Strål säkerhets myndigheten

Swedish Radiation Safety Authority

Author: SSM's Scientific Council on Electromagnetic Fields

Research

2015:19

Recent Research on EMF and Health Risk - Tenth report from SSM's Scientific Council on Electromagnetic Fields, 2015

Report number: 2015:19 **ISSN:** 2000-0456
Available at www.stralsakerhetsmyndigheten.se

SSM perspective

Background

The Swedish Radiation Safety Authority's (SSM) scientific council monitors the current research situation and provides the Authority with advice on the assessment of risks, authorization and optimization within the area. The council gives guidance when the Authority must give an opinion on policy matters when scientific testing is necessary. The council is required to submit a written report on the current research and knowledge situation each year.

Objectives

The objective of the report is to cover the previous year's research in the area of electromagnetic fields (EMF). The report gives the Authority an overview and provides an important basis for risk assessment.

Results

The present annual report is number ten in the series and covers studies published from October 2013 up to and including September 2014. It covers different areas of EMF (static, low frequency intermediate and radio frequent fields) and different types of studies such as biological, human and epidemiological studies. This report includes an update on key issues such as extremely low frequency (ELF) magnetic fields and childhood leukaemia, effects from mobile phones, health risk from transmitters and self-reported electromagnetic hypersensitivity. The report also has a section covering other relevant expert reports published recently.

Project information

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Reference: SSM2015-1759

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Preface

In 2002, the responsible authority in Sweden established an international scientific council for electromagnetic fields (EMF) and health with the major task to follow and evaluate the scientific development and to give advice to the authority. Up to 2008, the responsible authority was SSI (the Swedish Radiation Protection Authority). That year, the Swedish government reorganized the radiation protection work and the task of the scientific council since 2008 lies under the Swedish Radiation Safety Authority (SSM). In a series of annual scientific reviews, the Council consecutively discusses and assesses relevant new data and put these in the context of already available information. The result will be a gradually developing health risk assessment of exposure to EMF. The Council presented its first report in December 2003. The present annual report is number ten in the series and covers studies published from October 2013 up to and including September 2014.

The composition of the Council that prepared this report is:

Prof. Heidi Danker-Hopfe, Charité – University Medicine, Berlin, Germany

Prof. Clemens Dasenbrock, Fraunhofer Institute for Toxicology, Hannover, Germany

Dr Emilie van Deventer, World Health Organization, Geneva, Switzerland (observer)

Dr Anke Huss, University of Utrecht, the Netherlands

Dr Lars Klaeboe, Norwegian Radiation Protection Authority, Oslo, Norway

Dr Leif Moberg, Sweden (chair)

Dr Eric van Rongen, Health Council of the Netherlands, Hague, the Netherlands

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Mr Lars Mjönes, M.Sc., Sweden (scientific secretary)

Declarations of conflicts of interest are available at SSM.

Stockholm in March 2015

Leif Moberg

Chair

Update on key issues

ELF magnetic fields - childhood leukaemia and other health endpoints

In 2002 extremely low frequency (ELF) magnetic fields were classified by WHO's International Agency for Research on Cancer (IARC), as possibly carcinogenic for humans (group 2B). The fields generated from distribution and use of electricity have been associated with an increased risk of acute lymphoblastic leukaemia in epidemiologic research. However, experimental and mechanistic research has been unable to confirm this association. Therefore, the question whether extremely low frequency magnetic fields have any influence on the development of childhood leukaemia is still unresolved.

There have been some indications of an increased risk for Alzheimer's disease and the motor neuron disease Amyotrophic Lateral Sclerosis (ALS), mostly based on occupational studies. It has been hypothesized that electric shocks rather than magnetic fields could be involved in the development of ALS. However, two new studies on ALS support an association with ELF-MF exposure rather than with electric shocks. A new study on Parkinson's disease and occupational ELF-MF field exposure and electrical shock does not indicate an association for any of the exposure measures, which is in line with the previously observed absence of an association with these exposures. In conclusion, similar to previous research, recent studies suggest that an association between ELF-MF exposure and ALS and Alzheimer's diseases may exist, which warrants further investigation.

