9 CARDIOVASCULAR SYSTEM AND THERMOREGULATION

9.1 Cardiovascular system and autonomic nervous system

9.1.1 Epidemiological studies

Some symptoms related to the cardiovascular system were mentioned as part of the "microwave sickness syndrome" in the early Soviet and Eastern European literature, but only one epidemiological study on cardiovascular outcomes was described in the previous Environmental Health Criteria Monograph (WHO, 1993). This study reported an increased risk of heart disease among physiotherapists working with shortwave diathermy (Hamburger, Logue & Silverman, 1983), and the 1993 WHO report concluded that further studies were needed. However, few new epidemiological studies on outcomes related to the cardiovascular system have appeared since then. The literature search identified 8 relevant studies reported in 11 papers. One study was only reported in Russian language. All but one of the studies have used a cross-sectional design, which limits the possibility to draw conclusions about causality. Three of the studies have provided too little information to allow assessment of the representativeness of the included study persons. Only one cohort study has so far been published.

A prospective cohort study was conducted in the UK by Benson and co-workers, as part of the Million Women Study (Benson et al., 2013). The study was focused on cancer outcomes, but included also vascular diseases. Between 1996 and 2001, 1.3 million women were recruited to the cohort through the national breast cancer screening programme. The cohort is contacted with questionnaires regularly, and in 1999–2005, 65% of the originally recruited women answered baseline questions on mobile phone use: how often (never, less than once a day, every day) and how many years they had used a mobile phone. Mobile phone use was reported by 34% of the women who answered the questionnaire in 1999 and 79% reporting in 2005. In 2005, 32% had used a mobile phone at least 5 years. Incident vascular disease was defined as first hospital admission with a primary diagnosis of stroke (ICD-10 I60–69) or ischaemic heart disease (ICD-10 I20–25). In total, 791,710 women free of cancer at baseline were followed for occurrence of stroke or ischemic heart disease. In addition, women with a history of vascular disease at baseline were excluded [it is not stated how many]. The women were followed from the time they answered the 1999–2005 questionnaire until March 31, 2008 in England and December 31, 2008 in Scotland. Their mean age was 60.3 years with a standard deviation of SD 5.1 years. Cox regression models were used for analyses, and control of confounding was made for age, area based socioeconomic status, geographical region, height, BMI, smoking, alcohol, strenuous exercise, and menopausal hormone therapy. In total, 4073 women were identified with a first hospital admission for stroke and 12,592 for ischaemic heart disease during the follow-up period. Ever use of a mobile phone was associated with a RR for stroke of 0.88 (95% CI 0.82–0.94), and for ischemic heart disease 1.04 (95% CI 1.00–1.08). Daily mobile phone use was associated with a RR for stroke of 0.94 (95% CI 0.83–1.07), and for ischemic heart disease 1.25 (95% CI 1.17–1.34), while $\geq$10 years of mobile phone use was associated with a RR for stroke of 0.84 (95% CI 0.70–1.00), and for ischemic heart disease 1.01 (95% CI 0.92–1.11). [The strength of this large cohort study is the prospective design with individual information on amount of mobile phone use which prevents recall bias and selection bias, and reduces non-differential exposure misclassification. Adjustment was made for a large number of potential confounding factors, although stress related factors were not controlled for.]

Bortkiewicz and co-workers (1995; Bortkiewicz, Gadzicka & Zmyslony, 1996; 1997) performed a cross-sectional study of 71 technical personnel and security service workers, aged 20–68 years, at four AM broadcast stations transmitting at frequencies 0.7–1.5 MHz. The unexposed group was 22 workers at two radio link stations, aged 23–67 years. The purpose was to assess "the possible symptoms of impaired neurovegetative control of the cardiac function". Both groups worked in a 4-day cycle with 12 h alternating day and night shifts. Maximum (E_{max}) exposure levels at the broadcast stations were measured at 164.6 ± 187.0 V/m, and daily "doses" at 113.3 ± 75.4 Vh/m. Participants went through a general medical examination, Holter 24 h ECG and ambulatory blood pressure monitoring, and resting ECG measured in the morning before starting work, during 512 "consecutive, normal cardiac evolutions (cycles)", the latter for analyses of late ventricular potentials and heart rate variability. In addition, a questionnaire provided information about for example cardiological and family history of metabolic and circulatory diseases, smoking, alcohol consumption, dietary habits. Differences between exposed and unexposed workers were analysed using chi-square test and Student's t-test or non-parametric Mann-Whitney test. Results were considered significant at $p<0.05$. Selected parameters were analysed with multiple linear regression, including age as a covariate, but no other confounders. ECG abnormalities or pathologies were recorded in 69% of exposed and 50% of unexposed (the difference was not significant, and most of the abnormalities were of no clinical significance). None of the results from 24-h ECG recordings showed significant differences between groups, i.e. heart rate, heart beat duration, heart rate

variability (LF, HF and LF/HF ratio). No significant differences were found in overall 24 h ambulatory blood pressure measurements or in measurements during the day and night analysed separately. However, the day/night ratio for the systolic blood pressure differed significantly ($p<0.05$) between the exposed (1.14 ± 0.09) and unexposed group (1.18 ± 0.09). Additional analyses of the heart rate variability (Bortkiewicz, Gadzicka & Zmyslony, 1996) showed a significant correlation between age and several of the outcomes in the control group, but age was only correlated with a few outcomes in the exposed group. Age stratified analyses of the association between exposure and the outcomes were not presented. [It seems that all selected subjects agreed to participate, although it is unclear if all potentially eligible workers were invited. Based on a later study with similar study procedures it may be reasonable to assume that all workers were included. The study is limited by the cross-sectional design and small number of subjects, especially in the unexposed group. A large number of analyses were performed, and it is unclear if, and how, adjustment for multiple comparisons were made. A few significant differences were found, mainly in sub-analyses. Potential confounding was not controlled, although subjects were reported to have similar age distribution, BMI and working hours. The sex distribution is not described.]

Bortkiewicz and co-workers (Bortkiewicz et al., 2012b) performed another cross-sectional study in Poland with the aim to evaluate the autonomic regulation of the cardiovascular system in workers exposed to VHF and UHF EMF. They measured the heart rate variability of 71 male technical personnel and security service workers, aged 28–66 years, at four broadcast stations operating at frequencies 66–727 MHz, and 42 workers, aged 33–64 years, at four radio link stations. Heart rate variability was measured before work, using standard conditions, during 512 "consecutive, normal cardiac evolutions (cycles)" under resting conditions. A general medical examination was also undertaken, and blood pressure measured. Through an interview, participants provided information about cardiological and family history, dietary habits, and leisure time activities. The workers were divided into two exposure groups: 59 with low-level exposure (with mean electric field in the UHF band 0.1 V/m, in the VHF band 0.3 V/m, and in UHF+VHF bands 0.3 V/m) and 12 with high-level exposure (with corresponding mean electric field levels of 1.1, 2.5, and 2.7 V/m, respectively). The unexposed group consisted of the 42 workers of the four radio link stations, with similar work tasks and work organization as the exposed groups. [All workers currently employed were included in the study, thus there were no selection procedure or non-participation.] The groups differed in age distribution (the high exposure group were younger), alcohol consumption (the exposed groups consumed less alcohol), and self-reported cardiovascular symptoms (51% in the low-level exposure group reported such symptoms, compared to 42% in the high-level exposure group and 29% in the unexposed group). Analyses were made using chi-square test and Student's t-test or non-parametric Mann-Whitney test, Fisher's exact test, covariance analysis, and logistic regression analysis. The latter two included control of confounding from "age, tobacco smoking, alcohol consumption, etc." [it is unclear exactly which confounders were included]. For the time domain parameters of heart rate variability (standard deviation, average, median, modal, min, max of the R-R), the group with low-level exposure had a significantly lower mean standard deviation of the R-R compared to the unexposed group ($p=0.028$), while none of the other parameters differed significantly from the unexposed. No significant differences were found for the highly exposed group. For the frequency domain parameters, the VLF ($p=0.0005$) and LF ($p=0.0025$) bands, and the LF/HF ratio ($p=0.0016$) were significantly higher in the low-exposure group compared to the unexposed, while no significant differences were found between the high-exposure group and the unexposed. The odds ratio for having an LF/HF ratio >1 was significantly increased in the high exposure group compared to the unexposed group. The odds ratio of having a standard deviation of the R-R>27 was significantly increased in the high exposure group with exposure to both VHF and UHF [not stated how many subjects were included in this group], but not in those with only VHF or only UHF. [The study is limited by the cross sectional design and small number of participants in the three groups. A large number of analyses were performed, with no adjustment for multiple comparisons. Limited control of confounding.]

Studies with uncertainties related to inclusion criteria

Three additional cross-sectional studies were identified, but did not present enough details for the assessment of whether participants were representative of the population from which they were recruited. These studies are described below, but are not included in the table.

Bortkiewicz and co-workers performed a cross-sectional study in Poland among people living near mobile phone base stations (Bortkiewicz et al., 2012a), with the purpose to investigate subjective complaints (most of which are reported in Section 5.1.1), including also circulatory symptoms such as palpitations, piercing pain in the region of the heart, anginous pain, heartburn, dyspnoea, arterial hypertension, ischemic heart disease. Suitable flats with a total of 1154 inhabitants from five regions of Łódź were selected for the study according to the transmitting characteristics of base stations in the vicinity. Participants were selected using a uniform procedure. In total, 181 men and 319 women participated and were interviewed about their demographics,

occupational and environmental exposure to EMF, health conditions and subjective complaints. Electric field measurements were performed in the buildings located closest to the azimuth of the antennas and distance was obtained from the housing estate plan. Electric fields above 0.8 V/m were recorded in 12% of the flats. Electric field strength was not correlated with the distance between flats and base stations. Adjustment was made for age, sex, self-reported occupational ELF- and RF-EMF exposure as well as EMF-emitting household equipment. No associations were found between any of the circulatory symptoms and distance to the base station. [The cross-sectional design and assessment of the outcome through self-reports are limitations of the study. The effect risk estimates are not reported; the authors simply state that they found no associations between exposure and the outcomes. It is unclear whether participants were randomly selected and participation rates were not reported.]

In a cross-sectional study from Sweden, Wilén and colleagues included 35 operators of RF sealers from nine different companies and 37 control persons from the same companies (Wilén et al., 2004; 2007). All contacted companies agreed to participate, but it is not stated how subjects within the companies were selected, and no participation rates are reported. The age distribution was similar among exposed and unexposed, while fewer women were included in the exposed group (49%) compared to the control group (62%). Smoking was more frequent among RF operators (46%) than controls (32%). The mean body mass index was the same in exposed and unexposed. Electric and magnetic field strengths were measured in front of each RF sealer used by any of the study subjects at seven positions; head, trunk, waist, knees, feet, and both hands. For each operator daily mean exposure was calculated and induced current in the ankles and in the wrists during ordinary work was derived. A continuous ECG was recorded during a 24 h period, using a two-channel 24 h ambulatory Holter recorder. Data for all subjects were available between 3 pm to 6 am. In addition, cognitive tests and assessment of symptoms were conducted, which are reported in Section 5.1.1. The differences in 24 h heart rates were analysed with repeated measure ANOVA. No confounding control was made. Mean diastolic and systolic blood pressure did not differ between groups. The exposed group had significantly lower average heart rate and experienced more episodes of bradycardia compared to the unexposed. The lower heart rate was confined to night time. In the later publication, analyses of the heart rate variability (HRV) were presented, showing a higher HRV during night time in the exposed group compared to the unexposed. Rhythm disturbances were within normal values. According to the authors, the results indicate a relative increase in parasympathetic cardiac modulation. Exposure levels were quite high and exceeded the ICNIRP reference levels at 11 (16 in discussion) out of 46 measured workplaces. [This study has a small sample size and differences in the distribution of potential confounders between RF operators and controls, or between RF operators with different levels of exposure, were not considered in the analysis. Exposure assessment was very detailed, and the exposed group had very high exposure levels. A large number of outcomes were assessed, with no adjustment for multiple comparisons. The cross-sectional design is a limitation. The representativeness of participating subjects cannot be assessed, given the lack of information about the selection procedure and participation rates. Therefore, the results are not tabulated.]

Vangelova and co-workers performed a cross-sectional study in Bulgaria (Vangelova, Deyanov & Israel, 2006) with two exposed groups: 49 broadcasting station operators (6–25 MHz) and 61 TV operators (66–900MHz), and an unexposed group with 110 operators from radiorelay stations matched by sex, age and shift work schedules, and who had similar work characteristics [no information is provided about procedure for selection of participants or participation rates]. The mean time-weighted-average (TWA) exposure for broadcasting station operators was 3.10–3.96 mW/cm^2 and for TV operators 1.19–1.89 mW/cm^2. Measurements were made of arterial pressure, lipid profile (total cholesterol, HDL and LDL cholesterol, triglycerides and the ratio of total to HDL cholesterol, from fasting blood sample), BMI, waist/hip ratio, smoking habits, family history of cardiovascular diseases. Analyses were made with one-way ANOVA, correlation analysis, chi-square, odds ratio, and stepwise multiple regression. Results showed a higher prevalence of systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg, higher levels of total, HDL and LDL cholesterol, and a higher prevalence of waist/hip ratio >0.90 in the exposed groups compared to the unexposed. In a stepwise regression model that included these variables, age, and the TWA electromagnetic fields, the traditional risk factors for cardiovascular diseases (lipid profile, hip/waist ratio, age) were the only factors that entered the model with blood pressure as the dependent variable. For effects on the total and LDL cholesterol only the variables systolic blood pressure and TWA fields entered the model. [Several important confounding factors were not included in the analysis, e.g. physical activity, sedentary lifestyle, dietary habits. It is unclear whether any confounding control was made in the other analyses presented, or which variables were included in the step-wise regression analyses, e.g. variables such as smoking, alcohol consumption, or family history. With a cross-sectional design it is not possible to draw conclusions about cause and effect. Lack of information about selection procedures and non-participation makes it impossible to assess the representativeness of the persons included.]

Table 9.1. Epidemiological studies of cardiovascular outcomes

Outcome	Country Time period Age	Study population Design	Exposure and outcome categories		Results	Comments	Reference
Stroke, ischemic heart disease	UK 1999–2005 – followed through 2008 Mean age 60.3 (SD 5.1)	791 710 women participating in the UK Million Women Study, who answered a base-line questionnaire 1999 – 2005, excluding those with vascular disease at baseline Cohort study	*Mobile phone use* *Stroke* Ever Daily ≥10 years *Ischemic heart disease* Ever Daily ≥10 years	No. exposed cases 2080 263 137 7191 1055 477	RR (95% CI) 0.88 (0.82–0.94) 0.94 (0.83–1.07) 0.84 (0.70–1.00) 1.04 (1.00–1.08) 1.25 (1.17–1.34) 1.01 (0.92–1.11)	Prospectively collected self-reported information on mobile phone use. Definition of "user" did not require a minimal amount of use. Cox proportional hazards models adjusted for age, area based socioeconomic status, geographical region, height, BMI, smoking, alcohol, strenuous exercise, menopausal hormone therapy.	Benson et al. (2013)
ECG abnormalities,heart rate, heart beat duration, heart rate variability, blood pressure	Poland 1995 Age, exposed 20–68 Age, unexp. 23–67	71 workers at AM broadcast stations (exp.) 22 workers at radio relay stations (unexp.) Cross-sectional study	E_{max} 164.6 ± 187.0 V/m Daily dose: 113.3 ± 75.4 Vh/m No RF among unexposed	*ECG recordings:* *ECG abnorm:* Exposed Unexposed *Heart rate:* Exposed Unexposed *HRV LF:* Exposed Unexposed *HRV HF:* Exposed Unexposed *LF/HF ratio:* Exposed Unexposed *Ambulatory blood pressure measurements:* *Heart rate* Exposed Unexposed *Systolic BP* Exposed Unexposed *Diastolic BP* Exposed Unexposed	 *No. (%)* 60 (69%) 11 (50%) *Mean* 78.8 ± 8.7 79.9 ± 10.2 *Mean* 18.4 ± 8.2 18.5 ± 7.7 *Mean* 25.0 ± 5.5 25.1 ± 5.6 *Mean* 0.73 ± 0.48 0.78 ± 0.45 *24-h (mean)* 78.8 ± 10.7 76.3 ± 11.6 *24-h (mean)* 121.7 ± 15.7 124.3 ± 12.8 *24-h (mean)* 74.9 ± 11.9 77.5 ± 14.2	No description of selection procedures or participation rate. Correlation between age and HRV parameters differed between exposed and unexposed. No control of confounders. None of the differences were statistically significant at p<0.05.	Bortkiewicz et al. (1995; 1996; 1997)

Heart rate variability	Poland 2012 Age, exposed 28–66 Age, unexp. 33–64	71 workers at radio and TV broadcast stations (59 low exp., 12 high exp.) 42 workers at radio relay stations (unexp.) Cross-sectional study	Low exp. mean electric field in the UHF band: 0.1 V/m, in the VHF band: 0.3 V/m, and in UHF+VHF bands: 0.3 V/m High exp. mean electric field levels of 1.1, 2.5, 2.7 V/m, respectively No RF in unexp.	*HRV VLF:* Exposed, high Exposed, low. Unexposed *HRV LF:* Exposed, high Exposed, low. Unexposed *HRV HF:* Exposed, high Exposed, low. Unexposed *LF/HF ratio* Exposed, high Exposed, low. Unexposed	*Mean (SD)* 13.80 (5.40) 14.60 (3.67)* 12.85 (3.88) *Mean (SD)* 27.50 (7.60) 29.28 (5.94)* 24.35 5(.03) *Mean (SD)* 24.60 (6.50) 23.30 (5.27) 26.07 (3.77) *Mean (SD)* 1.00 (0.50) 1.31 (0.35) 0.95 (0.20)	States that all workers were included. 100% participation. * Significant differences ($p<0.05$) only for VLF and LF in the low expsoure group, no significant diferences for the group with high exposure.	Bortkiewicz et al. (2012b)

9.1.2 Volunteer studies

Exposure to RF EMF fields of sufficient levels to cause elevated temperature may cause cardiovascular responses and sweating as part of thermoregulation mechanisms (see 9.2.2.). These responses are controlled by the autonomic nervous system, and the question has been raised whether RF exposures at low levels may provoke cardiovascular responses and other responses regulated by the autonomic nervous system. Relevant endpoints have included respiratory rate, blood pressure, electrodermal activity[1], heart rate and heart rate variability. The autonomic nervous system is divided into the parasympathetic and sympathetic systems, which play different roles in the regulations of these endpoints. For instance, electrodermal activity in response to external stimuli like sounds is completely controlled by the sympathetic nervous system, while both the parasympathetic and the sympathetic systems control heart rate variability. Often the frequency spectrum of the heart rate variability is studied. Commonly the power in the low frequency range (0.025–0.15 Hz) and the high frequency range (0.16–0.35 Hz) are assessed, as well as the ratio between the power in the low frequency and high frequency ranges. The parasympathetic and the sympathetic nervous system have different roles in these frequency ranges (Lyskov, Sandström & Hansson Mild, 2001). There are indications that the functioning of the autonomic nervous system of people with IEI-EMF may deviate from healthy controls (e.g. (Lyskov, Sandström & Hansson Mild, 2001; Sandström et al., 2003; Wilén et al., 2006)). This has motivated studies testing potential effects of EMF, including some in the RF range, on functions regulated by the autonomic nervous system of people with IEI-EMF.

