar study, Kesari and Behari (2012) reported increased sperm caspase-3 activity, decreased serum testosterone and histological changes in the testes. Al-Damegh (2012) placed a GSM mobile phone capable of emitting at 900, 1800 or 1900 MHz at a distance of 50 cm from male rats for 15, 30 or 60 min/d during 14 days (n=30 in the exposed groups, 10 controls). The author reported a power density of 0.02 mW/cm^2 (0.2 W/m^2), but it is not clear how that value was determined. Histological changes in the testes and increased oxidative stress were reported, and vitamins C and E were reported to mitigate the effects. Çelic et al. (2012) exposed male rats (30 exposed, 15 controls) to mobile phones for 3 months. The phones (type and frequency not reported) were placed in animal cages. The phones were on, but it is not clear whether there was any control that they were transmitting. No differences were found in histopathological evaluations, testis weights and seminiferous tubule diameters. Some differences were described in electron microscopic findings, but these were not statistically tested. Mailankot et al. (2009) used a GSM phone capable of operating at 900 and 1800 MHz for exposing 6 male rats per group 1 h/d for 28 days. Distance between the phone and the animals was not given, and it is not clear whether the emissions were controlled (it is only stated that the phone was "in active mode"). No differences were found in sperm count. Reduced percentage of motile sperm was reported, as well as increased lipid peroxidation and decreased GSH in testis and epididymis.

Daşdağ et al. (2008) exposed male rats 2 h/d for 10 months in restrainers placed around an antenna emitting GSM-type 900 MHz fields. The power density was reported to be 0.012-0.149 mW/cm^2 (0.12-1.49 W/m^2) at the location of the testes. [The authors reported SAR values, but these were incorrectly calculated from the electric field measured in air, using an equation that describes the relationship between SAR and electric field in tissue.] No effects on apoptosis (as indicated by caspase-3 activity) were detected in the testes.

Esmekaya et al. (2011) exposed 10 male rats per group to 900 MHz pulsed GSM-type fields 20 min/d for 3 weeks using a horn antenna. The authors reported a SAR value, but this was incorrectly calculated from the electric field measured in air, using an equation that describes the relationship between SAR and electric field in tissue. Increased lipid peroxidation and nitric oxide, as well as decreased glutathione in testis were reported.

The study by Otitoloju et al. (2010) was not performed in controlled laboratory conditions. Mouse cages were placed at a distance of 1 m from existing mobile phone base stations, while the control group was placed further away (300 m) from any base station. No information was given concerning environmental differences (other than EMF level) between the exposed and control groups.

11.3.2 Developmental effects

Numerous studies have shown that RF EMF can cause increased embryo and foetal losses, increased incidence of foetal malformations and anomalies and reduced foetal weight at term, if the SAR level is high enough to raise the maternal body temperature considerably (for detailed review, see (Heynick & Merritt, 2003; ICNIRP, 2009; Juutilainen, 2005; WHO, 1993). The threshold temperature rise for teratogenic effects varies with timing and duration of exposure. The lowest observed thresholds in maternal temperature increase (in experiments with long-term exposure) have been around 1-2 °C, which is consistent with the lowest thresholds for effects from hyperthermia induced by other forms of heating In general, no effects have been found at non-thermal exposure levels, even with exposures that lasted for the whole gestation or continued during the postnatal period. Studies published since 1990 are reviewed below.

Nelson et al. (1998) conducted a study to determine whether the interactive developmental toxicity of RF EMF and the solvent 2-methoxyethanol (2ME) would be affected by environmental temperature. Ten 10 MHz fields sufficient to maintain colonic temperatures at the control value (38 °C), 39.0 °C or 40.0 °C for 2 or 4 h combined with either 0 or 100 mg/kg 2ME at environmental temperatures of 18, 24 and 30 °C were given on gestation day 13 to Sprague Dawley rats. The results were consistent with the view that colonic temperature (not SAR level) determines the developmental toxicity of RF fields (alone or in combination with 2ME).

Nelson et al. (1999) addressed combined effects of RF fields and the known animal teratogen salicylic acid on developmental toxicity in rats. Salicylic acid (0, 250, or 350 mg/kg) was administered by gavage on gestation day 9 or 13. The animals given the chemical on day 9 were also exposed to 10 MHz RF fields at a SAR that was sufficient to maintain colonic temperature at 41 °C for 60 min. The animals given salicylic acid on day 13 were also given 0 or 100 mg/kg 2ME. The foetuses were examined for external malformations. No evidence was found of synergistic interactions between RF radiation and salicylic acid. Limited evidence of antagonism was observed between 2ME and salicylic acid on foetal weights.