Effects from use of mobile phones

Based on some studies indicating an increased risk for glioma and vestibular schwannoma (acoustic neuroma) associated with wireless phone use, IARC in 2011 classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B). However, in previous reports the Scientific Council of SSM has concluded that studies of brain tumours and other tumours of the head (vestibular schwannoma, salivary gland), together with national cancer incidence statistics from different countries, are not convincing in linking mobile phone use to the occurrence of glioma or other tumours of the head region among adults. Recent studies described in this report do not change this conclusion although these have covered longer exposure periods. Scientific uncertainty remains for regular mobile phone use for time periods longer than 15 years. It is also too early to draw firm conclusions regarding risk of brain tumours in children and adolescents, but the available literature to date does not indicate an increased risk.

The most consistently observed biological effect from mobile phone exposure is an effect of the power of sleep EEG in human volunteer provocation studies. The observed effects, however, are weak and do not seem to translate into behavioural or other health effects.

In a number of experimental provocation studies, persons who consider themselves electromagnetically hypersensitive as well as healthy volunteers have been exposed to either sham or real fields from a mobile phone, but neither symptoms nor other effects were more prevalent during real exposure than during sham exposure of the experimental groups. While the symptoms experienced by patients with EHS are real and some individuals suffer severely, studies so far have not provided evidence that exposure to electromagnetic fields is a causal factor. Several studies have indicated a nocebo effect, i.e. an adverse effect caused by an expectation that something is harmful.

In the last year several studies have reported an association between mobile phone use in adolescents and the occurrence of symptoms. What remains unclear, however, is whether this could be due to the exposure to RF-EMF, confounding (e.g. personality type) or the usage of mobile phones or other electronic devices as such.

Health risks from transmitters

In line with previous studies, new studies on adult and childhood cancer with improved exposure assessment do not indicate any health risks for the general public related to exposure from radiofrequency electromagnetic fields from far-field sources, such as base stations and radio and TV transmitters. There is no new evidence indicating a causal link to exposure from far-field sources such as mobile phone base stations or wireless local data networks in schools or at home.

Executive Summary

Static fields

Exposure to static (0 Hz) magnetic fields much greater than the natural geomagnetic field can occur close to industrial and scientific equipment that uses direct current such as some welding equipment and various particle accelerators. However, the main sources of exposure to strong static magnetic fields, SMF, (> 1 T) are magnetic resonance imaging (MRI) devices for medical diagnostic purposes. Volunteer studies have demonstrated that movement in such strong static fields can induce electrical fields in the body and sensations such as vertigo and nausea. The thresholds for these sensations seem to vary considerably within the population. MRI workers are also affected by these transient symptoms.

Cell studies

The new *in vitro* studies support the previous Council conclusions on the induction of changes in some biological endpoints, including oxidative stress, apoptosis and protein expression. These studies should be repeated by applying rigorous experimental protocols before firm conclusions can be drawn.

Human studies

Three studies, which are all related to exposure from a 7 T MRI equipment, with various exposures and exposure combinations, show that in experimental studies on neurocognitive effects distance from the bore is a good proxy for personal exposure. Although an effect of exposure to an SMF alone on the vestibular system was sporadically observed, effects were reported more frequently for a combined exposure with time-varying magnetic fields.

As already stated in the previous Council report (SSM, 2014) studies with MRI exposure are usually not restricted to pure static magnetic fields. While exposure of workers in an MRI environment usually also includes a time-varying component induced by movements in the field, exposure of subjects in a scanner always additionally includes switched gradient magnetic fields in the kHz frequency range and radiofrequency (RF) EMF components.

Epidemiology

A recent study has shown that MRI workers are affected by transient symptoms. Movement of the workers through the static magnetic stray field around MRI equipment can cause low-frequency time-varying magnetic fields. Thus, this observational study cannot resolve whether the observed associations are due to the static or the time-varying magnetic fields. However, human experimental studies on neurocognitive effects discussed above suggest that static fields alone did not result in effects, whereas combined exposure with time-varying magnetic fields did. The specificity of the symptom pattern and the exposure-response relationship strongly supports the hypothesis that the symptoms are related to MRI work. Job titles were not equally distributed over the exposure conditions but seem to produce no bias according to sensitivity analyses. Potential long term health consequences of these transient symptoms are not known and were not assessed in this study. Of note, 10 % out of 103 exposed participants with symptoms indicated that their work practice had been affected by their symptoms, which indicates that these findings are relevant for the workers.