The WHO (1993) report on effects of RF exposure included no study on cardiovascular system or autonomic nervous system responses other than those exploring thermoregulation (see Section 9.2.2). The present literature search identified 47 relevant papers for these endpoints, of which eight were excluded because exposures conditions were not blinded to the participants or the study did not include sham exposure or two or more exposure levels under otherwise similar conditions; these studies are listed at the end of this section. The remaining 39 papers represented 36 studies (two studies had data published in two papers each (Eltiti et al., 2007; Eltiti et al., 2009) and (Wallace et al., 2010; Wallace et al., 2012), and two other studies were published in all together three papers (Borbély et al., 1999; Huber et al., 2000; Huber et al., 2003)). One of the included studies was a meta-analysis ((Augner et al., 2012) which will be described later, i.e. not yet included in the section). Seven other studies failed to control the exposure level, used a fixed order of sham and RF exposure or did not include statistical analyses of the data. These studies are not included in the tables and are briefly discussed at the end of the relevant section under the headline "Papers with uncertainties related to inclusion criteria".

The tables at the end of each section summarize the results of each study and provide information about their methods. Similar information is included in the following text, with the exceptions that the use of double-blind design, meaning that neither participant nor researcher was aware of the exposure conditions, is usually not reported in the text. Comments about particularly small samples sizes are made since the smallest

[1] Electrodermal activity is recorded as the skin conductance by electrodes on the skin. The skin conductance increases with higher skin moisture and therefore reflects the sweat rate.

samples are attached with highest uncertainties provided other study details are similar. Exposure was controlled in all studies that are included in the analysis. If SAR was provided, it is specified in both the tables and text. Otherwise, other exposure measures are provided, or at least output power along with other details of exposure setup.

9.1.2.1 Mobile phone handset related studies

Most volunteer studies exploring effects on the cardiovascular and autonomic nervous system by RF exposures have been performed with signals and localised exposures typical of those that occur when using mobile phones. A few of the studies with base station-like exposures have applied local exposures and exposure levels that are comparable to those caused by exposure when talking on a mobile phone. These are included in this section together with mobile phone handset-related studies.

Studies with healthy adults

In a single blind study, Mann et al. (1998) investigated the effects on heart rate variability of signals from a GSM 900 MHz mobile phone. The phone was placed 40 cm behind the head during sleep in 12 volunteers and resulted in an average power density of 0.5 W/m^2. After an adaptation night, the participants took part in two sessions, one with real exposure and one with sham exposure, in randomized order. Mean heart rate and heart rate variability by means of standard deviation, total spectral power and power in the very low frequency, low frequency and high frequency ranges as well as ratios between low and high frequency powers were analysed for three sleep stages: rapid eye movement (REM) stage, stage II and slow wave sleep (SWS). Inspection of sleep EEG data to specify the various sleep stages was done by personnel blinded to the exposure conditions (J. Röschke. E-mail correspondence with G. Oftedal 2014.05.18). Significant differences were observed between the sleep stages for most parameters, but no statistically significant effects of exposure or combined effects of sleep stage and exposure were observed. [No corrections for multiple analyses were done. The weight of the study is limited due to the low number of participants.]

Braune et al. (2002) exposed volunteers in a single blind study to sham and to RF signals from a GSM 900 MHz mobile phone for 50 minutes each. The phone was mounted in the typical phoning position on the right side of the head and maximal 10 g SAR was measured to be 0.5 W/kg. The sound generated by the phone was masked by applying an external similar sound and insulating material was used to avoid participants sensing heat from the phone. Both conditions were tested on two separate days; one day with the sham session first and one day with the RF session first, randomly determined. Systolic and diastolic blood pressures and heart rate were recorded on the right middle finger and capillary perfusion was measured with a laser Doppler flowmeter on the right index finger. Tests indicated no electromagnetic interference between the mobile phone signals and the measurement hardware used. All physiological parameters were recorded during exposure, for a period in a supine position, then tilted 70° up, and then back to supine. Between the two sessions there was a 15-minute break in a supine position. Seven of the 40 included volunteers suffered from a presyncope during the 10-minute upright tilt during one of the two exposure conditions. These were excluded from the further analysis, but none of the parameters showed statistically significant differences between the excluded group and all participants. Based on results from the remaining 33 participants, no effects of exposure were found.

Tahvanainen et al. (2004) measured heart rate and blood pressure responses to GSM mobile phone signals at 900 MHz (SAR = 1.58 W/kg) and 1800 MHz (SAR = 0.7 W/kg), for 35 minutes in 32 volunteers. Exposures were generated using a dual band mobile phone held next to the dominant-hand side of the head. Each volunteer participated in two sessions at least one week apart: one session included the 900-MHz exposure and a sham exposure and the other the 1800 MHz exposure and sham. The order of exposures was randomized and counterbalanced across the participants. To modulate the cardiovascular physiology and autonomic function during exposure, the participants underwent physiological challenges that consisted of controlled breathing and spontaneous breathing in supine position, a head-up tilt table test and two Valsalva manoeuvres in supine position. After exposure the participants underwent controlled, spontaneous and deep breathing tests. Systolic and diastolic blood pressure and heart rate were recorded with an arm cuff before and at the end of each test of autonomic regulation. Results for each of the GSM conditions were compared to sham separately without revealing any effect of exposure. [This result was obtained without corrections for multiple comparisons. Based on earlier data for systolic blood pressure, it was estimated that 64 participants were needed to obtain a statistical power of 0.08. An associated stopping rule was applied and the stopping criteria were satisfied after 32 participants. The provided SARs were said to be “maximal SAR values”; it is unclear whether the values were obtained by applying an averaged mass of 1 or 10 g.]

Barker et al. (2007) performed a study completed by 120 volunteers to follow up earlier studies with the primary focus on blood pressure. The probability to detect less than 1 mmHg difference in blood pressure was estimated to be 90%. The primary aim was to investigate effects of signals from GSM phones. In addition, TETRA-like signals were included. For both systems modulated as well as continuous wave exposures were used, all exposures resulting in SAR_{10g} of 1.4 W/kg with the mobile phone positioned against the left ear. Devices used for recording blood pressure and heart rate were screened and the distances to the mobile phone were much larger than that required to prevent electromagnetic interference. Each of the six exposures, which included sham for GSM and sham for TETRA, lasted 40 minutes and were separated by at least 7 days. The order of exposure conditions was determined by a balanced Latin square design and participants were randomly allocated to a sequence. Blinding of exposures was tested with no indication that the participants could distinguish between the different exposure conditions. Mean arterial blood pressure, derived from the systolic and diastolic measures, differed between the exposure conditions ($p = 0.04$) as revealed by repeated measures ANOVA. This difference was caused by 0.7 mmHg lower blood pressure (95% confidence interval 0.3–1.2 mmHg) during the GSM sham exposure compared to the other conditions. The blood pressure values during the other conditions, including the TETRA sham exposure, were grouped within a range of ± 0.13 mmHg. Blood pressure recordings were extended to 24 h after exposure. No association with exposure was indicated for the first or last 12 hours periods or for the whole 24 h period. A secondary aim of this study was to test markers for sympathetic nervous system activity: heart rate variability and catechol concentrations. Normalized powers of the high frequency and the low frequency bands of heart rate variability as well as the ratio between these were analysed. None of the three variables for heart rate variability indicated any effect of exposure during the first or last 20-minute periods of exposure or for the whole exposure period. (See Sections 7.2 for the hormone levels). [The only statistically significant finding in this study, the contrast in blood pressure between the GSM sham and the other conditions, is not likely to be a result of the RF signals. If the RF exposures had affected blood pressure, a similar difference would have been expected between the TETRA sham exposure and the RF exposures, which was not the case. The reason for this unexpected result is not clear. However, whereas a 20-minute adaptation period was applied to stabilise the physiological parameters, no information was provided about the time of day for the different exposures. Furthermore, there was no correction for multiple statistical tests and therefore a random significant finding cannot be excluded. In total, this extensive study in terms of number of participants and observation period, did not give evidence for effects of exposure from GSM or TETRA handsets. There was no information about carrier frequencies used in this study.]

Huber et al. (2003) reported results from two studies about heart rate and heart rate variability, derived from ECG recorded before sleep onset and during sleep. In both studies experts blinded to the exposure condition determined the sleep stages from the recorded EEG (P. Achermann. E-mail correspondence with G. Oftedal 2014.06.23). For heart rate variability, spectral power was analysed with a resolution of approximately 0.004 Hz. [This means that the probability to detect changes that might occur in very narrow frequency ranges would be much higher than when analysing the total power of predefined ranges (most commonly the low frequency and the high frequency ranges)]. Both studies applied GSM base station like signals, but with different exposure distributions while spatial maximum SAR averaged over 10 g was similar to those when talking in mobile phones (1 W/kg in both studies). To prevent interference of the exposure with recording equipment, amplifiers were shielded by placing them in metallic boxes and by using filters for all input and output connections. One study, also described by Borbély et al. (1999), used intermittent exposure (15 min on, 15 min off) during the night. The head of 24 male volunteers was exposed to RF signals with an antenna arrangement (three dipole antennas 30 cm behind the head) causing the exposure to be as homogenous as possible irrespectively of the sleeping postures. Each participant was exposed to RF and sham exposures at an interval of one week and in random order. Heart rate and heart rate variability were analysed for different time periods including before sleep onset. No effect on heart rate was observed. Similarly, the whole night average values of the heart rate variability spectra, exhibited no significant differences between the RF EMF and sham conditions, while two significant findings were reported when analysing the data separately for the time intervals: during the RF exposure, a 40.4% decrease in power ($p < 0.05$) was observed for a narrow range (0.10–0.11 Hz) in the low frequency range over the interval between light off and sleep onset, and a 55% increase in power ($p < 0.05$) was observed for a range (0.29–0.31 Hz) in the high frequency area over the first three non-REM sleep episodes. The whole night mean spectra did not reveal any difference between the sham and real exposure session. [The last result was based on only eight participants due to a criterion for minimum number of RR-intervals that could be used in the actual period.] In the other study by Huber et al. (2003), which was also described in another paper (Huber et al., 2000), 16 volunteers were continuously exposed for 30 minutes before a 3-hour sleep period in the morning. Sleep time in the preceding night was restricted to 4 hours. In this study planar antennas were mounted 11.5 cm at the sides of the head. Each volunteer participated in three sessions with right side, left side and sham exposures in random order separated by one week intervals. Sham exposure was compared to left side and right side exposures as well as to the average of recorded values after left and right side exposures. During the 30-

minute exposure period, no effect of exposure was observed for heart rate or heart rate variability. A few statistically significant results ($p < 0.05$) were reported for heart rate among a number of comparisons for the different stages after exposure. For heart rate variability a significant finding was reported for the whole 3-hour sleep period: when averaging the spectra from left and right side exposures, the power in the 0.18–0.22 Hz frequency range (in the high frequency range) was increased by 47.4% ($p<0.05$). However, no significant changes in heart rate variability were observed for the first half hour of the non-rapid eye movement (NREM) sleep period and not when analysing right hand side and left side exposure separately. [Uncertainties are attached to the results, because there are mathematical inconsistencies in some of the heart rate data provided in the paper (related to the calculation of the average heart rates over left and right side exposures). Given the passage of time since the study was performed, the authors have understandably been unable to resolve these issues (P. Achermann, e-mail correspondence with G. Oftedal, 01.02.2013). Furthermore, corrections for multiple tests were not reported for any of these two studies, despite of the high number of analyses.]

Two later sleep studies (Schmid et al., 2012a; Schmid et al., 2012b) were performed in the same laboratory as the ones reported by Huber et al. (2003). The main endpoints in these studies were cognitive effects during 30-minute exposure periods and sleep EEG during 8 hours of night-time sleep following exposure (see Sections 5.2.1 and 5.2.2.3). In addition ECG was recorded during sleep. Also in these studies staff evaluating sleep EEG for sleep stages were blinded to the exposure conditions (P. Achermann. E-mail correspondence with G. Oftedal 2014.06.23). In both studies the participants underwent two real exposure conditions and a sham at weekly intervals in randomized order. Each experimental night was preceded by an adaption night. In one study Schmid et al. (2012a) tested effects of different pulse modulation frequencies (14 and 217 Hz). The 900 MHz RF signals were emitted by planar antenna placed 115 mm from the left side of the head, resulting in a SAR_{10g} of 2 W/kg. Acoustic noise was used to mask any sound that might accompany the RF EMF exposure. Heart rate was averaged over each rapid-eye-movement (REM) episode and over each non-REM episode. No significant effects were reported. In the other study, Schmid et al. (2012b) specifically looked at effects of low frequency pulse modulation without higher harmonics as well as of a magnetic field pulsed at the same frequency. A 900 MHz EMF field pulsed-modulated at 2 Hz was emitted by a patch antenna 115 mm from left side of the head (SAR_{10g} = 2 W/kg) and a magnetic field pulsed at 2 Hz was produced by Helmholtz-like coils (spatial peak magnetic flux density = 0.70 mT). Heart rate was assessed in the same way as in the former study, and also this time without any indication of effect of exposure in any of the sleep stages. [No detailed results were provided for this secondary outcome in any of the studies, but according to information about statistical analysis (Schmid et al., 2012a), no adjustment for multiple comparisons was applied.]

Atlasz et al. (2006) conducted a study with 35 volunteers to test whether autonomic regulation of cardiac functions would be affected by a 10-minute exposure to 900 MHz GSM mobile phone signals. The phone was transmitting at maximum power (2 W during the pulse) and the "local maximum values" of SAR were 1.3 W/kg. The order of real and sham exposures was randomized and real and a dummy loads were used to create the same thermal effects with sham and RF exposures. While the position of the mobile phone during exposure was not clearly described, the authors explained that the same position was used under both exposure conditions. The cardiovascular parameters were recorded simultaneously with ECG and infrared surface plethysmogram. Recordings were done for 5 minutes in supine resting position followed by 5 minutes in standing position during exposure and recordings were also made immediately and 50 minutes after exposure. Neither heart rate nor heart rate variability, in terms of standard deviation of heart rate, differed significantly between sham and RF exposures.

Parazzini et al. (2007) aimed to investigate autonomic nervous system responses by means of standardized time and frequency domain indexes of heart rate variability during exposure to GSM 900 MHz signals. The 26 volunteers took part in one RF and one sham exposure session in random order and separated by at least 24 hours, always within a 4-hour time window in the morning. Each exposure lasted 26 minutes. Sham exposure was obtained by connecting a load to the phone so that the RF signals were dissipated to the load instead of transmitted to the antenna. During exposure the phone was operated at maximum output power (2 W during the pulse) while positioned against the side of head. SAR was measured for the area of interest, 10.5–13.5 cm of deepness in the brain, and in this area SAR was less than 0.02 W/kg. Blinding was tested and confirmed (see Section 5.2.4). The participants underwent a rest-to-stand protocol to elicit a sympathetic response and effects of exposure were assessed for rest, standing and for the difference between rest and standing by continuous measuring ECG. Most of the time domain as well as the three frequency domain analyses of heart rate variability (24 of 27 comparisons) exhibited no effect of exposure. This included all results from the rest condition. For the time domain, when standing, two of the six parameters, triangular interpolation of RR intervals and the triangular index, indicated lower variability during RF than sham exposure (114 vs. 126 and 14.9 vs. 15.9, respectively; $p < 0.05$), and between rest and standing the standard deviation of the individual's

peak intervals (RR) was reduced more under RF exposure than sham (- 9.6 vs. - 8.2; $p < 0.05$). The frequency range parameters consisted of low frequency and high frequency powers, as well as the ratio between them. The low frequency power was higher when standing during RF than during sham (3.00 vs. 2.9; $p < 0.05$) and it exhibited a larger increase between rest and standing when exposed to the GSM signals (0.09 vs. 0.06; $p < 0.05$). All observed changes were small, within the range of physiological variation (Parazzini et al., 2007). [Some caution in the interpretation of the results should be taken because of the large number of comparisons, no corrections for multiple testing and with the "significant" p-values close to 0.05. Therefore, probably none of the results would have been significant if corrections had been applied. Some uncertainty is also attached to the fact that sometimes outliers were excluded to obtain normal distributions, but no information was provided about the number of excluded outliers and the effect of excluding them. Furthermore, no information was provided about controlling for EMF interference with the recording equipment.]

Two studies have been performed with a main focus on superficial, local brain cortex oxygenation (see Section 5.2.3) (Curcio et al., 2009; Spichtig et al., 2012) while cardiovascular responses were also investigated. Curcio et al. (2009) assessed heart rate based on results from 11 female volunteers who participated in a session with 902.4 MHz signal from a GSM mobile phone placed about 1.5 cm from the left ear (SAR = 0.5 W/kg) and a sham session. The conditions were two days apart, at the same time of day and the order was determined randomly. Heart rate was recorded with a pulse oximeter using an adhesive finger probe. A linear decrease in heart rate was observed from the 10-minute adaptation period before exposure till the 10-minute recovery period after exposure, irrespectively of sham and RF exposure, but no effect of the exposure condition was observed. [Due to the low number of participants, it is less likely that potentially small changes in heart rate would have been revealed.]

Spichtig et al. (2012) aimed to test potential effect of exposure "on two different timescales: short-term (effects occurring within 80 s) and medium-term (effects occurring within 80 s to 30 min)". They applied intermittent (20 s on/60 s off) UMTS base station like signals emitted by a planar patch antenna placed 4 cm from the side of the head at two exposure levels with SAR 0.18 W/kg and 1.8 W/kg. Sixteen volunteers were sham and RF exposed for 22 minutes, on separate days at the same time of day. The order of exposures was randomized. Heart rate was derived by using near-infrared spectroscopy (NRIS) for registering brain circulation. Measures were taken to minimize potential EMF interference and test was performed without indicating any effect of exposure on the recorded signals. No effect on heart rate of exposure was observed for the initial 80-second period, but after this initial period and when applying the highest exposure level, the heart rate was less reduced than during sham (difference: 1.84 beats per minute, 99% confidence interval 1.16–2.52). The heart rate did not differ significantly at any time when the two exposure levels of the UMTS signals were compared.

The aim of the study by Ghosn et al. (2012) was to investigate the effects of GSM mobile phone exposure on middle cerebral artery blood flow (see Section 5.2.3). Heart rate was also recorded. Twenty-nine participants attended two 20-minute experimental sessions (one sham exposure and one real exposure session) in which a mobile phone was positioned on the left side of the head (900 MHz, SAR_{10g} = 0.49 W/kg). The sham exposure was obtained by connecting an external load to the external antenna connector of the phone resulting in no measurable SAR; a dummy load was used for the real exposure. The order of the sessions was randomized. The heart rate was recorded by transcranial Doppler sonography before, during and until 20 minutes after exposures. No significant changes of heart rate were observed in either exposure conditions. [Even though results from statistical analyses comparing real and sham were not explicitly provided, graphs suggest that there was no statistically significant difference for heart rate between real and sham sessions.]