Nakamura et al. (2000) exposed virgin and pregnant Wistar rats to continuous wave 2450 MHz RF EMF for 90 min at an incident power density of 2 mW/cm^2 (20 W/m^2), corresponding to an estimated whole-body SAR of 0.4 W/kg. The endpoints included uteroplacental blood flow (critical for successful pregnancy), progesterone, corticosterone, estradiol, prostaglandin E2 (PGE2), and prostaglandin F2a (PGF2a). Decreased uteroplacental blood flow and increased progesterone and PGF2a were observed in pregnant but not in virgin rats. These changes were not observed by pre-treatment with the uteroplacental vasodilator angiotensin II. Exposure-related increase in corticosterone and decrease in estradiol were observed independently of pregnancy and pretreatment with angiotensin II.

In a later study, the same group (Nakamura et al., 2003) compared the effects of RF EMF to those of conventional heating. Pregnant rats were exposed to continuous-wave 915 MHz RF fields or immersed in a water bath to induce an identical increase in colonic temperature. The RF exposures were 0.6 or 3 mW/cm^2 (6 or 30 W/m^2) (estimated SAR 0.4 or 2 W/kg), leading to increases of 1.0 or 3.5 °C in colonic temperature. The same increases in colonic temperature were obtained by immersion in water at 38 or 40 °C. The endpoints included uteroplacental circulation, as well as placental endocrine and immune functions. No differences were found between the effects observed in rats exposed to microwaves at 0.6 mW/cm^2 (6 W/m^2) and those immersed at 38 °C, indicating that heating explains RF field effects at 0.6 mW/cm^2. However, significant decreases in uteroplacental blood flow and estradiol were found in rats exposed to microwaves at 3 mW/cm^2 (30 W/m^2) in comparison to those immersed at 40 °C. [Interpretation of the latter finding is difficult without detailed information about SAR distribution in different parts of the body; identical colonic temperature is not sufficient for excluding significant differences in heating of relevant organs.]

Lee et al. (2009) studied the combined effects of simultaneous exposure to code division multiple access (CDMA) and wideband code division multiple access (WCDMA) RF signals. The total SAR was 4.0 W/kg (2.0 W/kg from both signals). Pregnant mice received two daily 45-min RF-field exposures separated by a 15-min interval throughout the gestation. No effects were observed in a rather complete teratological evaluation (including implantations, prenatal death, resorptions, growth retardation, placental and body weights, sex ratio, and external, visceral as well as skeletal abnormalities).

Ogawa et al. (2009) studied the effects of RF fields on rat embryogenesis using an exposure system that mainly targets the head region. Pregnant rats were exposed to a 1.95-GHz WCDMA field at two exposure levels for 90 min/d during gestational days 7–17. At the higher exposure level, brain average SAR was 1.5 W/kg, while the whole body average SARs were 0.2 W/kg for the dams and 0.11 W/kg for the foetuses. The low exposure group animals experienced SAR values that were one third of those of the high exposure group values. No adverse effects were observed on any reproductive and embryotoxic parameters, including number of live fetuses, dead or resorbed embryos, placental weights, sex ratios, weights or external, visceral or skeletal abnormalities.

Poulletier de Gannes et al. (2012) exposed pregnant Wistar rats for 18 days (2 h/d, 6 d/week) to a 2450 MHz WiFi signal at 0.08, 0.4 or 4 W/kg. Five dams per group were examined for prenatal effects by evaluating number of implantation sites, resorptions, live foetuses, postimplantation losses and macroscopic abnormalities in the foetuses. The remaining dams (15 per group) and their offspring were examined at delivery (number of live and dead pups, sex of the pups and anomalies) and observed for 28 days after delivery; the observations included mortality/morbidity, clinical examinations, body weights, food consumption, post mortem observations, and physical and functional development of the newborns. No exposure-related differences were observed in any of the variables measured.