Extremely low frequency (ELF) fields

The exposure of the general public to ELF fields is primarily from 50 and 60 Hz electric power lines and from electric devices and installations in buildings. Regarding the exposure to ELF magnetic fields (ELF-MF) and the development of childhood leukaemia, the latest studies did not consistently observe an association. However, these did not use new approaches and the same limitations as in previous research apply. Thus, the conclusion from previous Council reports still holds: associations have been observed, but a causal relationship has not been established.

Cell studies

As in the previous Council report, the conclusions on ELF *in vitro* studies can be summarized as follows: a) there is a large variety of biological and electromagnetic parameters investigated; b) few investigations aim to address the correlation between power frequency exposure and leukaemia. Moreover, as for static fields, several studies lack sham-controls and are therefore not interpretable.

Animal studies

Most studies used exposure levels of 0.5-1 mT. As stated in the previous report, these levels may be relevant for risk assessment, although exposures under real-life conditions are normally in the µT range.

Studies describing ELF-MF effects on brain function and physiology dominate this year. Single studies show, in the cortex, hippocampus and hypothalamus, an increase of nitric oxide, specific neurotransmitters and a subtle decrease of (new-born) nerve cell loss and dendritic spine density after ELF-MF exposure. Some further experiments describe a negative effect on learning ability and memory, while others do not.

With the exception of a few studies, the quality of the experiments and their description did not substantially improve compared to the previous years. Overall and similar to the previous Council report, the results of the described studies are not very consistent.

Human studies

There were no informative studies on ELF effects in humans during the reporting period.

Epidemiology

Over the last year, several publications appeared addressing pregnancy outcomes in relation to maternal ELF-MF exposure. Whereas two small studies observed an association between miscarriages and ELF-MF exposure, no effect on pre-term birth was seen in a large study from the UK with more than 250,000 singleton live births. However, this study found an association with decreased birth weights which warrants further investigation.

With respect to childhood leukaemia and distance to power line, a striking pattern of decreasing risks over time between 1962 and 2008 was observed in a large study performed in the UK. Since ELF-MF exposure in proximity to power lines have most likely not substantially changed over time, this observation might indicate that methodological issues or a, as yet unknown, risk factor is playing a role for the previously observed association. Such a factor must be a very strong risk factor for childhood leukaemia to have such an impact. No obvious candidate can be proposed, given the limited number of strong known risk factors for childhood leukaemia, apart from genetics, which is unlikely to change over time.

New studies on adult cancers indicated associations for some tumours, but the consistency of these findings was not very high and no new ground-breaking methods have been applied. Given the high number of similar papers already published in this area, the new studies do not change the view on the topic. There are some, but inconsistent, indications for an increased risk for adult leukaemia and central nervous system tumours. For other types of cancer the evidence is scarce.

One new study on Parkinson's disease and occupational ELF-MF field exposure and electrical shock does not indicate an association for any of the exposure measures, which corroborates the previously observed absence of an association with these exposures. Two new studies on Amyotrophic Lateral Sclerosis (ALS) rather support an association with ELF-MF exposure than with electric shocks, which were previously discussed to remain an open question in the research field. A Mexican study observed an association between ELF-MF exposure and an impaired cognitive function, but suffered from low statistical power. In conclusion, similar to previous research, recent studies suggest that an association between ELF-MF exposure and ALS or Alzheimer's diseases may exist, which warrants further investigation.

Intermediate frequency (IF) fields

The intermediate frequency (IF) region of the EMF spectrum is defined as being between the ELF and RF ranges. Exposure from such fields can arise from sources such as induction cooking, anti-theft devices and some industrial applications. Very few experimental studies are available on (health) effects of IF electromagnetic fields and no conclusions can be drawn at present. Additional studies would be important because human exposure to such fields is increasing, for example from different kinds of surveillance systems. Studies on possible effects associated with chronic exposure at low exposure levels are particularly relevant for confirming adequacy of current exposure limits.

In the last year only two studies, one on human cell cultures and one on chicken embryos, have been published. Although well conducted, no general conclusions can be drawn from these studies and thus as reported in the previous Council report no firm conclusions can be drawn for this frequency-range.

Radiofrequency (RF) fields

The general public is exposed to radiofrequency (RF) fields from different sources, such as radio and TV transmitters, cordless and mobile phones and their supporting base stations and wireless local area networks. Among parts of the public there is concern about possible health effects associated with exposure to RF fields. Particularly, in some countries, concern about the use of Wi-Fi in schools has grown in recent years.