Studies including children and adolescents

Two studies (Lindholm et al., 2011; Nam et al., 2006) were identified which included pre-adolescents and adolescents as participants, of which one (Nam et al., 2006) is not included in the overall analysis. Lindholm et al. (2011) hypothesized that it would be possible to detect consequences of central nervous temperature changes in the autonomic circulatory control of the body. They exposed teenage boys (14–15 year old) for 15 minutes to GSM 902.4 MHz mobile phone signals and sham, separated by a 5-minute break, with randomized order of conditions. The mobile phone was placed 4 cm from the right ear resulting in maximum head and brain SAR_{10g} of 2.0 and 0.66 W/kg, respectively. The battery and the loudspeaker of the phone were removed and the antenna was fed with signals from another identical mobile phone via a coaxial cable. Thereby, the temperature of the phone was constant during exposure, as confirmed by recording surface temperature of the phone. To assess effects on the circulatory control, mean arterial pressure, baroreflex sensitivity, the heart rate and heart rate variability from 23 participants were analysed. The heart rate variability was evaluated by means of the

power of the high frequency band. No endpoint exhibited any effect of exposure. Ear canal temperatures and superficial head temperatures did not differ between the exposure conditions.

Studies including IEI-EMF participants

In five studies individuals with IEI-EMF, and in some studies also healthy volunteers, were exposed to signals generated by mobile phones.

In a single blind study, Hietanen et al. (2002) recorded heart rate and blood pressures of 20 IEI-EMF individuals who described themselves as hypersensitive to RF fields emitted from mobile phones. They were exposed for 30 minutes to signals from an analogue mobile phone (NMT at 900 MHz, 1 W output power) and two digital mobile phones: GSM 900 MHz with 0.25 W mean output power and GSM 1800 MHz with 0.125 W mean output power. [SAR was not specified]. The phone was positioned a few centimetres from the right ear so that no heat from the phones should be sensed. The building applied for the test was at a remote place to reduce background exposure levels, which was less than 2 W/m^2 in the RF range. All exposure conditions, including sham, were on the same day, at least 60 minutes apart. The order of conditions was partly randomized so that the sham exposure always occurred as the first or the second one in the sequence of conditions. Compared to sham, the heart rate was lower during the GSM 900 exposure (68.6 versus 71.3, $p < 0.05$) and the systolic blood pressure was lower during the NMT and GSM 1800 conditions (137.3 and 140.9 versus 142, both $p < 0.05$). [These findings indicate reduced stress when exposed to RF signals, which is consistent with fewer reported symptoms during the RF exposures than during sham (see Section 5.2.4). This was not expected since the participants described themselves as sensitive to mobile phone exposure. The authors found a statistically significant effect of order of exposures, with higher blood pressure and heart rate during the first session. The sham exposure always occurred as the first or the second one. Therefore the order, rather than the exposure condition, is the likely explanation of the differences found between sham and real exposures. No information is provided about how blood pressure and heart rate were monitored.]

Wilén et al. (2006) investigated physiological responses to GSM mobile phone like signals in 20 volunteers with and 20 without mobile phone attributed symptoms. The signals were emitted by a base station antenna placed 8.5 cm from the head of the participants, resulting in a SAR_{10g} of 0.8 W/kg. Exposure occurred in a room that had been specially designed to ensure a low background level of power frequency and radiofrequency fields. Using a single blind design, the participants were exposed to sham and RF field sessions on two separate days at the same time of day and in randomized order. Heart rate variability, respiration rate, local finger blood flow and electrodermal activity recorded before and after the 30-minute exposure were analysed. During the recording, the participants underwent first critical flicker fusion threshold test and then memory test, which were considered as stressors with respect to the reactivity of the autonomic nervous system. ECG was used as bases for heart rate and heart rate variability by means of very low frequency, low frequency and high frequency powers as well as from normalized low and high frequency powers and the ratio between the power in the low and high frequency ranges. No effect of the exposure was observed. [Bonferroni correction for multiple comparisons was applied; however, all listed outcomes resulted in p-values much higher than 0.05.]

In a double blind study, Oftedal et al. (2007) used the same exposure system as Wilén et al. (2006), with a 902.4 MHz handset GSM-like signal and SAR_{10g} of 0.8 W/kg. The exposures were conducted in a shielded room. Volunteers who reported pain or discomfort in the head during or shortly after mobile phone calls which lasted between 15 and 30 minutes were invited to take part in an open exposure with the same equipment as used in the blinded tests. Only those who experienced symptoms during the non-blind experiment were allowed to continue to the double-bind test. Each of 17 volunteers underwent a maximum of four pairs of GSM and sham exposures in randomized and counterbalanced order. In total, they completed 65 sham and 65 RF exposures. While the main aim was testing effects on symptoms (see Section 5.2.4), also heart rate and systolic and diastolic blood pressure were monitored before, during and after the exposure, without any indication of an effect of exposure.

Nam et al. (2009) aimed to test whether EMF from CDMA mobile phones influences heart rate, heart rate variability and respiratory rate or gives rise to symptoms or perception. Eighteen individuals with symptoms attributed to CDMA phones and 19 without such symptoms were exposed for 31 minutes to sham and RF signals on separate days in randomized order. The mobile phone was operated in test mode. The lower part of the phone was wrapped with a 5-mm thick insulating material to prevent the participants from sensing heat from the phone when operating. Background exposure levels were measured and RF electric field was 0.7 V/m in the test room. The physiological data were recorded before exposure, after 15 minutes of exposure, immediately after and 10 minutes after exposure. No differences between sham and RF exposure were statistically significant for heart

rate, respiratory rate and heart rate variability as measured by the ratio between the low frequency and high frequency power. However, the heart rate variability parameter exhibited an elevation during the course of the sessions, with significant findings for both groups and both exposure conditions. Skin conductance data were not analysed because the skin conductance was significantly affected when the participants had to respond to questions during the exposure. [Manufacturer data for maximum SAR over 1 g was provided to be 1.22 W/kg. Since the mobile phone operated in test mode and with some distance to the skin by insulation material, the accuracy of the provided value is uncertain.]

Also Kwon et al. (2012) applied 3G (WCDMA) handset-like signals at 1950 MHz and tested almost the same endpoints as Nam et al. (2009). WCDMA modules transmitted signals continuously at constant mean output power resulting in SAR_{1g} of 1.57 W/kg. The modules were placed in a dummy handset 3 mm from the ear to prevent sensing the phone heating. Even though the room used for the tests was not shielded, low background exposure levels were obtained with 0.05 V/m in the 1920–1980 MHz range. Seventeen volunteers who attributed symptoms to 3G phones and 20 controls were exposed to 3G signals and sham for 32 minutes. Exposure sessions were separated by 1–10 days, and their order was randomized. For each participant both sessions were at approximately the same time of day. ECG and respiration was recorded immediately before, at two stages during exposure and again after exposure. The ratio between low and high frequency power of heart rate variability increased with time irrespectively of exposure condition and for both groups of participants. For this endpoint as well as for heart rate and respiratory rate no effect of exposure was observed.

Studies with uncertainties related to inclusion criteria

Three studies with healthy volunteers (Esen & Esen, 2006; Tamer, Gunduz & Ozyildirim, 2009; Yilmaz & Yildiz, 2010) and one with IEI-EMF participants (Mortazavi et al., 2011) have been performed without controlling the level of exposure from mobile phones. One of these (Yilmaz & Yildiz, 2010) and two others (Braune et al., 1998; Nam et al., 2006) applied fixed order of exposures.

Esen et al. (2006) included 15 undergraduate volunteer students. A GSM 900 MHz mobile was kept close to their ear and a "common ringing call for five minutes was used". Skin resistance response was elicited by tapping the patellar tendon. The latency of response was reported to be 200 ms higher during calling compared to sham condition. [No p-value (or confidence interval) for this comparison was provided.]

Tamer et al. (2009) used a dual band (900 and 1800 MHz) GSM mobile phone. In the sham-controlled part of the study, the phone was kept on the breast close to the heart of 24 volunteers for 1 minute, while three exposure conditions were used: the phone off, the phone on and the phone called up while on. None of the assessed variables, heart rate, other ECG derived parameters and blood pressure, differed significantly between the exposure conditions.

Yilmaz et al. (2010) compared a 7-minute period with a GSM 900 MHz mobile phone in standby mode being called up every 30 seconds. Nonlinear analyses of heart rate variability from 16 volunteers indicated higher complexity of the cardiovascular system during the ringing condition than during the stand-by condition.

Braune et al. (1998) tested the effect of exposure to signals from a GSM 900 MHz mobile phone on 10 volunteers. All volunteers underwent both 35 minutes GSM exposure and 35 minutes sham exposure on five days. After each of the exposures heart rate, blood pressure and peripheral capillary perfusion were recorded. The authors reported slightly, but statistically significantly, higher systolic and diastolic blood pressure and lower heart rate after RF than after sham exposure. [Few details about GMS exposure were provided. Furthermore, the sham session always preceded the RF session. In a follow-up study with counterbalanced order of the two exposure conditions (discussed above), Braune et al. (2002) found that the systolic and diastolic blood pressures increased slightly during the course of the tests, as in the study by Braune et al. (1998), but as stated above, no effects of the RF exposure were found. Therefore the observed findings by Braune et al. (1998) were most likely effects of time course and not of the RF exposure.]

Nam et al. (2006) included 42 volunteers, adolescents and adults, in a study where a 30-minute sham exposure was followed by a 30-minute break and then an equally long exposure to signals from a CDMA mobile phone. Changes in heart rate, respiratory rate, skin conductance and systolic and diastolic blood pressures were evaluated. For the analyses, the volunteers were grouped by age (adolescents versus adults) and by gender, respectively, in two separate sets of analyses. No effect of exposure was observed for the adult and female groups. For adolescents and males some statistically significant findings were observed for one of the six

endpoints. [Similar studies, but with counterbalanced design have to be conducted to be able to separate potential effects of exposure and sequence of exposures.]

In a study with 20 students who considered they were hypersensitive to signals from mobile phones, Mortazavi et al. (2011) observed no difference between real RF and sham exposure conditions with respect to heart rate, respiration rate, blood pressure and oral and peripheral temperatures. The participants were "exposed to real mobile microwave radiations" for 10 minutes. [No information was provided about the mobile phone system and mode of operation of the phone and there was no indication of control of exposure level.]

Table 9.2. Mobile phone handset related volunteer studies assessing effects on cardiovascular and autonomic nervous systems

Endpoint and Participants[a]	Exposure[b]	Response	Comment[c]	Reference
Studies with healthy adults				
Heart rate (HR) and heart rate variability (HRV) in time and frequency domains recorded during night exposure 12 male volunteers (21–34 years)	GSM mobile phone 40 cm from the vertex of head, 900 MHz Average power density 0.5 W/m^2 8 h	No effect of exposure.	Single blind, counterbalanced, cross-over. Small sample. No information about control of EMF interference with recording equipment. No correction for multiple analyses. For sleep EEG see Mann et al. (Mann & Röschke, 1996) Section 5.2.2.3.	Mann et al. (1998)
HR, systolic and diastolic blood pressure and capillary perfusion recorded during 4 physiological challenges before, during and after exposure 33 volunteers (20–34 years; 20 males, 20 females before 7 were excluded)	GSM mobile phone in test mode against right ear, 900 MHz SAR_{10g} 0.50 W/kg 2 x 50 min	No effect of exposure.	Single blind, randomized, counterbalanced, cross-over. Control of EMF interference. For endocrine results see Section 7.2.2.	Braune et al. (2002)
HR, systolic and diastolic blood pressure recorded before and at the end of 4 physiological challenges during and 3 of these after exposure 32 volunteers (22–55 years; 16 males, 16 females)	GSM mobile phone against the ear on the dominating hand side 900 MHz: SAR 1.58 W/kg 1800 MHz: SAR 0.7 W/kg 35 min	No effect of exposure.	Double blind, randomized, counterbalanced, cross-over. Statistical power calculated and stopping rule applied. No corrections for multiple analyses. For symptoms see Section 5.2.4.	Tahvainen et al. (2004)
Blood pressure recorded before, during and for 24 h after exposure, HR recorded before and during exposure 120 volunteers (18–65 years; 43 males, 77 females)	Generic mobile phone handset against left ear, 4 mobile phone like signals: GSM modulated wave, GSM carrier wave, TETRA modulated wave and TETRA carrier wave [no information about frequencies] SAR_{10g} 1.4 W/kg 40 min	No effect of exposure.	Double blind, randomized, counterbalanced, cross-over. EMF interference tested. High statistical power. For endocrine results see Section 7.2.2.	Barker et al. (2007)

HR and HRV in frequency domain (0.004 Hz resolution) recorded night sleep during exposure 24 male volunteers	GSM base station-like signals emitted by array of 3 half-wave antennas 30 cm from head and behind bed, 900 MHz; modulation frequency components 2, 8, 217, 1736 Hz and 50 kHz, 87.5% duty cycle SAR_{10g} 1 W/kg 15 min on, 15 min off intervals during the night	No effect on HR. During exposure decreased HRV power in the 0.10–0.11 Hz range in the interval between light off and sleep onset, and increased power in the 0.29–0.31 Hz range averaged over the first three non-REM sleep episodes. No effect of exposure on any all-night mean spectra.	Double blind, randomized, cross-over. Shielding to minimize EMF interference. n=8 in the period between light off and sleep onset. No correction for multiple tests. For sleep EEG see Section 5.2.2.3.	Borbély et al. (1999) Huber et al. (Huber et al., 2003)
HR and HRV in frequency domain (0.004 Hz resolution) recorded during and after exposure until end of a following 3 h sleep period 16 male volunteers (20–25 years)	GSM base station-like signals emitted by planar antenna 11.5 cm from head, left and right exposures in separate sessions, 900 MHz, PM 2, 8, 217, 1736 Hz and 50 kHz SAR_{10g} 1 W/kg 30 min prior to sleep	No effect on HR during exposure. HR reduced before sleep onset after right side exposure and in sleep stage 1 after left and right side exposures. No effects in other sleep stages. Increased HRV power in the 0.29–0.31 Hz range in the 3-h sleep period after exposure. No effect on HRV during the first half hour of non-REM sleep.	Double blind, randomized, cross-over. Shielding to minimize EMF interference. Uncertainties about calculation of average values from left and right side exposures. No correction for multiple tests. For sleep EEG see Section 5.2.2.3.	Huber et al. (2000; 2003)
HR recorded during 8-hour night sleep after exposure 30 male volunteers (20–26 years)	PM signal emitted by planar antenna 115 mm from left side of head, 900 MHz, PM 14 Hz with pulse width 2.3 ms and 217 Hz with pulse width 0.577 ms, respectively SAR_{10g} 2 W/kg 30 min	No effects of exposure.	Double blind, randomized, partially counterbalanced, cross-over. No correction for multiple comparisons. For cognitive effects see Section 5.2.1; for brain electrical activity see Section 5.2.2.3; for discrimination and symptoms see Section 5.2.4.	Schmid et al. (2012a)
HR recorded during 8-hour night sleep after exposure 25 male volunteers (20–26 years)	PM signal emitted by patch antenna 115 mm from left side of head, 900 MHz, PM 2 Hz SAR_{10g} 2 W/kg Pulsed magnetic field from Helmholtz coils over both sides, pulse frequency 2 Hz Peak magnetic flux density 0.70 mT 30 min	No effects of exposure.	Double blind, randomized, partially counterbalanced, cross-over. No correction for multiple comparisons. For cognitive effects see Section 5.2.1; for brain electrical activity see Section 5.2.2.3; for discrimination and symptoms see Section 5.2.4.	Schmid et al. (2012b)
HR and HRV in time domain recorded before, immediately and 50 min after exposure 35 volunteers (22.2±1.9 years; males and females)	GSM mobile phone, 900 MHz SAR 1.3 W/kg 10 min	No effect of exposure.	Double blind, randomized, cross-over. Position of mobile phone not clearly described.	Atlasz et al. (2006)

HR and HRV in time and frequency domains from ECG recorded during exposure 26 volunteers (21–28 years; 14 males, 12 females)	GSM mobile phone against ear at side of dominant hand, 900 MHz Output power 2 W in the pulse, local maximum SAR "in the area of interest" (10.5–13.5 cm from scull) <0.02 W/kg 26 min	For time domain of HRV, effect of exposure for 3 of 6 parameters, for each in 1 of 3 comparisons. For the frequency domain, effect of exposure for 1 of 3 parameters, in 2 of 3 comparisons.	Double blind, randomized, cross-over. Number of and consequences of excluded outliers not specified. No correction for multiple tests. For discrimination of exposures see Section 5.2.4.	Parazzini et al. (2007)
HR recorded before, during and after exposure 11 female volunteers (20–23 years)	GSM mobile phone ~1.5 cm from left ear, 902.4 MHz SAR_{10g} 0.5 W/kg 40 min	No effect of exposure.	Double blind, randomized, cross-over. Small sample. No EMF interference. For subjective endpoints see Section 5.2.4; for brain metabolism see Section 5.2.3.	Curcio et al. (2009)
HR recorded before, during and after exposure 16 male volunteers (26.8 ± 3.9 years)	UMTS base station-like signals, emitted by a planar patch antenna 4 cm from ear, 1900 MHz SAR_{10g} 0.18, 1.8 W/kg 22 min, 20 s on and 60 s off	No effect on HR in the initial 80 s of exposure, HR less reduced by 1.8 W/kg after the initial 80 s. No difference between exposures at 0.18 and 1.8 W/kg.	Double blind, randomized, cross-over. No EMF interference. Tukey correction for multiple comparisons. For subjective endpoints see Section 5.2.4; for brain metabolism see Section 5.2.3.	Spichtig et al. (2012)
HR recorded by transcranial Doppler sonography before, during and after exposure 29 volunteers (21–35 years; 10 males,19 females)	GSM mobile phone left side of head, 900 MHz SAR_{10g} 0.49 W/kg 20 min	No effect of exposure.	Double blind, randomized, cross-over. No correction for multiple comparisons. For autonomic nervous system responses see Section 9.2.1.	Goshn et al. (2012)
Studies including children and adolescents				
HR, HRV, arterial pressure, baroreflex sensitivity recorded before, during and after exposure 23 male volunteers (14–15 years).	GSM mobile phone 4 mm from right ear, 902.4 MHz SAR_{10g} 2.0 W/kg (head), 0.66 W/kg (brain) 15 min	No effect of exposure.	Double blind, randomized, cross-over. For brain metabolism see Section 5.2.3.	Lindholm et al. (2011)
Studies including IEI-EMF individuals				
HR, systolic and diastolic blood pressures recorded during exposure 20 IEI-EMF volunteers (37–67 years; 7 males, 13 females)	Mobile phone 1–5 cm from right ear Analogue NMT phone, 900 MHz: output power 1 W GSM phone, 900 MHz: average output power 0.25 W GSM phone, 1800 MHz: average output power 0.125 W 30 min	HR lower during the GSM 900 condition, systolic blood pressure lower during the NMT and GSM 1800 conditions. Highest HR and blood pressure in the first session.	Single blind, partly randomized order of exposures with sham first or second which may have influenced the results. Background RF fields less than 2 W/m^2. Results in opposite direction of expected. For subjective endpoints see Section 5.2.4.	Hietanen et al. (2002)