Aït-Aïssa et al. (2012) exposed pregnant Wistar rats for 2 h/day, 5 days/week to a 2450 MHz Wi-Fi signal at whole-body SARs of 0, 0.08, 0.4, and 4 W/kg. The dams were exposed from day 6 to 21 of gestation and 3 pups per litter were further exposed until day 35 postnatal. Sera from the offspring were screened for antibodies directed against 15 different antigens related to damage and/or pathological markers. No change in humoral response of young pups was observed, regardless of the types of biomarker and SAR levels. No effects were observed on body mass of the dams or pups, number of pups per litter, or clinical signs in the pups. Evaluation of genital tract anomalies (by measuring anogenital distance) showed no differences between the treatment groups.

Pyrpasopoulou et al. (2004) exposed pregnant Wistar rats to pulsed 9.4 GHz fields continuously during days 1–3 or days 4–7 post coitum. The power density applied was 5 $\mu W/cm^2$ (50 mW/m^2), corresponding to a SAR of 0.5 mW/kg. Changes were observed in the expression of bone morphogenetic proteins in newborn kidneys. However, no effects were found on kidney organogenesis.

Behavioural teratology, i.e., prenatal exposure of animals and subsequent assessment of postnatal neural or behavioural effects can be considered as one of the most sensitive systems for investigating possible developmental toxicity. Bornhausen and Scheingraber (2000) exposed Wistar rats to 900 MHz GSM-type fields continuously during pregnancy. The power density was 1 W/m^2 and the estimated SAR 17.5–75 mW/kg. The offspring were tested using nine tests of operant behaviour performance. No performance deficits were observed in the exposed animals.

In another behavioural teratology study, Cobb et al. (2000) exposed pregnant Sprague-Dawley rats to ultra-wideband (UWB) pulses (55 kV/m peak, 1.8 ns pulse width, 300 ps risetime, 1000 pulses/s, 0.1–1 GHz, SAR 0.45 mW/kg). The exposure was 2 min per day during gestation days 3–18, and was continued during 10 postnatal days for part of the animals. No changes were found in 39 of 42 endpoints. The authors concluded that there was no unifying physiological or behavioural relationship among the differences observed (more stress vocalizations, longer medial-to-lateral length of the hippocampus, less frequent mating in exposed males but no difference in fertility). The positive control (lead acetate), in contrast, caused significant effects in numerous endpoints.

Studies not included in the analysis

Several studies were conducted using a mobile phone for exposing the animals to RF EMF. Exposure levels in these studies are either not known or poorly characterized, and it is therefore difficult to interpret the findings.

Ferreira et al. (2006) exposed pregnant rats (six exposed, four controls) for 8.5 h/day to 834 MHz fields from an analogue mobile phone kept at a distance of 29.5 cm from the rat cage. The measured electric and magnetic field strengths were 27–40 V/m and 70–100 mA/m. [The authors also give SAR values, but these were incorrectly calculated from the electric field measured in air, using an equation that describes the relationship between SAR and electric field in tissue]. The main focus of the study was assessment of genotoxicity (by measurement of micronuclei) and indicators of oxidative stress. However, the number of pups per litter was also determined; this was not affected by RF exposure.

Fragopoulou et al. (2010) exposed pregnant mice (seven exposed, five controls) to RF fields from a GSM 900 MHz mobile phone for 21 days, 6 or 30 min/d. The measured electric field strength in the animal cage was 30 ± 5 V/m. No external or soft tissue abnormalities were observed. Skeletal variations in cranial bones and thoracic gage ribs were found in the exposed newborns examined immediately after birth. However, no exposure-related differences were observed in pups that were examined later, after the eruption of teeth.

Aldad et al. (2012) exposed pregnant mice (39 exposed, 42 controls) to a 800-1900 MHz mobile phone placed above the animal cage at 4.5–22.3 cm from the mice. The animals were exposed 9, 15 or 24 h/d for 18 days. The exposure level was not characterized. Hyperactivity and impaired memory was reported in the offspring. Differences were observed also in electrophysiological measurements. [This study is also discussed in Section 5.3.1 (Cognitive function).]

Gul et al. (2009) exposed 30 female mice per group during the whole pregnancy to a mobile phone (type and frequency not reported) kept under the cage. The phone was in speech mode for 15 min per day (standby mode for 11 h 45 min). Decreased number of follicles was reported in the ovaries of female progeny of the exposed rats.