Cell studies

A large number of *in vitro* studies dealing with several biological endpoints have been carried out, including studies on combined exposures to RF and chemical agents. Most of them do not indicate an effect of the exposure. Nevertheless, in some investigations effects on parameters related to oxidative stress is reported and in a few cases some slight and transient changes relative to sham-controls have been recorded. Moreover, the ability of RF exposure to induce adaptive response has been confirmed. These results should be repeated by independent investigators to draw firm conclusions.

Animal studies

In previous reports increased oxidative stress has been reported in brain and other tissues (SSM 2013, 2014), but a significant number of studies could not be interpreted due to missing or incomplete dosimetry or problems in the study design. Both trends continue in this year's review. So it seems that exposure to RF electromagnetic fields is capable of inducing increased oxidative stress under various circumstances in several tissues, but it is not a ubiquitous phenomenon and there is no obvious dose-response effect. Why this is the case is not clear.

Mixed results were obtained in learning and behavioural studies. Two studies on effects on memory were contradictory. In the first, exposure for 1 h per day to SARs of 0.05–0.18 W/kg resulted in some effect on spatial memory (but not in reference memory and working memory), while in the second lifetime exposure for 20 h per day to SARs up to 0.25 W/kg did not result in any effects on reflexes, mood and memory in three successive generations.

Studies into the effect of RF-EMF on the testes and the quality of sperm also provided mixed results. Two studies with low exposure levels (SARs of 0.018 and 0.001 W/kg) showed effects, while one study with a significantly higher level (SAR of 0.6 W/kg) did not. These results are contradictory to the assumption of an exposure-response relationship.

Finally, a study into metabolism and temperature regulation showed that even with exposure to whole-body SARs of 4 W/kg, Djungarian hamsters are capable of maintaining a constant body temperature by adjusting their metabolism.

Human studies

The papers published since the last Council report are very heterogeneous with regard to investigated outcomes and methods. There is just one sleep study, which did not observe effects from RF-EMF on the EEG power spectra during sleep. Studies on heart rate variability did also not observe any effects. The studies investigating neurophysiological parameters during wake showed some effects, partly with contradictory results.

Epidemiology

New studies on mobile phone use and tumours in the brain using retrospective exposure assessment are in line with previous research, where increased risks were observed in some of the highest exposure categories. However, it is not clear to what extent these risk estimates are affected by recall bias. A Swedish study collecting history of laterality of mobile phone use provided convincing evidence that reverse causality and detection bias play a relevant role in previously observed associations between mobile phone use and vestibular schwannoma. Since this slow growing tumour affects the hearing, mobile phone users might be more likely to notice the symptoms and obtain a diagnosis at an earlier stage of disease development.

A large Swiss study on childhood tumours and exposure to RF-EMF from broadcasting did not indicate an association, which is in line with two previous large case-control studies. These three studies are more reliable than earlier ecological studies that found such associations in the 1990s because in the new case-control studies individual exposure assessment was conducted. Further, the case-control studies were based on substantially larger samples and the investigators of the Swiss study also adjusted for potential confounders in their analysis.

New studies on associations between sperm quality and mobile phone use are of low quality and cannot be used to evaluate a potential association with RF-EMF exposure. Adjustment for potential confounders was not performed in these studies. This is a recurrent problem as many studies on this subject have been published, but none has tried to make a reasonable assessment of the exposure of the testicles.

In the last year several cross-sectional studies reported consistently an association between mobile phone use in adolescents and the occurrence of symptoms. What remains unclear, however, is whether this could be due to the exposure to RF-EMF, confounding (e.g. personality type) or the usage of mobile phones or other electronic devices as such.

In terms of exposure from mobile phone base stations or other RF-EMF transmitters, no new evidence has become available indicating a causal link between exposure and symptoms or EHS.

Sammanfattning på svenska

Statiska fält

Exponering för nivåer av statiska fält (0 Hz) som är mycket högre än det naturligt förekommande geomagnetiska fältet kan inträffa i närheten av industriell eller vetenskaplig utrustning som använder likström, som t.ex. elsvetsutrustning eller olika typer av partikelacceleratorer. Den viktigaste källan till exponering för starka statiska magnetfält (> 1 T) är emellertid användningen av magnetresonanstomografi (MR) för medicinsk diagnostik. Studier på frivilliga försökspersoner har visat att rörelser i starka statiska fält kan inducera elektriska fält i kroppen och orsaka yrsel och illamående. Tröskelvärdena för dessa effekter tycks dock variera avsevärt mellan olika individer. Personal som arbetar med MR påverkas av dessa övergående symtom.