HRV in frequency domain, respiration rate, local finger blood flow and electrodermal activity recorded during and after exposure 20 IEI-EMF volunteers (32–64 years; 16 males, 4 females) 20 healthy volunteers (29–65 years; 16 males, 4 females)	Signals from GSM test mobile phone emitted by a base station antenna 8.5 cm from right side of head, 900 MHz SAR_{10g} 0.8 W/kg 30 min	No effect of exposure.	Single blind, randomized, cross-over. Low background exposure levels. Bonferroni correction for multiple comparisons. For subjective endpoints see Section 5.2.4.	Wilén et al. (2006)
HR and systolic and diastolic blood pressure recorded 10 min before, during and after exposure 17 IEI-EMF volunteers (20–58 years; 12 males, 5 females)	Signals from GSM test mobile phone emitted by a base station antenna 8.5 cm from side of head, 902.4 MHz SAR_{10g} 0.8 W/kg 30 min, max. 4 times	No effect of exposure.	Double blind, randomized, counterbalanced cross-over. Shielding to minimize EMF interference. Low background exposure levels. For subjective endpoints see Section 5.2.4.	Oftedal et al. (2007)
HR, HRV in frequency domain, respiratory rate, skin conductance and facial skin temperature recorded before, during and after exposure 18 IEI-EMF volunteers (26.1 ± 3.4 years; 8 males, 10 females) 19 healthy volunteers (25.0 ± 2.3 years; 10 males, 9 females)	CDMA mobile phone next to left side of head, continuous clipped sine waves at 835 MHz (824.64–848.37 MHz) SAR_{1g} 1.22 W/kg 31 min	No effect of exposure.	Single blind, randomized, cross-over. Low background exposure levels. For subjective endpoints see Section 5.2.4.	Nam et al. (2009)
HR, HRV in frequency domain and respiration rate recorded before, during and after exposure 17 IEI-EMF volunteers (30.1 ± 7.6 y; 8 males, 9 females) 20 healthy volunteers (29.4 ± 5.2 years; 11 males, 9 females)	W-CDMA module in a dummy mobile phone 3 mm from ear, 1950 MHz SAR_{1g} 1.57 W/kg 32 min	No effect of exposure.	Double blind, randomized, counterbalanced cross-over. Low background exposure levels. For subjective endpoints see Section 5.2.4.	Kwon et al. (2012)

Abbreviations: CW: continuous wave; CDMA: Code Division Multiple Access; EEG: Electroencephalogram; GSM: Global System For Mobile Communication; HR: hear rate; HRV: Heart rate variability; IEI-EMF: Idiopathic environmental intolerance attributed to EMF; NMT: Nordic Mobile Telephony; PM: pulse modulated; pps: pulses per second; TETRA: Terrestrial Trunked Radio; TDMA: Time Division Multiple Access; UMTS: The Universal Mobile Telecommunications System; W-CDMA: Wideband Code Division Multiple Access.

[a] The maximal number of volunteers participating in analyses is provided. Numbers of male and female participants are provided in the table if included in the paper.

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

[c] Information about control of RF EMF interference with recording equipment is commented if provided in the paper.

9.1.2.2 Base station related studies

Studies with IEI-EMF participants

Four studies have tested potential effects of base station like exposures on cardiovascular and autonomic system responses. All studies included both IEI-EMF volunteers and a healthy control group. One study that was presented in two papers, (Eltiti et al., 2007; Eltiti et al., 2009) applied GSM (combined 900 and 1800 MHz) and UMTS (2100 MHz) base station like signals at low levels, 10 mW/m^2, i.e. similar to those from base stations in the UK (Wallace et al., 2010). The signals were emitted from a base station antenna placed 5 meters from the participant. The two RF exposures as well as a sham exposure were conducted at separate days

549 at the same time of day and with the conditions in randomized order. The tests were conducted in a shielded
550 room, with shielding effectiveness greater than 60 dB in the tested frequency range. Forty four volunteers with
551 IEI-EMF and 114 healthy controls were engaged in tasks causing low and high mental load, and cognitive tests
552 during the 50-minute exposure period. Effects on blood volume pulse (a measure for blood flow), heart rate and
553 skin conductance were analysed for the whole exposure period (Eltiti et al., 2007) as well as for each of the three
554 periods with different mental stress levels (Eltiti et al., 2009). In the latter case, 44 age-matched controls were
555 included in the analyses. No effect of exposure was found for all participants combined or for any of the two
556 groups separately. Mean values as well as standard deviations of the endpoints were analysed. Wallace et al.
557 (2010; 2012) conducted a study with the same study design (also published in two papers), but with TETRA base
558 station-like signals emitted by an antenna placed almost 5 meters in front of the participant. The resulting power
559 density was 10 mW/m^2, as in the previous study. [Only a crude estimate of whole body average SAR was given
560 (~ 0.3 mW/kg).] The tests took place in a shielded room and the shielding effectiveness at 420 MHz was 55–60
561 dB. In this study 48 IEI-EMF individuals and 132 healthy controls participated. For neither group was there any
562 indication of effects of the EMF exposure when the analyses were done for the whole 50-minute exposure period
563 (Wallace et al., 2010). During one of the cognitive tasks the standard deviation of heart rate exhibited a higher
564 difference between TETRA and sham for the IEI-EMF cases than the controls (2.10 versus -0.46, $p = 0.024$), but
565 this was not statistically significant after multiple tests correction ($\alpha = 0.008$, Bonferroni correction). No
566 statistically significant result was obtained for any other of the six parameters (Wallace et al., 2012). [For both
567 these studies the authors calculated that they would be able to detect small effects of exposure with a statistical
568 power of 90% by including 66 participants per group. While both studies were underpowered for the IEI-EMF
569 group, still the number of participants was high. Not all IEI-EMF participants in these studies attributed
570 symptoms to base station exposure; some attributed symptoms only to mobile handset exposure. If the RF
571 exposures applied were too weak to elicit reactions for a significant number of participants, the likelihood of
572 detecting effects, if any existed, would have been lower than expected.]

573 Furubayashi et al. (2009) included 11 women with and 43 women without symptoms attributed to
574 mobile phone handset or mobile phone base stations to assess effects of short term exposure to W-CDMA
575 mobile phone base station. W-CDMA 2140 MHz signals were emitted by antenna placed 3 meters behind the
576 participants, resulting in whole body averaged SAR of 0.0015 W/kg and maximum brain tissue SAR averaged
577 over 10 g of 0.0078 W/kg. A shielded room was used for the tests to assure low background exposure levels,
578 however, no measured levels were provided. The participants were exposed to four 30-minute conditions:
579 continuous exposure to the signal, intermittent exposure with the source turned on and off at random over 5-
580 minute intervals, a sham condition involving noise (65 dB) and a sham condition without noise. The four
581 sessions were conducted on two consecutive days, each day with two sessions separated by at least 2 hours. The
582 order of the different conditions was determined randomly. Heart rate, finger blood flow and temperature from
583 three 5-minute periods, the first, the middle and the last minutes of the 30-minute exposure period, were
584 assessed. There was no indication of any effect of RF exposure compared to sham, and no indications of any
585 difference in responses between the two groups of women. [Since the study included only 11 IEI-EMF
586 volunteers, it is unlikely that potentially small effects of exposure would have been detected in this group, or a
587 difference in effect between the two groups.]

588 *Papers with uncertainties related to inclusion criteria*

589 Havas et al. (Havas et al., 2010) exposed volunteers with and without IEI-EMF to pulse modulated
590 signals from a cordless phone base station. The authors claimed to find a consistent effect on autonomic
591 responses based on monitored heart rates, with similar results for those with and without IEI-EMF. [However, no
592 statistical tests were presented and concerns have been raised about the likely interference of the RF signals on
593 the heart rate monitors (Trottier & Kofsky, 2009). These concerns about artefacts are strengthened by the authors
594 own observation that heart rate responses and recovery were immediate in relation to the RF signals.]

Table 9.3. Base station related volunteer studies assessing effects on cardiovascular and autonomic nervous systems

Endpoint and Participants	Exposure[a]	Response	Comment[b]	Reference
Studies including IEI-EMF individuals				

Blood volume pulse (indication of blood flow), HR, and skin conductance recorded during exposure 44 IEI-EMF volunteers (Initial group (n=58): 46.1 ± 13.5 years; 57.1% males) 114[c] healthy volunteers (Initial group (n=121): 54.5 ± 15.2 years; 57.5% males)	Base station antenna 5 m from participant GSM, 900 and 1800 MHz: combined power density 10 mW/m^2 UMTS, 2020 MHz: power density 10 mW/m^2 50 min: concurrent 20 min low and 20 min high mental load in counterbalanced order, then 8 min cognitive tests	No effect of exposure.	Double blind, randomized, cross-over. Fewer participants than planned and dropouts/excluded caused unbalanced design (almost half of the IEI-EMF volunteers with UMTS exposure first). Low background exposure levels. For cognitive function see Section 5.2.1; for subjective endpoints see Section 5.2.4.	Eltiti et al. (2007; 2009)
Blood volume pulse, HR and skin conductance recorded during exposure 48 IEI-EMF volunteers (18–73 years; 19 males, 29 females) 132 healthy volunteers (18–80 years; 65 males, 67 females)	TETRA signals emitted by antenna 4.95 m in front of participant (upper legs and upwards exposed), 420 MHz, 25 kHz bandwidth, with timeslot occupancy 50% Power density 10 mW/m^2, whole body SAR ~0.27 mW/kg 50 min; concurrent 20 min low and 20 min high mental load in counter-balanced order, then 8 min cognitive tests	No effect of exposure.	Double blind, randomized, counterbalanced cross-over. Shielding and the use of fibre optic cables to avoid EMF interference with recording equipment. Low background exposure levels. Bonferroni correction for multiple tests. For cognitive function see Section 5.2.1; for subjective endpoints see Section 5.2.4.	Wallace et al. (2010; 2012)
Finger skin temperature, HR and local blood flow recorded before and during exposure 11 female IEI-EMF volunteers (27–57 years) 43 female healthy volunteers (21–51 years)	W-CDMA base station like signals emitted by horn antenna 3 m behind the participant, 2140 MHz Electric field strength 10 V/m, brain SAR_{10g} 0.0078 W/kg 30 min continuous and intermittent (randomly on and off at 5 min intervals)	No effect of exposure.	Double blind, randomized, counterbalanced cross-over. Small sample for IEI-EMF volunteers. Shielded room applied for the tests. For cognitive function see Section 5.2.1; for subjective endpoints see Section 5.2.4.	Furubayashi et al. (2009)

Abbreviations: GSM: Global System For Mobile Communication; HR: hear rate; IEI-EMF: Idiopathic environmental intolerance attributed to EMF; TETRA: Terrestrial Trunked Radio; UMTS: The Universal Mobile Telecommunications System ; W-CDMA: Wideband Code Division Multiple Access.

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

[b] Information about control of RF EMF interference with recording equipment is commented if provided in the paper.

[c] In some analyses a lower number of participants were included.

595

596 *9.1.2.3 Studies with other types of exposures*

597 Muller et al. (2004) used an automobile radar system emitting 77 GHz RF pulses at a pulse frequency
598 of 350 kHz) for 15 minutes. The radar was placed 2.5 meters from the participants and the mean power density
599 was 30 mW/m^2 at the site of the participants. Sham and RF sessions were 15 minutes apart and the order was
600 counterbalanced across participants. ECG, respiratory rate, skin temperature and conductance and systolic and
601 diastolic blood pressures were recoded before, during and after exposures. Based on the ECG signals, heart rate
602 and three other parameters (PQ, QS and ST) describing the time course of the signal, were assessed. Data from
603 48 volunteers were included in the analyses and indicated no effect of exposure. [The text incorrectly states that
604 the skin temperature changed slightly by exposure; the corresponding 95% confidence interval (-0.132 to 0.012,
605 Table 3) showed no effect (also before multiple tests corrections) and is correct (J. Müller. E-mail
606 correspondence with G. Oftedal, 07.01.2013).] In another study by the same group, Kantz et al. (2005) applied
607 identical study design as Muller et al. (2004) but the exposure characteristics differed. A much broader
608 frequency range (5.8–100 GHz) was achieved by applying a sequential pattern of microwaves (5 ms for each
609 frequency range), and the exposure level was nearly 20 times higher (597 mW/m^2). HR, skin temperature and

conductance and systolic and diastolic blood pressures were recorded before, during and after exposure. No effect of exposure was found. Despite of a 30 minutes adaptation period, both studies indicated effects of time course between the first and second session, irrespectively of order of the sham and RF sessions. In both these studies, EMF interference between the RF pulses and the recording systems were tested and ruled out before the exposure and the experimental room was "perfectly insulated against external microwaves".

Table 9.4. Volunteer studies with other types of exposure assessing effects on cardiovascular and autonomic nervous systems

Endpoint and Participants[a]	Exposure[b]	Response	Comment	Reference
Studies with healthy adults				
HR and ECG parameters, respiratory rate, skin temperature and conductance and systolic and diastolic blood pressures recorded before, during and after exposure 48 volunteers (18–36 years; 76% male[c], 24% female[c])	Automobile radar system 2.5 m from the participant, 77 GHz RF pulses (350 kHz pulse frequency, 35 ns pulse width) Mean power density 3 μW/cm^2 (30 mW/m^2), temporal peak value 0.24 mW/cm^2 (2.4 W/m^2) 15 min	No effect of exposure.	Double blind, counterbalanced, cross-over. Control of EMF interference. Shielded room applied for the tests.	Muller et al. (2004)
HR, skin temperature and conductance and systolic and diastolic blood pressures recorded before, during and after exposure 50 volunteers (16–78 years; 64% male, 36% female)	RF pulses emitted by array of antennas, six frequencies in the range 5.8–110 GHz presented sequentially, each for 5 ms, the sequence repeated every 35 ms Power density 59.7 μW/cm^2 (597 mW/m^2) 15 min	No effect of exposure.	Double blind, counterbalanced, cross-over. Control of EMF interference. Shielded room applied for the tests.	Kantz et al. (2005)

Abbreviations: HR: hear rate; ECG: Electrocardiogram.

[a] The maximal number of volunteers participating in analyses is provided.

[b] SAR specified if included in the paper.

[c] Calculated including dropouts/individuals whose data were excluded from analyses.

Excluded studies

Ahamed, Karthick & Joseph (2008)
Andrzejak et al. (2008)
Barutcu et al. (2011)
Celik & Hascalik (2004)
Faust et al. (2011)
Monfrecola, Moffa & Procaccini (2003)
Paredi et al. (2001)
Rezk et al. (2008)

9.1.3 Animal studies

The WHO (1993) report concluded that cardiovascular system responses to RF radiation, such as changes in heart rate and arterial blood pressure, are consistent with those associated with thermoregulatory responses to conventional heating. In general, an increase in body temperature elicits several cardiovascular changes, including increased blood flow to the skin, increasing skin thermal conductance, and increased cardiac output, primarily due to an increase in heart rate, in order to maintain arterial pressure within the normal range. For example, vasodilation of the superficial blood vessels of the skin in primates occurs above a threshold whole-body SAR of about 1 W/kg when the RF heating is largely superficial (Adair & Adams, 1980b). Similar responses occur during exposure of primates to 'resonant' frequencies which result in more uniform, less superficial heating (Lotz & Saxton, 1987; 1988) but is associated with larger rises in rectal temperature because the less effective stimulation of skin temperature receptors results in reduced thermoregulatory performance.

Heart rate was increased in rabbits exposed to 2.45 GHz at whole-body SARs sufficient to raise body temperatures by 0.5 ℃ (Chou, Han & Guy, 1980).

The present search resulted in 101 papers, 24 were in a language where expertise was not available for reviewing or translating and 22 were on blood-brain barrier and are discussed in Section 5.3.3. That left 52 papers to be extracted.

9.1.3.1 Effects on the heart

Idikio and Humen (1991) exposed the hearts of five anesthetized Mongrel dogs to an RF current at 740 kHz up to a total energy of 150–300 J in 3–5 s. This was compared with exposures to direct current of 25 J. The hearts were removed at 2–4 h after direct current shock and 24–48 h after RF exposure. At the light microscopic level they observed no differences in the pathology of the heart, but at the electron microscopic level more vascular damage after the RF exposure was found compared to after sham exposure. This is a descriptive study ony, no quantification of the damage is provided. [This high-energy exposure is not relevant for environmental exposures of humans.]

A research group from Pisa, Italy, exposed young and aged Wistar rats to 2.54 GHz at 41 mW/cm^2 (410 W/m^2) for 45 min (Pellegrini et al., 1994) (eight rats per group) or for 45 min per day for 45 days (Soldani et al., 1995) (five rats per group). Within 10 min after the last exposure the animals were killed and the heart and aorta removed. They histologically investigated noradrenergic fibres and determined agonist activity (isoprenaline, noradrenaline) in the heart and aorta. After the single exposure they observed an increase in noradrenic fibres in the atria, ventriculi and aorta of both young and old animals ($p<0.01$), while after the repeated exposures an increase was observed in the atria and ventriculi of young animals ($p<0.005$), and in the ventriculi ($p<0.01$) and aorta of aged animals ($p<0.005$). The response to agonists decreased in the atria and increased in the aorta after single exposure in old animals ($p<0.05$), while no changes were observed in the young rats. With repeated exposures similar responses were observed in both age groups.

Lu et al. (1999) exposed groups of five Wistar-Kyoto rats for 6 min to pulsed ultrawide-band (UWB) EMFs. The low UWB had a frequency range of 0.09–2.78 GHz, pulsed at 500 Hz, and an whole-body SAR of 0.07 W/kg. The frequency range of the high UWB was 0.10–2.50 GHz, pulsed at 1000 Hz, and had an whole-body SAR of 1.21 W/kg. Immediately and up to 4 weeks after exposure heart rate and blood pressure were measured, while body weight was determined up to 4 weeks after exposure. No changes in body weight and heart rate were observed, but after each of the exposures the blood pressure was reduced ($p<0.05$ compared to shamexposure) during the follow-up period of 4 weeks.