Jing et al. (2012) exposed eight rats per group by keeping a mobile phone (type and frequency not reported) at the ear of the pregnant rat for 10, 30 or 60 min three times per day during 20 days. Exposure level was not characterized. Changes in antioxidant enzyme activities and noradrenaline and dopamine levels were reported in foetal rat brain.

11.3.3 Studies addressing both fertility and developmental effects

Sommer et al. (2009) conducted a multi-generation study to evaluate the effects of 1966 MHz UMTS exposure on fertility and development in mice. Male and female mice experienced life-long exposure (24 h/day) at power densities of 1.35, 6.8 or 22 W/m^2. For adult animals at the time of mating, the mean whole-body SARs were 0.08, 0.4 and 1.3 W/kg. Development and fertility of the animals were observed over four generations by investigating histological, physiological, reproductive and behavioural functions. No effects were observed on measures of male reproductive function, female reproductive function, gross external malformations, or development of the pups. Decreased food consumption was observed in exposed animals. This may be related to energy absorption from the RF field.

Takahashi et al. (2010) exposed pregnant rats during gestation and the progeny during lactation to 2140 MHz RF EMF for 20 h per day. Two exposure levels were used. At the higher exposure level, the average SAR was 0.066–0.093 W/kg for the dams and 0.068–0.146 W/kg for the foetuses and the progeny. At the lower level, the SARs were about 43% of these. The variables measured included growth, gestational condition and organ weights for dams and survival rates, development, growth, physical and functional development, hormonal status, memory function and reproductive ability of the F1 offspring, as well as embryotoxicity and teratogenicity in the F2 rats. No effects were observed in the dams, the F1 generation, or in the F2 offspring. . [This study is also discussed in Section 5.3.1 (Cognitive function).]

Poulletier de Gannes et al. (2013) evaluated the effects of the 2450 MHz WiFi signal on fertility and development in Wistar rats. The exposure was 0.08 or 4 W/kg for 1 h/d, 6 d/week. Males were exposed for 3 weeks and females for 2 weeks. The animals were then mated and the couples were further exposed for 3 weeks. No effects were observed on male or female reproductive organs or fertility. No macroscopic abnormalities were found in the foetuses.

11.3.4 Non-mammalian species

Spiers and Baummer (1991) exposed quail embryos to 2450 MHz RF EMF 8 h/d for 15 days. The eggs (14–34 per group) were subjected to reduced ambient temperatures, and two microwave exposure levels

(3.3–3.8 or 13.2–15.2 W/kg) were used to increase egg temperature by 1.9 or 7.3 °C. No indication of abnormal development was observed in the exposed embryos. The authors concluded that microwaves can be used to increase egg temperature in below-normal incubation temperatures.

Studies not included in the analysis

Saito et al. (1991) exposed chicken eggs continuously to a 428 MHz field. The exposure between two electrodes was apparently not well controlled, and there were inconsistencies in field strengths, power densities and SAR values. Measured electric fields were 14–40 V/m and the estimated SAR values were 3.1 to 47 mW/kg. The findings included decreased hatching, increased mortality and functional abnormality in hatched chickens of the exposed group. The interpretation of these results is difficult due to uncertainties in dosimetry and the fact that the exposed and the sham-exposed control eggs were not incubated simultaneously.

Panagopoulos et al. (2007a) used GSM 900 MHz or DCS 1800 MHz mobile phones for exposing *Drosophila melanogaster* fruit flies 6 min/d for 6 days. The antenna of the mobile phone was held in contact with the glass vial where the flies were grown. Power densities were reported to be 0.283–0.407 mW/cm^2 (2.83–4.07 W/m^2), but these values are probably not correct, as they were measured in the near field, in direct contact or very near to the mobile phone antenna. SAR was not determined. Decreased reproductive capacity, measured as the number of F1 pupae, was reported. In studies with the same experimental model and similar exposure arrangements, the same group has reported increased ovarian cell death (Panagopoulos et al., 2007b), decreased reproductive capacity (Chavdoula, Panagopoulos & Margaritis, 2010; Panagopoulos, Chavdoula & Margaritis, 2010; Panagopoulos & Margaritis, 2010a; b), increased cell death (Panagopoulos, Chavdoula & Margaritis, 2010), increased DNA fragmentation and cytoskeleton disorganization (Chavdoula, Panagopoulos & Margaritis, 2010), and reduced ovarian size (Panagopoulos, 2012). Interpretation of these findings is difficult because of uncertainties in exposure level.