Cellstudier

Nya *in vitro*-studier bekräftar slutsatserna i Rådets tidigare rapporter att det är stora variationer för några biologiska utfall, bl.a. oxidativ stress, apoptos och proteinuttryck. Dessa studier måste upprepas med mycket noggrant genomförda experiment innan några bestämda slutsatser kan dras.

Studier på människa

Tre studier, som alla utförts vid exponering från 7 T magnetresonanstomografer med olika exponeringar och kombinationer av exponeringar, visar att avståndet från öppningen av tomografen är ett bra mått för att uppskatta personalens exponering. Även om en effekt på balanssystemet från exponering för enbart statiska magnetfält kunde iakttas sporadiskt, så rapporterades effekter mycket oftare vid kombinerad exponering med tidsvariabla magnetfält.

Som redan konstaterades i Rådets föregående rapport (SSM 2014) är exponeringen från magnetresonanstomografer vanligen inte begränsad till enbart statiska magnetfält. Medan exponering av personal vanligtvis också innefattar en tidsvariabel komponent orsakad av att de rör sig i fältet, så exponeras patienten i tomografen alltid också för magnetfält i kHz-området och för radiofrekventa fält.

Epidemiologi

En nyligen genomförd studie har visat att personal som arbetar med magnetresonanstomografi drabbas av övergående symtom. När de rör sig genom det statiska magnetfältet omkring en magnetresonanstomograf påverkas de av ett lågfrekvent tidsvariabelt magnetfält. Den aktuella observationsstudien kan inte avgöra om de observerade sambanden orsakas av de statiska eller de tidsvariabla magnetfälten. Experimentella studier av neurokognitiva effekter på människor, som nämnts ovan, antyder emellertid att enbart exponering för statiska fält inte gav några effekter medan exponering för en kombination av statiska och tidsvariabla fält gav besvär. Den speciella symtombilden och sambandet mellan exponering och respons ger ett starkt stöd för hypotesen att symtomen har samband med arbete med magnetresonanstomografi. Tjänstetitlar, som användes som mått på exponeringen, var inte likformigt fördelade över exponeringsförhållandena men det tycks inte innebära någon snedfördelning (bias) enligt känslighetsanalysen. Möjliga långsiktiga hälsoeffekter av dessa övergående symtom är inte kända och undersöktes inte i denna studie. Det är notabelt att en tiondel av de 103 exponerade med symtom uppgav att deras arbetsrutiner hade påverkats av deras symtom, vilket antyder att dessa fynd är relevanta för personalen.

Lågfrekventa (ELF) fält

Allmänheten exponeras för lågfrekventa (ELF) fält i första hand från kraftledningar med frekvenserna 50 och 60 Hz och från elektriska installationer och apparater i byggnader. När det gäller sambandet mellan exponering för lågfrekventa magnetfält och utvecklingen av barnleukemi visar nya studier inte samstämmigt på samband. Inga nya undersökningsmetoder har dock använts i dessa nya studier som därför har samma begränsningar som tidigare forskning. Därför gäller fortfarande slutsatsen från Rådets tidigare rapporter: samband har observerats men något orsakssamband har inte kunnat fastställas.

Cellstudier

Liksom i Rådets föregående rapport kan slutsatserna för *in vitro*-studier för lågfrekventa fält summeras på följande sätt: a) det finns stora variationer i de undersökta biologiska och elektromagnetiska parametrarna; b) endast ett fåtal studier syftar till att undersöka sambandet mellan lågfrekventa magnetfält och leukemi. Liksom för statiska fält så saknar ett flertal studier oexponerade kontroller och kan därför inte utvärderas.

Djurstudier

De flesta studierna har använt exponeringsnivåer på 0,5 – 1 mT. Som konstaterades i Rådets föregående rapport så kan dessa nivåer i och för sig vara relevanta för riskuppskattning, men exponering av allmänheten ligger normalt i µT-området. Under året har studier som beskriver effekter av lågfrekventa magnetfält på hjärnans funktion och fysiologi dominerat. Enstaka studier visar en ökning av kväveoxider och specifika signalsubstanser i cortex, hippocampus och hypotalamus samt en liten minskning av förluster av (nybildade) nervceller och täthet av dendritutskott efter exponering för lågfrekventa magnetfält. Några studier beskriver en negativ effekt på inlärningsförmåga och minne, medan andra inte gör det.