Ronchi et al. (2004) exposed Sprague Dawley rats in the near field to a broadband signal (0.2–20 MHz) and measured normal heart function and heart function after ischemia and reperfusion. They used two exposure levels: low (30 V/m, 11.4 µT) and high (200 V/m, 36.1 µT). Exposures were given 5 days per week for 3 weeks, the low field for 2 min per day and the high field for 10 min per day. After the last exposure the hearts were removed and either frozen for determination of heat shock protein 70 (HSP70) and malondialdehyde (MDA) (n=9), or used for the ischemia and reperfusion (n=12). Following ischemia and reperfusion they observed an increased diastolic pressure with the lower exposure level only ($p=0.01$). [It is puzzling that for diastolic pressure stronger effects were observed with the lower exposure level and shorter exposure time. The results for HSP70 and MDA are discussed in Section 9.3.1.4.]

Studies not included in the analysis

Colak et al. (2012) exposed Wistar rats (n=7–9) to a UMTS signal from a mobile phone and assessed the effect of administration of melatonin on heart rate, blood pressure and ECG parameters. The phone was mentioned to be held for 20 min in listening mode, 20 min in speaking mode, and standby for the rest of the time. No effect was observed of the UMTS exposure alone or in combination with the administration of melatonin on any of the endpoints compared to the sham-exposed group. [Since the actual exposure was not determined, the results of this study cannot be properly interpreted.]

Table 9.5. Animal studies on effects of RF exposure of the heart

Endpoint, animals, number per group, age or weight at start	Exposure: source, schedule, level, freely moving or restrained	Response	Comments	Reference

Light and electron microscopic lesions in heart Dog: Mongrel (n=5) Age/weight not provided	750 kHz 3–5 s Heart: 150–300 J Anaesthetized	No difference observed with light microscopy, more vascular damage after RF at ultrastructural level.	Local high energy deposition to the heart (shock).	Idikio and Humen (1991)
Histology of noradrenergic fibres and agonist activity (isoprenaline, noradrenaline) in heart and aorta sections Rat: Wistar (exposed, sham: n=8; cage control: n=8) 3 or 21 months	2.45 GHz 45 min 41 mW/cm^2 (410 W/m^2) Restrained	Increased noradrenic fibres in atria, ventriculi and aorta of young and old animals; response to agonists decreased in heart, increased in aorta in old animals.		Pellegrini et al. (Pellegrini et al., 1994)
Histology of noradrenergic fibres and agonist activity (isoprenaline, noradrenaline) in heart and aorta sections Rat: Wistar (exposed, sham: n=5; cage control: n=8) 3 or 21 months	2.45 GHz 45 min per day, 45 days 41 mW/cm^2 (410 W/m^2) Restrained	Increased noradrenic fibres in atria of young animals, ventriculi of young and old animals and aorta of aged animals; response to agonists decreased in heart, increased in aorta in young and old animals.		Soldani et al. (1995)
Body weight, heart rate, blood pressure Rat: Wistar-Kyoto (n=5) 71–89 d	UWB: low: 0.09–2.78 GHz high: 0.10–2.50 GHz 6 min low: WBA SAR: 0.070 W/kg high: WBA SAR: 0.121 W/kg Restrained	No effect on body weight and heart rate; decreased blood pressure with both UWB levels.	Effect below exposure limit.	Lu et al. (1999)
Blood pressure, resistance to ischemia/reperfusion Rat: Sprague Dawley (n=12) 200–250 g	Broadband: 0.2–20 MHz low field: 30 V/m, 11.4 µT, 2 min/day high field: 200 V/m, 36.1 µT, 10 min/day, 5 days/week, 3 weeks Free or restrained not reported	Increased diastolic pressure after ischemia and reperfusion with lower level exposure.	Absence of effects with higher exposure level and longer exposure time puzzling. Oxidative stress parameters described in 9.3.1.4.	Ronchi et al. (2004)

Abbreviations: E-field: electric field; H-field: magnetic field; UWB: ultra wide-band; WBA SAR: whole body average SAR.

683

684 *9.1.3.2 Effects on blood vessels*

685 Miura and Okada (1991) studied vasodilatation in the skin of the web of frogs. The exposure level was
686 too low to result in any heating, and the web was perfused with a Ringers solution kept at 20 °C, so any vascular
687 effects would not be the result of heating. They exposed the skin to RF fields of 0.1, 1 or 10 MHz applied in
688 bursts of 0.05 ms, 500 pulses/burst, for 60 min, at two exposure levels per frequency (see Table 9.6) with 6–30
689 frogs in each group. Vasodilatation was observed with all frequencies and field strengths. When Ca^{2+} was
690 removed from the perfusate, RF-induced vasodilatation was increased, while when the Ca^{2+} level was increased
691 to twice the normal level, it was decreased. Removing Na^{+} from the perfusate had no effect on vasodilatation.
692 The authors suggest that RF exposure may induce an outflow of Ca^{2+} through the plasma membrane of smooth
693 muscle cells, and/or an influx of Ca^{2+} into the sarcoplasmatic reticulum through activation of guanylate cyclase.

Masuda and colleagues investigated the effect of acute (Masuda et al., 2007a) or subchronic (Masuda et al., 2007b) exposure to 1439 MHz RF fields to the brain in Sprague Dawley rats on the microcirculation in the brain. The acute exposure lasted for 10 min and the brain SARs were 0.6, 2.4 and 4.8 W/kg; the animals (6 per group) were restrained and anaesthetized and measured before and after exposure. The subacute exposure was for 60 min per day, 5 days per week during 4 weeks at a brain SAR of 2.4 W/kg; these animals were restrained but not anaesthetized and a sham exposure group was used (n=11). No effect of either treatment on the brain microcirculation was observed. The subacute exposure also did not result in any increase in brain temperature, but with the highest SAR in the acute exposure, a slight increase in brain temperature of 0.7 °C was measured ($p<0.05$). [The authors also studied the effects on the blood-brain barrier permeability; this is discussed in Section 5.3.3.]

Studies not included in the analysis.

McMeeken and Bell (1990) investigated the effects of microwave irradiation on blood flow in the dog hind limb. They exposed 11 Mongrel dogs for 10 min to the signal from a commercial microwave generator and measured an increased temperature in the skin and muscle, as well as an increased blood pressure (no p-values provided), heart rate ($p<0.01$) and blood flow ($p<0.05$). [The lack of any information on the type and dose level of the RF field makes it impossible to interpret this study.]

Burton et al. (1991) exposed rabbits to a 2450 MHz field for 7–15 min. They intended to produce a regional hyperthermia in the liver and measured hepatic blood flow. They observed a decreased blood flow in the hepatic artery ($p<0.01$), but no effect in the portal vein. [No dose level is provided, therefore this study cannot be interpreted.]

Table 9.6. Animal studies on vascular effects

Endpoint, animals, number per group, age or weight at start	Exposure: source, schedule, level, freely moving or restrained	Response	Comments	Reference
Arteriole diameter Frog (n=6–30) 20–30 g	0.1, 1, 10 MHz, in 0.05 ms bursts, 500 pulses/burst 60 min 10 MHz: 0.219 kV/m, 0.73 µT; 0.900 kV/m, 3.01 µT 1 MHz: 1.611 kV/m, 5.39 µT; 7.978 kV/m, 26.68 µT 0.1 MHz: 17.417 kV/m, 58.23 µT; 84.276 kV/m, 281.78 µT Restrained	Vasodilatation observed with all frequencies and field strengths, without heating; increased Ca^{2+}: reduced vasodilatation; no Ca^{2+}: increased vasodilatation; no effect Na^{+}. Suggestion: Ca^{2+} outflow from plasma membrane of smooth muscle, influx in sarcoplasmatic reticulum through activation of guanylate cyclase.	Co-financed by industry.	Miura and Okada (1991)
Leukocyte behaviour, plasma velocity, vessel diameter Rat: Sprague Dawley (n=6) 10–11 weeks	1439 MHz 10 min Brain SAR: 0.6, 2.4, 4.8 W/kg Anaesthetized	No effect on brain microcirculation, slight brain temperature increase only with 4.8 W/kg.	Also discussed in 5.3.3 (Blood brain barrier).	Masuda et al. (2007a)
Leukocyte behaviour, plasma velocity, vessel diameter Rat: Sprague Dawley (n=10) 10–11 weeks	1439 MHz 60 min/day, 5 days/week, 4 weeks Brain SAR: 2.4 W/kg Restrained	No effect on brain microcirculation, temperature increase.	Also discussed in 5.3.3 (Blood brain barrier).	Masuda et al. (2007b)

9.1.3.3 *Oxidative stress*

Several studies investigated parameters associated with oxidative stress in elements of the cardiovascular system.

In a study described in Section 9.3.1.1, Ronchi et al. (2004) exposed Sprague Dawley rats in the near field to a broadband signal (0.2–20 MHz) and measured normal heart function and heart function after ischemia and reperfusion. After the last exposure the hearts were removed and frozen for determination of heat shock protein 70 (HSP70) and malondialdehyde (MDA) (n=9). They observed an increased HSP70 level in heart muscle only after the low field exposure ($p=0.01$) and an increased MDA level after both the low ($p<0.05$) and the high field exposures ($p=0.008$). Overexpression of HSP70 is considered to be cardioprotective (Benjamin & Christians, 2002), while MDA is indicative of oxidative stress. [It is puzzling that for HSP70 stronger effects were observed with the lower exposure level and shorter exposure time. The effects on ischemia and reperfusion are discussed in Section 9.3.1.1.]

Kim and Rhee (2004) exposed groups of 10 Sprague Dawley rats for 15 min to 2.54 GHz at a whole body SAR of 9.2 W/kg with or without green tea catechin, which is supposed to be a radical scavenger. The catechin was administered in the food, either at 0.25% or 0.5%. Six days after exposure the hearts were removed and analysed for several indicators of oxidative stress. Increased levels of cytochrome P450, NADPH cytochrome P450 reductase, superoxide radical, lipid peroxide, carbonyl value and lipofuscin, and a reduced level of superoxide dismutase and glutathione peroxidase were observed, indicating increased oxidative stress (all $p<0.05$). Catechin had a dose-dependent anti-oxidant effect, but there were still changes after the RF EMF exposure.

Esmekaya, Ozer and Seyhan (2011) studied the effect of exposure to a 900 MHz, 217 Hz pulsed RF field at a whole-body SAR of 1.2 W/kg, applied for 20 min per day for 3 weeks to Wistar rats (n=10). In the liver, lung, heart and testis they found malondialdehyde (indicating lipid peroxidation) and nitric oxide to be increased and glutathione to be decreased ($p<0.001$–0.05). [This indicates an increased level of oxidative stress in these tissues.]

Türker et al. (2011) investigated in Wistar rats the effect of exposure to a 2.54 GHz, 217 Hz pulsed signal in the presence or absence of selenium or L-carnitine. Groups of 6 animals were exposed for 60 min per day during 28 days at a whole-body SAR of 0.143 W/kg, but the animals were exposed primarily to the head, since they were facing the exposure source. [From the figure of the exposure setup it can be derived that the E-field at the location of the heart is approximately 10–12 V/m, corresponding to an SAR of 0.12–0.17 W/kg.] They measured several indicators for oxidative stress in heart tissue. After RF exposure alone malondialdehyde level was increased ($p<0.01$); with concomitant administration of selenium or L-carnitine no significant change was observed. Vitamine A, C, E were reduced after RF exposure ($p<0.001$–0.05), no reductions were observed after selenium and L-carnitine administration. No changes in glutathione, glutathione peroxidase and β-carotene levels were observed in heart tissue in the RF exposed animals. Thus there were some indications for oxidative stress, but there was no increase in antioxidants.

Studies not included in the analysis.

Ozguner et al. (2005) exposed anesthetized Sprague Dawley rats (n=10 per group) for 30 min per day during 10 days to a 900 MHz, 217 Hz pulsed signal with or without the radical scavenger caffeic acid phenethyl ester (CAPE). The whole-body SAR was reported to be 0.016 W/kg, the SAR in the head was 4 W/kg. In the heart they measured increased levels of malondialdehyde and nitric oxide and decreased levels of the antioxidants superoxide dismutase, catalase and glutathione peroxidase, indicating increased oxidative stress. These changes were not observed when CAPE had been administered. [The exposure configuration is not clear. The antenna appears to be parallel to the body, which would result in a rather homogeneous exposure, but the reported high SAR in the head contradicts this. Consequently the SAR in the heart, the organ of interest in this study, is unknown.]

Table 9.7. Animal studies on oxidative stress in the heart

Endpoint, animals, number per group, age or weight at start	Exposure: source, schedule, level, freely moving or restrained	Response	Comments	Reference

Myocardial protein expression Rat: Sprague Dawley (n=12) 200–250 g	Broadband: 0.2–20 MHz low field: 30 V/m, 11.4 µT, 2 min/day, high field: 200 V/m, 36.1 µT, 10 min/day, 5 days/week, 3 weeks Free or restrained not reported	Increased myocardial HSP70 after lower level exposure; MDA in heart increased in low and high field.	Absence of effects with higher exposure level and longer exposure time puzzling. Blood pressure parameters described in 9.3.1.1.	Ronchi et al. (2004)
Cytochrome P450, NADPG cytochrome p450 reductase, SOD, GSH-Px, superoxide, lipofuscin, carbonyl value, lipid peroxidase, in heart Rat: Sprague Dawley (n=10) 100 g + 1 week acclimatization	2.54 GHz with/without green tea catechin (0.25% or 0.5% in food) 15 min WBA SAR: 9.2 W/kg Free or restrained not reported	Increased cytochrome P450, NADPH cytochrome P450 reductase, superoxide radical, lipid peroxide, carbonyl value & lipofuscin, reduced SOD, GSH-Px, dose-dependent anti-oxidant effect of catechin.	Increase in oxidative stress 6 days after exposure, partially counteracted by catechin.	Kim and Rhee (2004)
MDA, GSH, NOx in heart, liver, lung, testis Rat: Wistar (n=10) 2 months	900 MHz, 217 Hz pulsed 20 min/day, 3 weeks WBA SAR: 1.2 W/kg Restrained	MDA and NOx increased; GSH decreased.	Results indicate increased oxidative stress in tissues.	Esmekaya, Ozer and Seyhan (2011)
MDA, GSH, GSH-Px, β-carotene, vitamin A, C,E in heart Rat: Wistar (n=6) 3 months + 1 week acclimatization	2.54 GHz, 217 Hz pulsed with/without selenium or L-Carnitine 60 min/day, 28 days WBA SAR: 0.143 W/kg Restrained	MDA increased, at control level with Se and L-Carnithine administration; vitamin A, C, E reduced, no effect after Se and L-Carnithine; no effect RF on GSH, GSH-Px, β-carotene.	SAR to the heart can be calculated to be approximately 0.12–0.17 W/kg.	Türker et al. (2011)

Abbreviations: GSH: glutathione ; GSH-Px: glutathione peroxidase; MDA: malondialdehyde; NADPG: nicotinamide adenine dinucleotide phosphate; NOx:nitric oxide ; Se: selenium; SOD: superoxide dismutase; WBA SAR: whole-body SAR.

9.2 Thermoregulation

9.2.1 Volunteer studies

During exposure to RF fields, part of the RF energy is absorbed by the body as heat. The aim of this section is to review changes in body temperatures and physiological responses to heat load caused by RF exposure in volunteer studies. Additional information about temperature elevations as well as about SAR in humans during RF exposure have been obtained in studies applying data simulations or phantoms. These studies are reviewed in Sections 3.3 and 3.4. RF exposure is one of many factors that may add to the thermal load of the body. Thermoregulation in response to increased heat load in general is discussed first, as a basis to evaluate physiological thermoregulation during RF exposure.

9.2.1.1 Thermoregulation in humans

Hot environments and physical activities are important factors contributing to the heat load of the body. The potential temperature elevation of the body depends on the absorbed environmental energy, environmental factors like humidity and air flow, total metabolic heat production (including that from working muscles) and thermoregulation mechanisms. In the following, background information is provided about heat stress and temperature regulation. This is also discussed by WHO (1993), Adair and Black (2003) and Donaldson, Keatinge and Saunders (2003).

The body core temperature is relatively constant at about 37 °C with a circadian variation of ± 0.5 °C, but an increase in the core temperature naturally occurs in pathological conditions with fever. Temperature regulation maintains the body core temperature within a narrow range. The brain centre for autonomic thermoregulation controls the body temperature based on signals from temperature sensors and activates thermoregulatory responses. The sensors are distributed around the body, in the brain, spinal cord, abdominal structures and the skin (Adair & Black, 2003).

During environmental heat exposure or physical exercise, thermoregulation is activated by cardiovascular responses, which includes increased skin blood flow enhancing heat loss to the environment by radiation and convection, and by increased sweat rate resulting in higher evaporative heat loss (Adair & Black, 2003; Donaldson, Keatinge & Saunders, 2003). Environmental temperature, humidity and air flow are essential factors for the heat loss. In addition to these autonomic responses, body temperature is regulated by behaviour such as regulating clothing and the level of physical activities (Adair & Black, 2003; Schlader, Stannard & Mundel, 2010).

Crandall and González-Alonso (2010) have reviewed cardiovascular functions in humans under heat stress at rest and during physical exercise. During passive heating the increase in skin blood flow causes an increase in the total vascular conductance. The arterial blood pressure is preserved with no or only minimal reductions due to increased heart rate and decreased vascular conductance of non-cutaneous beds. The venous blood pressure, however, is pronouncedly reduced, which hampers the filling of the left ventricle, but due to increased left ventricular contractility, the stroke volume is preserved. Physical activity in combination with environmental heat exposure challenges the thermoregulatory capacity, not only because of the extra metabolic heat production, but also because of the need for additional blood supply to the active muscles. Intense whole body physical activity in hot environments may result in significant cardiovascular strain characterized by reduced cardiac output, stroke volume, arterial pressure and blood flow to the brain, skin and exercising muscles. Dehydration is also a factor that adds to the strain of the cardiovascular system and is important for sweat response as well.

Change in the body's heat storage is determined by the metabolic heat production and the heat exchange with the environment. The metabolic heat production at rest is around 1 W/kg, and can reach up to some 10 W/kg during heavy exercise and even more during sport activities. The values, however, vary greatly between individuals (Donaldson, Keatinge & Saunders, 2003). During moderate heat exposure the body core temperature is maintained, but the total body heat storage will increase slightly by increasing the peripheral body temperature (Adair & Black, 2003; Donaldson, Keatinge & Saunders, 2003). During physical exercise, the core temperature rises until autonomic regulation has resulted in a balance where heat loss equals heat gain. The resulting core temperature depends on the intensity of the physical activity and little on the ambient temperature in the range 5–30 °C (Schlader, Stannard & Mundel, 2010)**.** Prolonged severe environmental heat loads, and particularly in the combination with physical exercise may ultimately lead to an unacceptable elevation of the core temperature. For some individuals elevation in body temperature will be regarded as intolerable after 1-2 hours of increases in heat storage at rates of 0.5–1.0 W/kg (Donaldson, Keatinge & Saunders, 2003).

As illustrated above, humans have a large capacity for autonomic regulation of body temperature by increasing skin blood flow and sweating. The cardiovascular strain by environmental heat stress strongly depends on the level of physical activity and is also worsened by dehydration.