Batellier et al. (2008) exposed chicken embryos to 900 MHz mobile phones during the whole incubation period. Dosimetry to determine SAR was not done. Electric field strengths expressed in dB V/m were reported to be from 0.31 to 15.4. Increased embryo mortality was observed in the exposed and sham-exposed groups compared to incubator controls (conditions and handling were different for the incubator controls). Mortality was higher in exposed than in sham group during one of four periods during incubation, but there was no significant relationship between field strength and mortality.

Weisbrot et al. (2003) exposed *Drosophila melanogaster* flies 2 x 60 min/d for 10 days by placing 1900 MHz GSM mobile phones next to the glass vials where the flies were grown. Electric field strengths of 1.3–3.3 V/m were reported, measured 2.5 cm from the antenna. Increased number of offspring were reported, as well as elevated hsp70 levels, increased serum response element DNA binding and induction of the nuclear transcription factor ELK-1.

Table 11.3.1. Animal studies on fertility, reproduction and development

Endpoint, number, age at start	Exposure	Response	Comment	Reference
Male fertility				
Rat: Sprague-Dawley (n=10) Age not reported, 200-250 g Sperm count, sperm morphology, weight and histology of testis and epididymis	9.45 GHz 1 h/d, 13, 26, 39 or 52 d WB SAR 1.8 W/kg	Decreased sperm count at 52 d, increased percentage of abnormal sperm, changes in testis and epididymis weights and morphology.	Approximate WB SAR by a simple dosimetric model. Testis SAR may have been high.	Akdağ et al. (1999)
Mouse: NMRI (n=11–12) 9-10 weeks Testis histology, testosterone	GSM 1800 MHz 2 h/d, 5 d/week, 2 weeks WB SAR 0.018–0.023 W/kg Free	Increased testicular testosterone. No histological changes.		Forgács et al. (2006)

Rat: Sprague-Dawley (n=20) 30 d Sperm count, spermatogenesis stages, apoptosis in testis, malonaldehyde, protein expression	CDMA 848.5 MHz 90 min/d, 5 d/week, 12 weeks WB SAR 2 W/kg Testis SAR 1.8 W/kg Free	No effects.		Lee et al. (2010)
Rat: Sprague Dawley (n=20; cage control n=5) 4 weeks Sperm count, spermatogenesis stages, apoptosis in testis, testosterone, malonaldehyde, protein expression	CDMA 849 MHz and WCDMA 1950 MHz combined 45 min/d, 5 d/week, 12 weeks WB SAR 4.0 W/kg Free	No effect on serum testosterone; testis, epididymis malondialdehyde, sperm count, apoptosis.	Clear response to γ-radiation (positive control).	Lee et al. (2012)
Rat:Wistar (n=6) 60 d Cell cycle and apoptosis in sperm cells, oxidative stress	50 GHz 2 h/d, 45 d WB SAR 0.86 mW/kg Free	Changes in cell cycle, increased apoptosis, changes in indicators of oxidative stress.	Approximate SAR by a simple dosimetric model.	Kesari and Behari (2010)
Rat: Wistar (n=6) 70 d Several parameters in sperm cells	10 GHz 2 h/d, 45 d WB SAR 0.014 W/kg Free	Changes in sperm cell cycle, increased apoptosis, increased reactive oxygen species and decline in histone kinase.	Approximate SAR by a simple dosimetric model.	Kumar et al. (2011)
Rat: Wistar (n=6) 70 d Spermatozoa: caspase-3, DNA strand breaks, testosterone, electron microscopy	10 GHz 2 h/d, 45 d WB SAR 0.014 W/kg Free	Increased DNA damage and caspase-3, decreased testosterone, testis weight and tubule diameter.	Approximate SAR by a simple dosimetric model.	Kumar et al. (2013)
Rat: Sprague-Dawley (n=24) 5 weeks Body weight and reproductive organ weights, sperm motility and morphology, testis histology, sperm counts	W-CDMA 1950 MHz 5 h/d, 7 d/week, 5 weeks WB SAR 0.08, 0.4 W/kg; testis 0.2, 1 W/kg Free	Testicular sperm count increased at the higher SAR. No other effects.		Imai et al. (2011)
Foetal development				
Rat: Sprague Dawley (n=6) Age not reported, 175–200 g Foetal weights, external malformations	10 MHz 2 or 4 h SAR 8 W/kg initially, then reduced to maintain target temperature Restricted	Developmental toxicity was found to be associated with colonic temperature, not SAR.	Interaction with 2-methoxyethanol was addressed.	Nelson et al. (1998)
Rat: Sprague Dawley (n=10) Age not reported, 200–300 g Resorptions, external malformations	10 MHz 60 min after reaching colonic temperature of 41 ^{o}C WB? SAR 8 W/kg initially, then reduced to maintain 41 ^{o}C Restrained	Increased resorptions. No interaction with salicylic acid.	The study was designed to address interaction of hyperthermia and salicylic acid.	Nelson et al. (1999)