Med undantag för några få studier har kvaliteten på experimenten och beskrivningen av dem inte ökat nämnvärt jämfört med föregående år. Sammanfattningsvis, och i likhet med Rådets föregående rapport, så är resultaten av de beskrivna studierna inte särskilt samstämmiga.

Studier på människa

Det har inte publicerats några informativa studier avseende effekter av lågfrekventa magnetfält på människa.

Epidemiologi

Under det senaste året har flera studier publicerats som rör hur moderns exponering för lågfrekventa fält påverkar graviditeten och barnet. Medan två mindre studier observerat ett samband mellan missfall och exponering sågs inte någon effekt på för tidig födsel i en stor brittisk studie som omfattade fler än 250 000 födda barn (ett barn per förlossning). Den studien fann emellertid ett samband med minskad födelsevikt som kräver ytterligare undersökning.

Med avseende på barnleukemi och avstånd till kraftledningar har ett slående mönster av minskande risker över tid mellan 1962 och 2008 observerats i en stor brittisk studie. Eftersom exponering för lågfrekventa magnetfält i närheten av kraftledningar knappast har ändrats särskilt mycket med tiden så kan denna observation indikera att metodfrågor, eller en tidigare okänd faktor, spelar en roll för det tidigare observerade sambandet mellan lågfrekventa magnetfält och barnleukemi. Detta måste vara en mycket kraftig riskfaktor för barnleukemi för att ha en sådan påverkan. Det finns idag ingen uppenbar kandidat till en sådan riskfaktor eftersom endast ett fåtal starka riskfaktorer för barnleukemi är kända, bortsett från ärftliga faktorer, som knappast ändras över tid.

Nya studier av cancer hos vuxna antyder samband för visa tumörtyper, men samstämmigheten hos dessa fynd är inte särskilt stor och inga nya banbrytande metoder har använts. Med tanke på det stora antalet liknande artiklar som redan publicerats inom detta område så ändrar inte de nya studierna synen på riskerna. Det finns några, dock inte samstämmiga, indikationer på en ökad risk för leukemi hos vuxna och tumörer i centrala nervsystemet. För andra typer av tumörer är beläggen knapphändiga

En ny studie av Parkinsons sjukdom och yrkesexponering för lågfrekventa magnetfält och elektriska stötar tyder inte på något samband för någon av exponeringstyperna, vilket stöder tidigare observationer av en frånvaro av samband med dessa exponeringar. Två nya studier av ALS (amyotrofisk lateralskleros) stöder snarare ett samband med exponering för lågfrekventa magnetfält än med elektriska stötar, vilket tidigare har betraktats som en öppen fråga inom forskningsområdet. En mexikansk studie har observerat ett samband mellan exponering för lågfrekventa magnetfält och försämrad kognitiv förmåga, men studien har låg statistisk styrka.

Sammanfattningsvis, i likhet med tidigare forskning så antyder nyare studier att det kan finnas ett samband mellan exponering för lågfrekventa magnetfält och ALS eller Alzheimers sjukdom, vilket kräver ytterligare studier.

Intermediära (IF) fält

Det intermediära frekvensområdet av EMF-spektret ligger definitionsmässigt mellan ELF- och RF-områdena. Exponering för sådana fält kan uppkomma t.ex. vid användning av induktionsspisar, vid larmbågar i butiker och vid vissa industriella tillämpningar. Mycket få experimentella studier rörande hälsoeffekter från exponering för intermediära fält finns tillgängliga, och inga slutsatser kan dras för närvarande. Ytterligare studier skulle vara värdefulla eftersom människor exponeras för sådana fält i ökande grad, till exempel från olika typer av elektroniska övervakningssystem. Studier av möjliga effekter av kronisk exponering för låga nivåer är särskilt betydelsefulla för att bekräfta gällande rikt- och gränsvärden.

Under det senaste året har endast två studier publicerats, en på kulturer av mänskliga celler och en på kycklingembryon. Även om de är väl genomförda så kan inga allmänna slutsatser dras från dessa studier och därför kan, som redan konstaterades i förra årets rapport, inga säkra slutsatser dras för detta frekvensområde.