9.2.1.2 Thermoregulation during RF exposure

During RF exposure, heat absorption may occur to varying degrees in the whole body or in a part of the body. Heat absorbed by a part of the body is distributed to other parts primarily by the blood flow and eventually lost to the environment. Based on the general knowledge about heat stress and responses as summarised above, it would be expected that the heat load resulting from RF exposure causes increased sweat rate and cardiovascular responses which include increased skin blood flow, reduced venous blood pressure and possibly also increased heart rate. Furthermore, changes in skin temperatures may be recorded and if the total heat load is high, elevation of body core temperature may also occur.

WHO (1993) summarised a few studies where volunteers had been exposed in connection with MRI. During searches for literature, it appeared that a higher number of studies published before 1992 might be relevant to include. To obtain a broad basis for drawing conclusions it was decided that also older relevant studies should be assessed for the current Monograph, including those already included in the former Monograph. In total 25 older and newer studies were found to be potentially relevant based on titles and

abstracts. Of these, 19 remains to be further assessed and are listed at the end of this section, while six papers have been reviewed and are discussed below. None of these publications provided statistical analyses for thermoregulatory responses, only one for core and skin temperatures (Adair, Mylacraine & Cobb, 2001a). Therefore, no table providing results of the studies is included here. In the following, the main methodological features and the main trends of results from these studies are provided; when statistical analyses were provided this is indicated.

The included studies (Adair et al., 1998; Adair et al., 1999; Adair, Mylacraine & Cobb, 2001a; b; Adair, Mylacraine & Allen, 2003; Adair et al., 2005) were performed by Adair and colleagues as a series of experiments with similar features with respect to design and thermal environmental conditions. The aim was to obtain knowledge of human thermoregulatory efficiency in RF environments. Six or seven healthy adult volunteers, both men and women, participated in the different studies. They were seated during exposure and wore bathing suits. All RF exposure conditions, including sham, were repeated with ambient temperatures at 24, 28 and 31 °C. Air humidity was relatively low and there was a constant air flow (Adair et al., 1998; Adair et al., 1999; Adair, Mylacraine & Cobb, 2001a; b). In all experiments, a 30 min acclimation period preceded dorsal RF EMF exposure for 45 minutes. Exposure frequencies, power densities and modulation varied between the studies (see Table 9.8). For the highest frequencies (450 and 2450 MHz), the dorsal part of the head, trunk and upper arms, representing about 36% of the total skin, was exposed. Whole body exposure was achieved in the studies with 100 and 220 MHz exposures.

Table 9.8. Exposure conditions in volunteer studies on thermoregulatory responses

Exposure frequency (MHz)	Modulation	Power density (W/m^2)	Peak surface SAR (W/kg)	Whole body SAR (W/kg)	Reference
450	CW	0, 180, 240	0, 6.0, 7.7	-	Adair et al. (1998)
2450	CW	0, 270, 350	0, 5.9, 7.7	-	Adair et al. (1999)[a]
2450	CW	0, 500, 700	0, 11.0, 15.4	-	Adair, Mylacraine & Cobb (2001b)[b]
2450	PM	0, 270, 350	0, 5.9, 7.7	-	Adair, Mylacraine & Cobb (2001a)[b]
100	CW	0, 40, 60, 80	-	0, 0.27, 0.41, 0.54	Adair, Mylacraine & Allen (2003)
220	CW	0, 90, 120, 150	-	0, 0.41, 0.54, 0.68	Adair et al. (2005)[c]

Abbreviations: CW: Continuous wave; PM: Pulse modulated.

[a] Included also data from Adair et al. (1998)

[b] Included also data from Adair et al. (1999)

[c] Included also data from Adair, Mylacraine & Allen (2003)

In all studies body core temperature (recorded with oesophageal probe), skin temperatures, metabolic heat production and sweating rates were recorded before, during and after exposures. Local skin blood flow was recorded in all studies but the first one, and heart rate was recorded in the three last studies (Adair, Mylacraine & Cobb, 2001b; Adair, Mylacraine & Allen, 2003; Adair et al., 2005). In addition, all but one study (Adair et al., 1999) reported results from volunteers' perception of thermal sensation and comfort. When responses from different exposure levels were compared, changes from the last 10 minutes of the acclimatisation period to the last 10 minutes of the exposure period were applied, except in the study including the highest exposure levels (Adair, Mylacraine & Cobb, 2001b) in which changes between the last 5 minutes in these periods were applied.

The total thermal exposure influenced thermoregulation and sensed temperature. With no RF exposure, the ambient temperature of 24 °C was judged as "slightly cool", 28 °C as close to "neutral" and 31 °C as "warm" (Adair et al., 1998). RF exposure at 450 or 2450 MHz increased the sensation of warmth. Especially in the higher ambient temperatures, the thermal comfort decreased with RF exposure concomitant with a preference to reduce the temperature (Adair et al., 1998; Adair, Mylacraine & Cobb, 2001b). By exposure to the lowest frequencies, 100 and 220 MHz, with significantly less superficial absorption of the energy, judgement of thermal sensation changed little with exposure level, but the thermal comfort deteriorated. This was most prominent at the highest ambient temperatures and exposure levels (Adair, Mylacraine & Allen, 2003; Adair et al., 2005).

For all exposure frequencies, elevated local skin temperatures were noted at least at the highest exposure levels. Changes in skin temperatures mimicked largely the thermal sensation. For 2450 MHz at

continuous wave and pulse modulated exposures, increases in back skin temperatures depended on exposure level ($p \leq 0.001$) and were higher during RF exposure than sham. The average temperature elevations were about 1.3–2.7 °C. Chest and forehead temperatures did not change statistically significantly with exposure. Upper back temperatures increased significantly more during pulse modulated than continuous wave exposures ($p = 0.005$) (Adair, Mylacraine & Cobb, 2001a). Post hoc analysis suggested that this finding was due to a significant difference between the "sham pulse modulated" and the "sham continuous wave" conditions since the difference between pulse modulation and continuous wave exposures was not significant for the 270 and 350 W/m^2 exposures, respectively. Data provided suggested that 450 MHz exposures resulted in lower average back skin temperatures than 2450 MHz exposures with the same local peak SARs but higher power densities (Adair et al., 1999). Exposures at 100 and 220 MHz, which are closer to whole body resonance frequency, resulted in almost no elevation of back skin temperatures, but in hot spots with partly clearly elevated temperatures (Adair, Mylacraine & Allen, 2003; Adair et al., 2005). Skin temperature of the ankle increased with up to about 4 °C as the average for the participants. In all exposure conditions the ambient temperature appeared to be of importance.

The increases in local temperatures were not reflected in significant alterations in the core temperatures. The only statistical analyses provided for the core temperature showed no statistically significant dependence on power density (0, 500 and 700 W/m^2) for pulse modulated and continuous wave exposures at 2450 MHz (Adair, Mylacraine & Cobb, 2001a). Under no experimental condition, individual elevation in core temperature exceeded 0.48 °C. In all studies and under all conditions the metabolic rate was stable.

Physiological responses of importance for thermoregulation were noted under several of the experimental conditions. Some main trends for skin blood flow and sweat rates were suggested, even though diagrams providing standard deviations (Adair, Mylacraine & Cobb, 2001a) demonstrated great variability between individuals. Sweat rate of the back and chest appeared to increase with increasing exposure level and increasing ambient temperatures (Adair, Mylacraine & Cobb, 2001a; b; Adair, Mylacraine & Allen, 2003; Adair et al., 2005) and in conditions with the lowest thermal loads (low exposure levels and low ambient temperatures), sweat responses seemed not to be present (Adair, Mylacraine & Cobb, 2001b; Adair, Mylacraine & Allen, 2003). At 2450 MHz, local skin blood flow at the back appeared to increase during exposure irrespectively of ambient temperatures (Adair, Mylacraine & Cobb, 2001a; b). In studies with 100 and 220 MHz exposures skin blood flow data were provided only for exposures to the highest power densities and small increases were suggested by the provided diagrams (Adair, Mylacraine & Allen, 2003; Adair et al., 2005). Moderate increases in heart rates (maximum average less than 15%) were observed for 2450 MHz exposures and 220 MHz exposures during the highest exposure levels (Adair, Mylacraine & Cobb, 2001b; Adair, Mylacraine & Allen, 2003). Much smaller changes, with no obvious effect of exposure level, were observed for the 100 MHz exposure (Adair et al., 2005). Heart rate was not assessed during exposure at 450 MHz.

These volunteer studies had well-controlled and documented exposure conditions both with respect to the RF exposures and the environmental conditions of importance for thermoregulation. Uncertainties are attached to the findings because not all results were provided and because of the limited number of participants combined with the large variability for many of the endpoints. Without statistical analyses and even without indications of variability in five of the six studies, it is uncertain whether some of the suggested trends were statistically significant or appeared by chance. However, some results, such as those concerning core temperature, were consistent across studies, and are also as expected based on normal thermoregulatory responses such as the sweat response and increased skin blood flow.

Studies to be assessed

Listed below are studies having been identified as potentially relevant for this section based on title and abstract but thus far not assessed.

(Shellock, Gordon & Schaefer, 1986)
(Shellock et al., 1986)
(Shellock & Crues, 1987)
(Shellock & Crues, 1988a)
(Shellock & Crues, 1988b)
(Shellock, Schaefer & Crues, 1989)
(Shellock, Rothman & Sarti, 1990)
(Shellock & Schatz, 1992)
(Shellock, Schaefer & Kanal, 1994)

(Kido et al., 1987)
(Vogl et al., 1988)
(Adair & Berglund, 1992)
(Schwarz et al., 2000)
(van den Bergh, van den Boogert & Heerschap, 2000)
(Brix, Reinl & Brinker, 2001)
(Bryan et al., 2006)
(Yang et al., 2006)
(Boss et al., 2007)
(Machata et al., 2009)

9.2.2 Animal studies

This section includes several early studies that were not discussed in WHO (1993) in addition to newer studies. Since thermoregulatory data form the basis for the current exposure guidelines (ICNIRP, 1998; IEEE, 2005) it is considered important to discuss this data here. WHO (1993) concluded on the basis of the studies presented that most responses in different animal species have been reported at SARs above about 1–2 W/kg, but that due to species differences in responses direct quantitative extrapolation to humans is difficult. The most sensitive animal responses to heat loads are thermoregulatory adjustments, such as reduced metabolic heat production and vasodilation, with thresholds ranging between about 0.05 and 5 W/kg, depending on environmental conditions (WHO, 1993). Rodents are not a good model for human physiological thermoregulation because they lack sweat glands. The studies on non-behavioural thermoregulation in rodents have been included in this section, but they are of limited use for human health risk analysis.

9.2.2.1 Studies investigating hyperthermia and thermal breakdown

Jauchem and colleagues investigated the cardiovascular and respiratory responses of rats anesthetised with ketamine to intense RF radiation. The experiments were often continued until the animals died. The nature of these experiments was such that inclusion of a sham-exposed group was not relevant, so these studies therefore deviate from the general requirement for animal studies that a sham-exposed group should be included.

The effect of orientation of the RF field on thermal and physiologic responses in Sprague Dawley rats was investigated by Jauchem, Frei and Padilla (1990). The restrained and anaesthetized animals (15 per group) were exposed to a continuous 1200 MHz field. They were either oriented in the direction of the electric or the magnetic field component and the whole body SAR in either case was 8 W/kg. The study did not include sham controls, but was a comparison between two treatment modalities. Starting from a core temperature of 36.3 ± 0.3 °C, the animals were heated to 39.5 °C. Exposure was then discontinued until the core temperature reached 38.5 °C upon which exposure was started again. This was repeated three times for both orientations and the average time for the 1 °C core temperature increase was determined. With the animals oriented parallel to the magnetic field the increase in core temperature was slower (10.2 ± 0.8 vs. 8.9 ± 0.6 min, $p<0.05$) and the peripheral temperature increase in 3 out of 4 locations was less than with animals aligned with the direction of the electric field ($p<0.05$). The two modalities did not result in any differences in heart rate, blood pressure and respiration rate.

The effect of ketamine anaesthesia was studied by Jauchem and Frei (1991) in 6 restrained Sprague Dawley rats exposed to 2.8-GHz fields at a whole-body SAR of 14 W/kg until a core temperature of 39.5 °C was attained, in three cycles according to the same experimental schedule as described with the previous study. After the third cycle the animals were anesthetized and the procedure was repeated. The unanesthetized animals were loosely restrained and trained to adjust to this situation, so stress effects were expected to be minimal. In anesthetized animals the core temperature increased slower and the subcutaneous temperature increased to higher levels than in conscious animals. An increase in blood pressure was only observed in unanesthetized animals ($p<0.05$). Heart rate increased during RF exposure ($p<0.05$) with no significant difference between the conscious and anesthetized state of the animals. The respiratory rate did not change during RF exposure, neither in conscious nor in anesthetized rats. [Since the exposures under anesthaetisia always were performed after the exposures without anaesthesia, an effect of order of exposures cannot be excluded when comparing these conditions.]

Jauchem and Frei (1997) investigated in 14 anesthetised Sprague Dawley rats the effects of exposure to a sub-resonant RF frequency (350 MHz) at a whole-body SAR of 13.2 W/kg on the cardiovascular and

respiratory responses. The animals were exposed either until the body core temperature increased by 1°C or until death. They observed that heart rate increased with rising body temperature, but that mean arterial pressure and respiratory rate were largely unaffected until body temperatures rose above around 42 °C, whereupon they declined, indicating thermal breakdown.

In a subsequent study, Jauchem, Ryan and Frei (2000) investigated the effects of exposure to 1 GHz, 10 GHz, or combined 1 and 10 GHz RF radiation at whole-body SARs of 12 W/kg until the death of the animal. Groups of 8–10 anesthetized Sprague Dawley rats were used. Two orientations of the fields were studied: in the E-field orientation the electric field component was parallel to the body length axis and in the H-field orientation this was the case for the magnetic component. With both orientations, the core temperature at death was highest in the 1 GHz exposure group, indicating a more uniform heating, whereas subcutaneous temperature on the side facing the antenna was highest in the 10 GHz exposure group, reflecting more superficial heat deposition and greater temperature gradients resulting from exposure to a higher frequency. In the E-field orientation the survival time was lowest with 1 GHz ($p<0.05$), but there were no differences in heart rate, temperature and blood pressure between the various frequencies. In the H-field orientation the survival time with 1 GHz and with 1 + 10 GHz were lower than with 10 GHz alone ($p<0.05$). Variable differences in skin temperature were observed, depending on the frequency, orientation and time after exposure, but heart rate and blood pressure did not differ between groups exposed to different frequencies.

In a series of experiments, the effects of exposure to 35 GHz were investigated, all applying a whole-body SAR of 13 W/kg. Frei et al. (1995) exposed 14 anaesthetized Sprague Dawley rats to the left side of the body until death, which occurred between 32 and 69 minutes. They observed that blood pressure decreased when the left subcutaneous temperature was increased up to 45 °C ($p<0.05$). Heart rate continuously increased, and was significantly higher than the pre-exposure control values when the left subcutaneous temperature was increased up to 40 °C ($p<0.05$). At death the core temperature was 40.3 °C, but the skin temperature had risen to 48.0 °C.

In a subsequent study, Ryan et al. (1997b) investigated the effects of 35-GHz exposures at a whole-body SAR of 13 W/kg on food-restricted anesthetised Sprague Dawley rats of different ages: 3–4, 15–16, or 24–25 months (n=8 per group). They observed no effect of age on the core temperature at death, on the heart rate, the blood pressure, the respiration rate and on the time until death.

In further studies, the effect of various pharmacological manipulations was investigated. Ryan et al. (1997a) found in groups of 8 anaesthetised Sprague Dawley rats no effect of nitric oxide administration after or before exposure to 35 GHz at a whole-body SAR of 13 W/kg on the time to reach a mean arterial blood pressure of 75 mm Hg, or death.

Jauchem et al. (1997) exposed groups of 8 anaesthetised Sprague Dawley rats to 35 GHz EMF at a whole-body SAR of 13 W/kg until a mean arterial blood pressure of 75 mm Hg was reached, or until death. The administration of esmolol, a β-adrenoreceptor antagonist, during the exposure resulted in decreased blood pressure, shorter survival time, and a lower core temperature at death (all $p<0.05$).

In previous experiments it had been observed that when Sprague Dawley rats were exposed to 35 GHz EMF and the mean arterial blood pressure decreased until 75 mm Hg, death would ensue even when the exposure was discontinued (Jauchem et al., 1997; Ryan et al., 1996; Ryan et al., 1997a). In another series of experiments, Jauchem, Ryan and Tehrany (2004) found, using groups of 8 anaesthetised rats, that administration of histamine receptor blockers at this point did not reverse this process, but even decreased the time to death ($p<0.05$). Administration before exposure had no effect. This study applied the same exposure frequency and SAR as the previous ones.

In experiments using exposure to the lower frequency of 2.45 GHz and a whole-body SAR of 14 W/kg, Jauchem and Frei (1994) studied in anaesthetised Sprague Dawley rats (n=7–10) the effect of the central and peripheral β-adrenoceptor antagonist propanolol, the peripheral β-adrenoceptor antagonist nadolol and the α1 and β-adrenoceptor antagonist labetolol. With all drugs they observed that death occurred at a lower core temperature ($p<0.05$), and that the survival time was lower. Administration of the highest dose of propanolol resulted in a higher respiration rate, while labetolol administration was associated with a lower core temperature rise. Neither drug had an effect on the RF-induced changes in heart rate and blood pressure.

In a follow-up study applying the same exposure, Jauchem et al. (1995) investigated in groups of 6–9 anaesthetised Sprague Dawley rats the effects of the α-adrenoceptor antagonists phentolamine and prasozin, and

the β-adrenoceptor antagonist metoprolol. No effect of any of these drugs on any RF-induced changes of cardiovascular parameters was measured.

Frei et al. (1990) exposed ketamine-anaesthetized Sprague Dawley rats in groups of 15 to a 5.6 GHz field at a whole-body SAR of 14 W/kg in either E-field or H-field orientation. In contrast to observations from a previous study using 2.45 GHz exposure (Frei et al., 1989), the orientation had no effect on the observed increase in heart rate and blood pressure. However, the temperature increase at various locations of the body differed between the orientations: the temperature increase in the tail and left subcutaneous site were greater with the E-orientation, while the right subcutaneous temperature increase was greater with the H-orientation (all $p<0.05$). Similar observations were made in a subsequent study, where Frei and Jauchem (1992) exposed Sprague Dawley rats (n=12 per group) with their body length oriented parallel to the E- or H-component of a 9.3 GHz field at a SAR of 12.5 W/kg.