Rat: Wistar (n=6) Virgin females 283±17 g; pregnant females at 9 to 11 days of gestation Uteroplacental circulation, endocrine and biochemical variables	CW 2450 MHz 90 min Power density 2 mW/cm^2 (20 W/m^2), WB? SAR 0.4 W/kg	Decreased uteroplacental circulation, increased PGF2α in pregnant rats. Increased corticosterone and decreased estradiol in virgin and pregnant rats.		Nakamura et al. (2000)
Rat: Wistar (n=6) Age not reported, 269±2.3 g Uteroplacental circulation, placental endocrine and immune functions	CW 915 MHz 90 min Power density 0.6, 3 mW/cm^2 (6, 30 W/m^2), WB? SAR 0.4, 2 W/kg	Uteroplacental circulation and estradiol decreased at 2 W/kg in comparison to water bath at 40^{o}C, which caused identical increase in colonic temperature.	Treatment of controls was not clearly described.	Nakamura et al. (2003)
Mouse: ICR (n=14–12) 8-10 weeks Comprehensive teratological evaluation	CDMA 848.5 MHz or CDMA and WCDMA 1.95 GHz combined 2 x 45 min/d, 18 d WB SAR 2, 4 W/kg Free	No effects.		Lee et al. (2009)
Rat: CD(SD) IGS (n=20) 10 weeks Comprehensive teratological evaluation	WCDMA 1950 MHz 90 min/d, 11 d Dam: brain SAR 0.5, 1.5 W/kg; WB SAR 0.067, 0.2 W/kg. Foetus: WB SAR 0.037, 0.11 W/kg Restrained	No effects on any reproductive or embryotoxic parameters.		Ogawa et al. (2009)
Rat: Wistar Received at day 2 postcoitum Comprehensive evaluation of prenatal and postnatal effects of in utero exposure	WiFi 2450 MHz 2 h/d, 6 d/week, 18 d WB? SAR 0.08, 0.4, 4 W/kg Free	No effects.	Only external abnormalities were examined.	Poulletier de Gannes et al. (2012)
Rat:Wistar (n=10–12) Age not reported Number of pups per litter, anogenital distance,body mass of pups and dams, antibodies against 15 antigens	2450 MHz WiFi 1 h/d, 5 d/week, 16 d WB SAR 0.08, 0.4, 4 W/kg Free	No effects.		Aït-Aïssa et al. (2012)
Rat: Wistar (n of pregnant females not reported; 20–26 newborns per group) Age not reported External malformations, kidney histology, bone morphogenetic protein expression in kidney	9.4 GHz, 50 Hz pulse modulation days 1–3 or days 4–7 post coitum Power density 5 µW/cm^2 (50 mW/m^2), WB? SAR 0.5 mW/kg Free	Changes in the expression of bone morphogenetic proteins in newborn kidney. No effects on kidney morphogenesis, no external malformations.		Pyrpasopoulou et al. (2004)
Rat: Wistar (n=12) 3 months Operant-behaviour performance after in utero exposure	GSM 900 MHz 21 d WB? SAR 17.5–75 mW/kg Free	No effects.		Bornhausen and Scheingraber (2000)