Ebert et al. (2005) investigated thermoregulation and the thermal breakdown threshold in mice. Male and virgin and pregnant female B6C3F1 mice, and male NMRI mice were exposed in groups of 8 to 905 MHz for 2 h at whole-body SARs up to 20 W/kg. The animals were restrained, but had been trained for 3 weeks to this situation. Thermoregulation was measured by comparing the core temperature 10 min after cessation of the exposure with that measured during the last 10 min of exposure. A decrease in core temperature was considered to indicate that thermoregulation occurred as a result of the exposure. This was found to start to occur at a SAR between 2 and 5 W/kg. Thermal breakdown, defined by a linear increase in core temperature and reaching a core temperature of 41 °C, occurred at 10.1 ± 4.0 W/kg for the B6C3F1 mice and at 7.7 ± 1.6 W/kg for the NMRI mice. It was primarily dependent on body weight, not on gender. The threshold was considered to be a SAR of ~6 W/kg. [It may be higher for free roaming animals, because the restraining may impair the dissipation of heat to the environment.]

These studies of intense heating effects provide insight into the processes and mechanisms associated with the development of heat shock and subsequent death in animals, but they are of little direct relevance to occupational or public exposures.

Table 9.9. Animal studies investigating hyperthermia and thermal breakdown

Endpoint, animals, number per group, age or weight at start	Exposure: source, schedule, level, freely moving or restrained	Response	Comment	Reference
Blood pressure, temperature, respiratory rate Rat: Sprague Dawley (n=15) 240–300 g	1200 MHz, CW Until core temperature of 39.5 °C E-field-orientation of rats: WBA SAR: 8.0 ± 0.3 W/kg H-field orientation of rats: WBA SAR: 8.1 ± 0.4 W/kg Anesthetized	H-orientation: slower increase colon temperature than E-orientation; less increased peripheral temperature; no difference in heart rate, blood pressure, respiration rate.		Jauchem, Frei and Padilla (1990)
Blood pressure, temperature, respiratory rate Rat: Sprague Dawley (n=6) 212–273 g	2.8 GHz Until core temperature of 39.5 °C WBA SAR: 14 W/kg Anesthetized	Anaesthetized: colon temperature increase slower and subcutaneous temperature to higher level compared to unanesthetized. Unanaesthetized: increase blood pressure. Increase in heart rate similar in both groups; no effect on respiratory rate.	Hyperthermia / lethal experiment. The two conditions (with and without anaesthesia) were in fixed order.	Jauchem and Frei (1991)

Heart rate , blood pressure, respiration rate Rat: Sprague Dawley (n=14) 346–370 g	350 MHz Until 1 ℃ core temperature increase or until death WBA SAR: 13.2 W/kg Anesthetized	Heart rate increased with rising body temperature, no effect on blood pressure and respiratory rate until core temperatures >42 ℃, then decline.	Hyperthermia / lethal experiment.	Jauchem and Frei (1997)
Survival time, temperature, blood pressure, heart rate Rat: Sprague Dawley (n=8–10) 325–375 g	1, 10, 1+10 GHz, animals E-field and H-field oriented Until death WBA SAR: 12 W/kg Anesthetized	E-field orientation: lower survival time at 1 GHz, no effect of frequency on heart rate increase, temperature increase, blood pressure. H-field orientation: lower survival time: 1 GHz & 1+10 GHz < 10 GHz, variable differences in skin temperature between frequencies, no effect of frequency on heart rate, blood pressure.	Hyperthermia / lethal experiment.	Jauchem, Ryan and Frei (2000)
Temperature at different body sites, heart rate, blood pressure Rat: Sprague Dawley (n=14) 388–528 g	35 GHz Until death WBA SAR: 13 W/kg Anesthetized	Blood pressure decreased, heart rate increased, death at core temperature of 40.3 ℃ and skin temperature of 48.0 ℃.	Hyperthermia / lethal experiment.	Frei et al. (1995)
Blood pressure, temperature, respiratory rate Rat: Sprague Dawley (n=8) 3–4, 15–16, 24–25 months	35 GHz Until death WBA SAR: 13 W/kg Anesthetized	No age difference for temperature at death, heart rate, blood pressure, respiration rate, time to death.	Hyperthermia / lethal experiment.	Ryan et al. (1997b)
Time to reach mean arterial blood pressure of 75 mmHg (10.1 kPa), or death Rat: Sprague Dawley (n=8) 325–380 g	35 GHz with/without NO donor (SNAP) before or after exposure Time to reach a mean arterial blood pressure of 75 mm Hg, or death WBA SAR: 13 W/kg Anesthetized	No effect of SNAP after or before exposure.	Hyperthermia / lethal experiment.	Ryan et al. (1997a)
Blood pressure, temperature, respiratory rate, survival time, lethal body temperature Rat: Sprague Dawley (n=8) 338–397 g	35 GHz with/without esmolol (β-adrenoreceptor antagonist) Time to reach a mean arterial blood pressure of 75 mm Hg, or death WBA SAR: 13 W/kg Anesthetized	Esmolol caused decreased blood pressure, shorter survival, lower core temperature at death.	Hyperthermia / lethal experiment.	Jauchem et al. (1997)

Time to reach mean arterial blood pressure of 75 mmHg (10.1 kPa), or death Rat: Sprague Dawley (n=8) 350–400 g	35 GHz with/without histamine receptor antagonists (before or after exposure) Time to reach a mean arterial blood pressure of 75 mm Hg, or death WBA SAR: 13 W/kg Anesthetized	Antihistamines after RF decreased survival time, no effect when administered before exposure.	Hyperthermia / lethal experiment.	Jauchem, Ryan and Tehrany (2004)
Blood pressure, temperature, respiratory rate, survival time, lethal body temperature Rat: Sprague Dawley (n=7–10) 320–363 g	2450 MHz with/without propanolol (central & peripheral β-adrenoceptor antagonist), nadolol (peripheral β-adrenoceptor antagonist), labetolol (α1 & β-adrenoceptor antagonist) Until death WBA SAR: 14 W/kg Anesthetized	Lower core temperature at death with all drugs, lower survival time, higher respiration rate with high dose propanolol, lower rate of temperature rise with labetolol; no effect on heart rate, blood pressure.	Hyperthermia / lethal experiment.	Jauchem and Frei (1994)
Blood pressure, temperature, respiratory rate, survival time, lethal body temperature Rat: Sprague Dawley (n=6–9) 329–370 g	2450 MHz with/without phentolamine, prasozin (α-adrenoceptor antagonists), metoprolol (β-adrenoceptor antagonist) Until death WBA SAR: 14 W/kg Anesthetized	No effect of drugs on parameters measured.	Hyperthermia / lethal experiment.	Jauchem et al. (1995)
Blood pressure, temperature, respiratory rate Rat: Sprague Dawley (n=15) 315–350 g	5.6 GHz, animals E-field and H-field oriented Until colon temperature of 39.5 °C WBA SAR: 14 W/kg Anesthetized	Increase in heart rate, blood pressure, no effect of orientation; local temperature increase dependent on orientation.	Hyperthermia / lethal experiment.	Frei et al. (1990)
Blood pressure, respiration rate, temperature Rat: Sprague Dawley (n=12) 327–363 g	9.3 GHz, animals E- and H-oriented Until death WBA SAR: 12.5 W/kg Anesthetized	Increase in heart rate, blood pressure, no effect of orientation.	Hyperthermia / lethal experiment.	Frei and Jauchem (1992)
Core temperature; regulation and breakdown threshold Mouse: B6C3F1 (male, female, pregnant), NMRI (n=8) B6C3F1: 4, 12 weeks, 20, 24, 29 g NMRI: 12 weeks, 39 g	905 MHz 2 h WBA SAR: 0, 2, 5, 7.2, 10, 12.6, 20 W/kg Anesthetized	Thermoregulation: start between 2 and 5 W/kg. Thermal breakdown at SAR 10.1 ± 4.0 W/kg (B6C3F1), 7.7 ± 1.6 W/kg (NMRI) (depends on body weight); threshold ~6 W/kg.	Thermal breakdown threshold may be higher for free roaming animals.	Ebert et al. (2005)

Abbreviations: CW: continuous wave; E-field: electric field; H-field: magnetic field ; NO: nitric oxide; SNAP: S-nitroso-N-acetylpenicillamine; WBA SAR: whole-body averaged SAR.

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9.2.2.2 Studies investigating RF exposure at non-hyperthermic levels

Experiments with monkeys: non-behavioural thermoregulation

Adair, Adams and Hartman (1992) determined in four squirrel monkeys, a non-human primate, the effects of exposure to EMF at the resonant frequency of 450 MHz on the metabolic heat production, core and skin temperature, with different ambient temperatures. [In general, a cool environment will result in an increase in metabolic heat production, an effect that is counteracted by the heat production resulting from RF exposure.] In the first protocol, five 10-min exposures with SARs increasing in fixed order from 0.8 to 2.5 W/kg and separated by 20 min rest periods were applied with each ambient temperature of 15, 20, 25 or 34 °C. The second protocol consisted of single 90-min exposures at whole-body SARs ranging from 0.8 to 2.5 W/kg applied at an ambient temperature of 20 °C; three sessions were performed on each monkey [the time between sessions is not provided, merely that there was a 30 min restabilization period after each session; the order in with the increasing SARs were given is also not provided]. The data were compared with those from previous experiments using similar protocols but the higher frequency of 2450 MHz (Adair & Adams, 1982). With 10-min exposures the reduction in metabolic heat production was larger with the higher frequency than with the resonant frequency in a cool environment (15 or 20 °C). In a thermoneutral environment (26 or 30 °C) such difference was not observed. [No statistical analysis of this data was performed; the differences were read from the figures.] Skin warming was reported to be greater with the higher frequency, but no data were provided. [It cannot be excluded that there were carry-over effects from the closely-spaced subsequent exposures.] With 90-min exposures the reduction in the metabolic heat production with the resonant frequency was not able to prevent an increase in the core temperature. This did not occur with the higher frequency. [The number of animals was low (four), but each animal was tested in three separate and independent sessions.]

Adair et al. (1997) investigated the effect of exposure to the same frequencies, as in the previous experiments, 450 MHz or 2450 MHz, on thermoregulatory responses during experimentally-induced fever in four conscious squirrel monkeys at thermoneutral ambient temperature (26 ± 0.5 °C). They found that during 2450 MHz exposure (whole-body SARs of 1.65 and 3.3 W/kg for 30 min) the magnitude of the fever remained the same, but the absorption of RF energy proportionately reduced the fever-generated increase in endogenous heat production. However, during exposure at 450 MHz, a resonant frequency in the squirrel monkey, at whole-body SARs of 2 and 3.3 W/kg for 30 min, energy is deposited deep within the body and the fever was augmented. In addition, the fever was exacerbated when exposure occurred during the period that the fever abates and body temperature begins to fall. Thus the RF-induced heat production interfered with the autonomous heat production during fever.

Nelson et al. (2003) exposed the skin of Sprague Dawley rats, rhesus monkeys and humans (n=4 per species) to pulsed 94 GHz fields at power densities of 0.175 W/cm^2 (1.75 W/m^2) for 180 s or 1 W/cm^2 (10 kW/m^2) for 3 s and measured the resulting temperature increase. [The ambient temperature is not provided.] They compared that with calculations using the bio-heat model. With the high-field short-term exposure there was a large similarity in skin temperature increase (7 °C) between the three species, corresponding to a model with no blood flow. The low-level longer-duration exposures resulted in species differences: the temperature increase at the end of the 3-min exposure period in human and monkey skin was 8.5 °C and that in the rat skin was 10 °C. The human and rat skin data corresponded to a model with low blood flow, with a plateau in humans due to vasodilatation. The monkey data was better explained by a high blood flow model. [Anaesthesia could have influenced the rat and monkey data.]

Experiments with monkeys: behavioural thermoregulation

Adair and Adams (1980a) exposed 5–7 year old squirrel monkeys to 2450 MHz continuous fields. The animals were trained to regulate the environmental temperature by selecting the inflow of cold or warm air in the experimental room. In the first experiment, three monkeys were exposed at levels increasing in six steps from 1 to 10 mW/cm^2 (10–100 W/m^2); each step lasted for 10 min and was separated from the next step by 10 min without exposure. This schedule was repeated five times for each subject. In a second series of tests, the same protocol was applied to two monkeys with higher levels: 8–22 mW/cm^2 (80–220 W/m^2). Two monkeys were used for control exposure to infrared radiation. Regulation of the environmental temperature was induced with a threshold exposure of 6–10 mW/cm^2 (60–100 W/m^2) (corresponding to whole-body SARs of 0.96–1.5 W/kg); no effect was observed with 4 mW/cm^2 (40 W/m^2, 0.6 W/kg). With increasing exposure levels, decreased environmental temperatures were selected. As a result, no increase in core temperature was measured with any exposure level. Exposure to IR that resulted in increases in skin temperature comparable to those of RF exposure

had no influence on thermoregulatory behaviour. [The number of animals was low (two or three), but each animal was tested in five separate and independent sessions.]

Adair and Adams (1983) continued the experiments described above with two 7-9 year-old squirrel monkeys that were trained to regulate the environmental temperature by selecting the inflow of cold or warm air in the experimental room. The animals were exposed to continuous 2450 MHz fields. In the first series of experiments they were exposed to 4 or 10 mW/cm^2 (40 or 100 W/m^2, whole-body SAR 0.6 or 1.5 W/kg) at exposure times increasing from 5 to 25 min with an interval between successive exposures of the same length as the preceding exposure duration. In the second series they were exposed for 2.5 h at 10 or 20 mW/cm^2 (100 or 200 W/m^2, whole-body SAR 1.5 or 3.0 W/kg). Regulation of the environmental temperature in order to maintain a constant core temperature occurred with SARs of 1.5 and 3.0 W/kg, irrespective of the duration of the exposure. [The number of animals was low (two), but each animal was tested in five or six separate and independent sessions.]

In a study intended to follow up on the previous ones, Adair et al.(1984) exposed three 6–7 year old squirrel monkeys trained to regulate the environmental temperature to a continuous 2450 MHz field for 5 x 10 min at whole-body SARs increasing from 0.6–2.1 W/kg, and repeated this 5 times. In a second series (repeated four times), two animals were exposed according to the same protocol to repeated 1.5 W/kg exposures that were considered to be above the threshold for induction of cooling behaviour. The third series consisted of a 2.5 h exposure to an SAR of 3.0 W/kg, and was repeated five times in each of the three monkeys. In these experiments both the core (rectal) temperature and that of the brain (hypothalamus) were measured. They observed that with exposures that resulted in regulation of the environmental temperature, the brain temperature was increased by 0.2–0.3 °C, but the rectal temperature was not increased. The SAR threshold for induction of regulation of the environmental temperature varied with subject and was 1.2, 1.5, or 1.8 W/kg, respectively. [The number of animals was low (two or three), but each animal was tested in four or five separate and independent sessions.]

In a subsequent study, Adair et al. (1985) used four 4–7 year-old squirrel monkeys, again trained to regulate the environmental temperature, for a study on the effects of long-term exposure to a 2450 MHz field on thermoregulatory behaviour and on a number of physiological parameters. The long-term exposure was for 8 h per day, 5 days per week and 15 weeks to an SAR of 0 (sham), 0.21 or 1.05 W/kg, at ambient temperatures of 25, 30 or 35 °C. At 4, 8, 12 and 16 weeks after the start of chronic exposure, a test sequence of 4 or 5 exposures of 10 min duration was given with increasing SARs of 0.6–1.8 W/kg to determine the threshold for induction of thermoregulatory behaviour. Each group consisted of 4 animals. No effect of the chronic exposure at any of the three ambient temperatures was observed on the thermoregulatory behaviour and on the SAR threshold for the induction of this behaviour, which varied per animal. At 2, 6, 10 and 14 weeks after the start of chronic exposure, and 3 and 7 weeks after its end, a number of physiological parameters were measured: body mass, several blood parameters, metabolic rate, skin and core body temperature, and sweating rate. The metabolic rate, core temperature, sweating rate and blood parameters were not consistently altered by the chronic exposure. Body mass was mostly reduced in the chronically exposed animals at all ambient temperatures tested (n=2 in all cases), but this was also the case for the sham exposed animals (n=4) at 30 and 35 °C. Only at 25 °C the sham exposed animals gained weight, as did the ones exposed to 0.21 W/kg, while in the group exposed to 1.05 W/kg the body mass reduced. [No statistical test was performed, so no conclusion can be drawn on any difference.] Effects on skin temperature were tested in a protocol using increasing ambient temperatures. For some groups significant effects on skin temperature were observed ($p<0.05$), but there was already a large variability of pre-exposure skin temperature in especially the sham-exposed animals and the groups were small (n=2–4). Hence, no consistent and meaningful effects could be discerned. The authors consider this to be an exploratory study, due to the large number of variables and the small number of subjects (14 animals in total). [Only the data on thermoregulatory behaviour are considered useful for the overall analysis.]

In the last of this series of studies with squirrel monkeys, Bruce-Wolfe and Adair (1985) trained four monkeys to regulate the environmental temperature by selecting either cold (10 °C) or warm (50 °C) air inflow into the experimental room to maintain a constant core temperature. Next, theyinvestigated whether the animals could use RF EMF exposure instead of warm air to this purpose. The sessions started with an inflow of cool air and the monkeys could use continuous-wave 2450 MHz fields accompanied by an inflow of 30 °C air for heating. In different session, SARs of 3.0, 3.75 or 4.5 W/kg were tested in three or four animals. The animals were able to maintain a constant core temperature by exposing themselves to RF EMF. There was no difference in time they chose to be exposed to SARs of 3.0 and 3.75 W/kg, but the time spent exposed to the SAR of 4.5 W/kg was less ($p<0.001$). The skin temperature and the overall ambient temperature were lower when using RF EMF instead of hot air for warming [no p-values provided]. [The number of animals was low (three or four), but each animal was tested in three or more separate and independent sessions.]

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Table 9.10. Animal studies investigating RF exposure at non-hyperthermic levels: experiments with monkeys

Endpoint, animals, number per group, age or weight at start	Exposure: source, schedule, level, freely moving or restrained	Response	Comment	Reference
Non-behavioural thermoregulation				
Colon, skin temp, metabolic heat production, under ambient temperatures of 15, 20, 25, 30 °C Monkey: Squirrel (n=4) 8–18 years	450, 2450 MHz 10, 90 min 450 MHz: WBA SAR: 0–6 W/kg 2450 MHz: WBA SAR: 0–9 W/kg Restrained	Brief exposures: SAR-dependent reduction of heat production, more at high than at resonant frequency (450 MHz). Skin warming greater with high frequency. Long exposures: less reduction of heat production, more increase in colon temperature with resonant than with high frequency.	Low number of animals, but each tested in 3 independent sessions.	Adair, Adams and Hartman (1992)
Temperature in hypothalamus, colon, skin in artificially fevered animals Monkey: Squirrel (n=4) 6–15 years	450, 2450 MHz 30 min 450 MHz: WBA SAR: 2, 3.3 W/kg 2450 MHz: WBA SAR: 1.65, 3.3 W/kg Ambient temperature 26 ± 0.5 °C Restrained	2450 MHz: endogenous heat production reduced. 450 MHz: no effect on endogenous heat production.	RF heat production interferes with autonomous heat production during fever.	Adair et al. (1997)
Skin surface temperature measured / modelled Rat: Sprague Dawley Monkey: Rhesus Human volunteers (all n=4) Rat: 4 months Monkey: 4–5 years	94 GHz, pulsed Low: 180 s, 175 mW/cm^2 (1.75 kW/m^2) High: 3 s, 1 W/cm^2 (10 kW/m^2) Restrained (rat, monkey)	High exposure: skin temperature increased in all species. Low exposure: monkey, human skin temperature increase 8.5° C, rat skin 10 °C.	High: results correspond to model with no blood flow. Low: correspondence with low blood flow model for rats and humans, plateau in human presumably due to vasodilatation; monkey data: correspondence with high blood flow model. Ambient temperature not provided. Anaesthesia could have influenced rat and monkey data.	Nelson et al. (2003)
Behavioural thermoregulation				
Regulation of ambient temperature; temperature in colon, skin Monkey: Squirrel (n=2, 3) 5–7 years	CW 2450 MHz 6x10 min on, 10 min off, repeated 5x 1–22 mW/cm^2 (10-122 W/m^2, WBA SAR 0.15–1.5 W/kg) Restrained	Regulation of environmental temperature induced with 0.96–1.5 W/kg, not 0.6 W/kg, without increase in rectal temperature; no effect of IR at the same intensity.	Low number of animals, but each tested in 5 independent sessions.	Adair and Adams (1980a)

Regulation of ambient temperature; temperature in colon, skin Monkey: Squirrel (n=2) 7–9 years	CW 2450 MHz 1) increasing exp time: 5, 10, 15, 20, 25 min at 4 or 10 mW/cm^2 (40 or 100 W//m^2,WBA SAR 0.6, 1.5 W/kg) 2) 2.5 h at 10 or 20 mW/cm^2 (100 or 200 W//m^2, WBA SAR 1.5, 3.0 W/kg); all repeated 5–6 x Restrained	Regulation of environmental temperature induced with 1.5, 3.0 W/kg with all exposure durations, not with 0.6 W/kg, without increase in rectal temperature.	Low number of animals, but each tested in 5 or 6 independent sessions.	Adair and Adams (1983)
Regulation of ambient temperature; temperature in colon, hypothalamus Monkey: Squirrel (n=3) 6–7 years	CW 2450 MHz 1) 5x10 min,WBA SAR increasing 0.6-2.1 W/kg, repeated 4 or 5 x 2) 2.5 h, WBA SAR 3.0 W/kg, repeated 5 x Restrained	Regulation of environmental temperature induced with brain temperature increase of 0.2-0.3 °C, without increase in rectal temperature. Threshold varies with subject: 1.2, 1.5, 1.8 W/kg.	Low number of animals, but each tested in 4 or 5 independent sessions.	Adair et al. (1984)
Regulation of ambient temperature; temperature in colon, skin; sweating; blood parameters Monkey: Squirrel (n=4) 4–7 years	CW 2450 MHz 8 h/day, 5 days/week, 15 weeks WBA SAR 0.21, 1.05 W/kg; ambient temperature 25, 30, 35 °C Test: 4 or 5 x 10 min, increasing SAR 0.6–1.8 W/kg Restrained	No effect of chronic exposure and ambient temperature on thermoregulation and on SAR threshold. No or no consistent effect on physiological paramaters.	Exploratory study: large number of variables, small number of subjects.	Adair et al. (1985)
Regulation of heating by warm air or RF EMF exposure; temperature in colon, skin Monkey: Squirrel (n=4) 850-1100 g	CW 2450 MHz 3, 3.75, 4.5 W/kg upon demand Restrained	Core temperature well regulated, no difference between SARs; mean air temperature and mean exposure time lower with 4.5 W/kg.	Animals were trained to regulate body temperature by choosing between 10 °C or 50 °C ambient air. Low number of animals, but each tested in 3 or more independent sessions.	Bruce-Wolfe and Adair (1985)

Abbreviations: CW: continuous wave; WBA SAR: whole-body averaged SAR.

Experiments with rodents: non-behavioural thermoregulation

Lu et al. (1992) exposed Sprague Dawley rats (n=11–12) locally to the head and neck to 1.25 GHz fields, either continuous or pulsed at 0.5 or 16 Hz. The SARs in the brain were 9.5 (0.5 Hz pulsed) and 34.3 W/kg (16 Hz pulsed) and in the neck 30.4 and 109.7 W/kg, respectively. The 900-s exposures resulted in changes in heart rate (both increased and reduced) and pulse pressure (no p-values calculated). These effects appeared to be random, but exclusion of outliers resulted in a decreased pulse pressure in the animals exposed to the highest SARs. No effect was recorded on mean arterial pressure and respiration rate. [The random nature of the changes in heart rate and pulse pressure, and the fairly large number of outliers, ranging from 2/12 to 5/11, and their effect on the results is troublesome.]

Walters et al. (1998) investigated in groups of 4–5 Sprague Dawley rats the effect of regional brain heating with 2.06 GHz fields, and body heating with warm-water immersion, elevated environmental temperature and exercise on the temperature in the hypothalamus and the cortex and on core temperature. The RF exposure was for 30 or 240 s and the SAR in the hypothalamus was 122.4 or 1224 W/kg and in the cortex 49.3 or 493 W/kg. The high-level exposure resulted in a faster and greater temperature rise in the hypothalamus

than in the cortex ($p<0.05$). The rise time of the core temperature was equal to that in the cortex, but it plateaued at a lower level. With the low-level exposure there was no difference in the temperature rise in the two brain regions, but the rise time of the core temperature was less. The various non-RF heating protocols resulted in a uniform core and brain temperature rise. [A rather low number of animals per group was used.]

Nakamura et al. (1997b; 2000a; b) performed a series of experiments on the effects of single, 90-min exposures to 2450 MHz RF EMF on hormone levels in female Wistar rats that have been described in Chapter 7.2. In these studies also thermoregulatory measurements were done and these are described here. [It is difficult to understand whether the effects described in these studies with anesthetized animals would also occur in conscious animals, and thus what their meaning is for the situation in pregnant women.]

Nakamura et al. (1997b) studied the effect of a 90-min whole-body exposure to 2450 MHz at a power density of 10 mW/cm^2 (100 W/m^2, corresponding to 1.8–2.2 W/kg, (Nakamura et al., 1997a)) on the core temperature in virgin and pregnant rats (n=6). They also assessed several immune and hormonal parameters that might be involved in the temperature regulation. These are discussed in Sections 10.3 and 7.2.2, respectively. In pregnant animals the core temperature increased from approximately 36.8 °C to 39.8 °C, and in the virgin animals to approximately 42.2 °C ($p<0.01$ for the difference in temperature increase).

In Nakamura et al. (2000b) groups of 6 virgin and pregnant animals were exposed for 90 min with and without concurrent administration of α-helical corticotropin releasing hormone (α-CRH) to a field level corresponding to a whole-body SAR of 0.36–0.44 W/kg. After the RF exposure the core temperature had increased in both virgin and pregnant rats (from 36.8 °C to 38.3 °C; $p<0.001$ compared to sham-exposed animals), administration of α-CRH had no significant effect on the core temperature. In virgins, RF exposure and α-CRH administration had no significant effect on uterine blood flow. In pregnant animals, on the contrary, a decreased uteroplacental blood flow was observed after RF exposure ($p<0.01$) while no effect on blood flow was found when RF exposure was preceded by administration of α-CRH. [The SAR in these experiments was very low, and therefore a 1.5 °C increase in core temperature is puzzling. This study is also discussed in Section 7.3.2. (Neuroendocrine system – Other hormones).]

When anesthetized animals were exposed at a whole-body SAR level of 0.4 W/kg (Nakamura et al., 2000a), the uteroplacental blood flow in pregnant rats was decreased (n=6; $p<0.05$). With administration of the vasodilator angiotensin II before exposure no such change was observed. In this study also the effect of exposure on reproductive hormones was studied and it is therefore also discussed in Section 7.3.2. The authors concluded that the RF EMF exposure resulted in uteroplacental circulatory disturbances that are consistent with ovarian and placental dysfunction in pregnant rats, and hypothesize that this is probably through a non-thermal mechanism involving prostaglandin $F_2\alpha$.

Hirata et al. (2006) exposed the eyes of Dutch rabbits (n=3) to 2.45 GHz at 300 mW/cm^2 (3 kW/m^2) up to 60 min and investigated the temperature increase with and without anesthesia using measurements and calculations. The SAR distribution in the eye was calculated in 1 mm^3 voxels using a rabbit phantom constructed from CT images and found to vary from 20 W/kg at the top and bottom of the eyeball to 180 W/kg in the anterior vitreous chamber. The calculated temperature increase did not match the SAR distribution: the increase was largest (>42 °C) in the centre of the eye. The measured temperature increase in the unanesthetized animals was used to adjust the parameters of the computational model. In Kojima et al. (2004) they observed that the measured temperature increase was higher with anesthesia (see Section 6.3.3.1). Hirata et al. (2006) used these data for comparison with calculations and observed a good correlation between the measured and computed temperature increase. They concluded that anesthesia interfered with the homeostatic control of body temperature. [Even though there was no sham-exposed group, this study is included in the analysis because of the comparison between measured and computed data. The number of subjects is very limited, however.]

Jia et al. (2007) investigated the role of blood flow on the RF-induced skin temperature increase in rabbit ears. The ears (38 per group) were exposed to 1500 MHz fields for 20 min at SARs of 2.3, 10 and 34.3 W/kg (averaged over 1 g ear tissue). Skin temperature was recorded with an infrared camera. Under normal blood flow conditions the skin temperature did not increase even with the highest SAR. When blood flow was occluded, the skin temperature increased from 0.8 °C with the SAR of 2.3 W/kg to 2.5 °C with 34.3 W/kg.

Masuda et al. (2011) locally exposed the brain cortex of Sprague Dawley rats to 1950 MHz RF EMF for 18 min at SARs (averaged over 4.04 mg brain tissue) of 10.5, 40.3, 130 and 263 W/kg (n=7 per group). In the exposed area they assessed the blood flow and temperature, and also measured the core temperature and that in the calf. They observed a SAR-dependent increase in local blood flow ($p<0.01$) and temperature in the brain ($p<$

0.05), but a temperature increase in remote areas only with the SARs ≥40.3 W/kg. The increase in local blood flow was correlated with the increase in the brain and core temperature, but seemed to be driven by the local increase in temperature.

Hirata et al. (2011) locally exposed the brains of anaesthetized young and adult Sprague Dawley rats (n=3 per group) to RF EMF of 1457 MHz for 6 min at SARs of up to 300 W/kg. The aim was to assess whether thermoregulation differs between young and adult animals and whether model calculations adequately can predict local temperature changes at both ages. Because anaesthesia reduces thermoregulation, the body temperature of the animals was maintained using a heated waterpad. They observed that the temperature increase in the brain was SAR-dependent, up to approximately 12 °C with the highest SAR level, and not different between 4 and 8-weeks old animals. For the temperatures in the brain, there was a good correspondence with the model calculations for the young animals, but less for older ones, where the measured temperatures were higher than the computed ones. For the core temperature, on the other hand, which rose maximally by about 2 °C with the highest SAR level, the calculated values were higher than the measured ones: 40% for the young and 10% for the older animals. [No statistical analysis was performed. The number of animals per group was very low.]

Pelletier et al. (2013) exposed young Wistar rats starting at an age of 3 weeks to 900 MHz CW for 23.5 h per day during 7 weeks at a fixed level of 1 V/m, resulting in a whole-body SAR that declined from 0.3 to 0.1 W/kg as the animals grew. In the 6th week of exposure, they assessed at two different ambient temperatures, 24 and 31 °C, various sleep parameters, food intake, and body temperature, which is reported here. With an ambient temperature of 31 °C, the cortical and peripheral temperatures in the sham-controls were increased ($p<0.001$). In exposed animals the peripheral temperature was lower than in the unexposed ($p<0.001$) with the ambient temperature of 31 °C, but not with 24 °C, indicating vasoconstriction. This was confirmed by the administration of the vasodilator Prasozin, that counteracted this effect. The authors concluded that the peripheral vasomotor tone was dampened by the RF exposure.

Experiments with rodents: behavioural thermoregulation

A number of studies on behavioural thermoregulation in rodents that were not discussed in WHO (1993) were identified in the systematic searches in PubMed (Akyel et al., 1991; D'Andrea et al., 1988; Lebovitz, 1981; 1983; Levinson et al., 1982; McRee et al., 1979; Mitchell et al., 1989; O'Connor, 1988; Quock et al., 1987; Shandala et al., 1979; Thomas et al., 1975; Thomas, Schrot & Banvard, 1982; Vitulli et al., 1987). Since the importance of rodent studies for this endpoint is considered less than that of primate studies, these papers are not discussed here either.

Hirata et al . (2010) exposed restrained rabbit to a 2.54 GHz field with power densities of 110, 220 730 or 980 W/m^2 (calculated whole-body SARs 1.3, 2.6, 8.6 and 11.6 W/kg). In the 14 unanesthetized animals they observed thermoregulatory behaviour (increased breathing rates, repetitive movement in the plastic holder, nose licking, slobbering and movement of the ear lobe) when the rectal temperature increased by approximately 0.9–1.0 °C, but there was considerable individual variation. The corresponding SAR threshold was approximately 1.3 W/kg.

Table 9.11. Animal studies investigating RF exposure at non-hyperthermic levels: experiments with rodents

Endpoint, animals, number per group, age or weight at start	Exposure: source, schedule, level, freely moving or restrained	Response	Comment	Reference
Non-behavioural thermoregulation				

Heart rate , blood pressure, respiration rate, temperature Rat: Sprague Dawley (n=11, 12) 10–12 weeks + 2 weeks acclimatization	1.25 GHz, 0.5 or 16 Hz pulsed or CW to head/neck 900 s Brain SAR: 0.5 Hz pulsed: 9.5 W/kg 16 Hz pulsed: 34.3 W/kg Neck SAR: 0.5 Hz pulsed: 30.4 W/kg 16 Hz pulsed: 109.7 W/kg Anesthetized	No effect on mean arterial pressure, respiration rate. Changes in heart rate, pulse pressure.	Random nature of changes and effect of outliers is troublesome.	Lu et al. (1992)
Temperature hypothalamus, cortex, rectum Rat: Sprague Dawley (n=4–5) 309 ± 11; 336 ± 12 g	2.06 GHz 30, 240 s SAR: hypothalamus: 122.4, 1224 W/kg cortex: 49.3, 493 W/kg Restrained	High level: faster, greater temperature rise in hypothalamus vs cortex, core temperature rise time similar to that in cortex, lower plateau. Low level: no difference temperature rise brain regions, rise time core less; non-MW heating: uniform temperature rise.	Low number of animals.	Walters et al. (1998)
Colonic temperature Rat: Wistar (n=6) Virgin: 290 ± 16.4 g Pregnant: 295 ± 17 g	2450 MHz 90 min 10 mW/cm^2 (according to Nakamura et al. (1997a) corresponding to WBA SAR 1.8–2.2 W/kg) Anesthetized	Lower temperature increase in pregnant rats.	Also discussed in 7.2.2 and 10.3.	Nakamura et al. (1997b)
Core temperature, utero/uteroplacental blood flow Rat: Wistar (n=6) Virgin: 268 ± 5.6 g Pregnant: 271 ± 7.7 g	2450 MHz with/without α-helical corticotropin releasing hormone (α-CRH) 90 min 2 mW/cm^2 (20 W/m^2) (corresponding to WBA SAR 0.36–0.44 W/kg) Anesthetized	Increased core temperature in virgins & pregnant rats, no effect of α-CRH. No effect of RF and α-CRH on uterine blood flow in virgins; decreased uteroplacental blood flow in pregnant rats. No effect of RF in combination with α-CRH.	Very low SAR, 1.5 °C temperature increase not likely a result of the RF exposure. Also discussed in 7.3.2. (Neuroendocrine system – Other hormones).	Nakamura et al. (2000b)
Core temperature, utero/uteroplacental blood flow Rat: Wistar (n=6) Virgin: 283 ± 17 g; Pregnant: 279 ± 17.6 g	2450 MHz with/without angiotensin 90 min WBA SAR: 0.4 W/kg Anesthetized	No effect on body temperature, decrease in uteroplacental blood flow in pregnant rats; no such effect when angiotensin was administrated; no effect in virgin rats.	Also discussed in 7.3.2. (Neuroendocrine system – Other hormones)	Nakamura et al. (2000a)

Eye temperature, comparison measured/modelled, with/without anaesthesia Rabbit (n=3) Young adult	2.45 GHz up to 60 min 300 mW/cm^2 (3.0 kW/m^2) Restrained,with/ without anesthesia	No good match between calculated SAR and temperature distribution in eye. Good correlation measured/modelled temperature increase.	Low number of animals.	Hirata et al. (2006)
Skin temperature with IR camera Rabbit: white (n=38) 2.5–4.5 kg	1500 MHz 20 min SAR(1 g ear tissue): 2.3, 10, 34.3 W/kg Restrained	No skin temperature increase when blood flow present, without blood flow temperature increase even with 2.3 W/kg.	Co-financed by industry.	Jia et al. (2007)
Local cerebral blood flow, temperature (brain, rectum, calf) Rat: Sprague Dawley (n=7) 8 weeks	1950 MHz 18 min SAR (averaged over 4.04 mg): 10.5, 40.3, 130, 263 W/kg Anesthetized	Increase in local cerebral blood flow and temperature, temperature increase in remote areas only with SAR ≥40.3 W/kg.		Masuda et al. (2011)
Brain temperature, comparison measured / modelled Rat: Sprague Dawley 4, 8 weeks	1457 MHz 6 min Brain SAR: 4 weeks: 17, 57, 167 W/kg; 8 weeks: 75, 150, 300 W/kg Restrained	Brain temperature increase, SAR dependent; good correspondence with model for 4-week olds, less for 8-week olds.	No statistical analysis. Low number of animals.	Hirata al et. (2011)
Temperature; effect of ambient temperature (24 vs 31 ℃) and vasodilatator Prasozin Rat: Wistar (n=11–13) 3 weeks	900 MHz CW 23.5 h per day, 7 weeks WBA SAR 0.3–0.1 W/kg Free	At 31 ℃ increased cortical and peripheral temperatures in sham, lower increased peripheral temperature in exposed due to vasoconstriction. Prasozin: peripheral temperature in exposed similar to sham.	Peripheral vasomotor tone dampened by RF.	Pelletier et al. (2013)
Behavioural thermoregulation				
Core temperature, thermoregulatory behaviour Rabbit (n=14) 2 kg ± 10%	2450 MHz Variable exposure times, so body temperature increase would not exceed 1.5 ℃ WBA SAR 1.3, 2.6, 8.6, 11.6 W/kg Restrained	Behavioural changes with core temperature increase ~1 ℃; considerable individual variation.		Hirata et al. (2010)

Abbreviations: α-CRH: α-helical corticotropin releasing hormone; CW: continuous wave; IR: infrared; WBA SAR: whole body SAR.

Excluded studies

Nakamura et al. (2003)
Millenbaugh et al. (2006)

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