Rat: Sprague-Dawley (n=6) Age not reported, 198.5±2.4 g Behavioral, functional and morphological evaluation of offspring after prenatal and postnatal exposure	Ultra-wideband pulses 0.1–1 GHz 2 min/d, 16 d prenatally, 10 d postnatally WB? SAR 45 mW/kg Restrained	Increased stress vocalizations, increased medial-to-lateral length of the hippocampus, male offspring mated less frequently. No effects on 36 out of 42 endpoints measured.	Clear responses to positive control (Pb).	Cobb et al. (2000)
Both fertility and development				
Mouse: C57 BL (n=64 males; 32 females) 9–10 weeks Male and female reproductive function, external malformations and development of pups	UMTS 1966 MHz 24/d, life-long Power density 1.35, 6.8, 22 W/m^2, SAR 0.074–2.34 W/kg Free	Decreased food consumption, which might be related to RF energy absorption. No other effects.	A four-generation study.	Sommer et al. (2009)
Female? Rat: CR1:CD(SD) (n=12) 10 weeks Growth and organ weights in dams. Survival, physical, functional and behavioural development, hormonal status, reproduction in the F1 offspring. Embryotoxicity and macroscopic abnormalities in F2 offspring	WCDMA 2140 MHz 20 h/d, from d 7 of gestation until 21 d after delivery Dams: WB? SAR 0.066–0.093, 0.028–0.04 W/kg; Foetuses/progeny: WB? SAR 0.068–0.146, 0.029–0.067 W/kg Free	No effects.	Also discussed in 5.3.1.1 and 5.3.1.2.	Takahashi et al. (2010)
Rat: Wistar (n=12) 6–7 weeks Fertility of males and females, histology of reproductive organs, macroscopic abnormalities in foetuses	Wi-Fi 2450 MHz 1 h/d, 3 weeks (males) or 2 weeks (females) + 3 weeks during gestation WB? SAR 0.08, 4 W/kg Free	No effects.		Poulletier de Gannes et al. (2013)
Non-mammalian species				
Japanese quail (n=14–34) Embryo mass, metabolic rate	2450 MHz 8 h/d, 15 d Whole egg? SAR 3.3–3.8, 13.2–15.2 W/kg	No indication of abnormal development.	Eggs were exposed to reduced ambient temperatures, and RF fields were used to increase egg temperature by 1.9 or 7.3 °C	Spiers and Baummer (1991)

Excluded studies

(Atasoy et al., 2013; Atli & Ünlü, 2006; Balmori, 2010; Bas et al., 2009; Inalöz et al., 1997; Magras & Xenos, 1997; Meo et al., 2010; Meo et al., 2011; Ozguner et al., 2005; Rağbetli et al., 2009; Ribeiro et al., 2007; Tsybulin et al., 2012; Yan et al., 2007a; Zareen & Khan, 2008; Zareen, Khan & Minhas, 2009a; b)

11.4 In vitro studies

The previous WHO monograph (WHO, 1993) included no in vitro studies on fertility, reproduction and development. The present literature search identified seven relevant papers in this area. Two papers were obtained from other sources. That left nine papers to be extracted. Among the relevant publications, eight were excluded because sham exposed samples were not included in the study design and thus they did not meet the inclusion criteria for in vitro studies, and references are quoted at the end of this chapter. One paper did not completely comply with the quality criteria for inclusion due to methodological issues, therefore it is only presented in the text.

Studies not included in the analysis

Wu et al. (2012) investigated the effect of RF EMF on rat spermatogenesis. They exposed primary rat Sertoli cells to S-band microwave radiation (power density 100 mW/cm^2) for 4 min and measured cytokine levels. The results of three experiments showed an increase in tumour necrosis factor alpha (TNFα), interleukin (IL)1βand IL6 (cytokines that may act as a pro-apoptotic factor to induce germ cells apoptosis). Moreover, germ cells co-cultured with exposed Sertoli cells showed a significantly higher apoptosis rate than the control germ cells. In addition, germ cell apoptosis was associated with the upregulation of Bax/Bcl-2 and caspase-3, which can interrupt spermatogenesis. The authors summarize that their results suggest that cytokines produced by microwave-radiated Sertoli cells may disrupt spermatogenesis. [In this study, neither dosimetric information nor details on the exposure system set-up are provided. Moreover, it is not clear if the sham controls are actually sham. This study has also been described in Section 12.3.4 (Apoptosis).]

Excluded studies

(Agarwal et al., 2009; De Iuliis et al., 2009; Erogul et al., 2006; Falzone et al., 2008; Falzone et al., 2010; Falzone et al., 2011; Klug et al., 1997; Lukac et al., 2011).

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