Radiofrekventa (RF) fält

Allmänheten exponeras för radiofrekventa fält från en mängd olika källor som radio- och TV-sändare, trådlösa telefoner och mobiltelefoner och deras respektive basstationer samt trådlösa datornätverk. Bland delar av allmänheten finns en oro för möjliga hälsoeffekter från exponering för radiofrekventa fält. Framför allt har oron för användningen av trådlösa datornätverk i skolor ökat under senare år i en del länder.

Cellstudier

Ett stort antal *in vitro*-studier som rört flera olika biologiska utfall har genomförts, bl.a. studier av kombinerad exponering för radiofrekventa fält och olika kemiska agens. Flertalet av dem tyder inte på någon effekt av exponeringen. Likväl rapporteras i några undersökningar effekter på parametrar som har samband med oxidativ stress och i några få fall har några små och övergående förändringar jämfört med oexponerade kontroller registrerats. Dessutom har RF-exponeringens förmåga att inducera adaptiv respons bekräftats. Dessa resultat bör upprepas av andra forskargrupper för att säkra slutsatser skall kunna dras.

Djurstudier

I tidigare rapporter har en ökad oxidativ stress rapporterats i hjärnan och andra vävnader (SSM 2013, 2014), men ett stort antal studier kunde inte utvärderas p.g.a. frånvaro av, eller ofullständig, dosimetri, eller andra problem med studiernas utformning. Båda dessa trender kan ses även i årets genomgång. Det verkar vara möjligt att exponering för radiofrekventa fält kan inducera en ökad oxidativ stress i flera olika vävnader under vissa förutsättningar, men det är inte ett fenomen som uppträder alltid och det finns inget uppenbart samband med exponeringens storlek. Varför detta är fallet är oklart.

Studier rörande inlärning och beteende gav blandade resultat. Två studier av effekter på minnet gav motsägande resultat. Den första, med exponering 1 timme per dag med SAR-värden mellan 0,05 och 0,18 W/kg, resulterade i vissa effekter på rumsminnet (men inte på referensminnet eller arbetsminnet). Den andra studien med livstidsexponering, 20 timmar per dag för SAR-värden upp till 0,25 W/kg, gav inte några effekter på reflexer, humör eller minnesfunktion i tre på varandra följande generationer.

Studier av effekten av RF-exponering av testiklarna och spermakvalitet gav också blandade resultat. Två studier med låga exponeringsnivåer (SAR-värden på 0,018 och 0,001 W/kg) visade effekter medan en studie med avsevärt högre nivåer (SAR 0,6 W/kg) inte gjorde det. Dessa resultat strider mot antagandet att det finns ett exponerings-responsberoende.

En studie av ämnesomsättning och temperaturreglering visade att, även med helkroppsexponering för SAR-värden på 4 W/kg, kan dvärghamstrar behålla en konstant kroppstemperatur genom att justera sin ämnesomsättning.

Studier på människa

De artiklar som publicerats sedan Rådets senaste rapport är mycket heterogena med avseende på undersökta utfall och metoder. Endast en sömnstudie har publicerats. Studien observerade inte några effekter av radiofrekvent exponering i EEG under sömn. De studier som undersökte neurofysiologiska parametrar under vaken tid visade vissa effekter, delvis med motstridiga resultat.

Epidemiologi

Resultaten från nya studier av mobiltelefonanvändning och tumörer i hjärnan med användning av retrospektiv exponeringsuppskattning ligger i linje med tidigare forskning där en förhöjd risk kunde observeras i de högsta exponeringskategorierna. Det är emellertid inte klart i vilken utsträckning dessa riskuppskattningar har påverkats av minnesbias. En svensk studie som har undersökt hur lateraliteten (vid vilket öra man håller mobiltelefonen) utvecklats över tid ger övertygande evidens för att omvänd kausalitet och detektionsbias (upptäcktsbias) spelar en viktig roll i tidigare observerade samband mellan användning av mobiltelefon och hörselnervstumör. Eftersom denna långsamt växande tumör påverkar hörseln så kan mobiltelefonanvändare vara mer benägna att upptäcka symtomen och därmed få en diagnos i ett tidigare stadium av sjukdomsutvecklingen.

En stor schweizisk studie av tumörer hos barn och exponering från radiosändare tyder inte på något samband, vilket ligger i linje med två stora tidigare fall-kontrollstudier. Eftersom individuell exponeringsuppskattning genomfördes i dessa tre studier är de mer pålitliga än tidigare ekologiska studier som funnit samband på 1990-talet. Dessutom baserades alla de tre fall-kontrollstudierna på betydligt större material än de ekologiska studierna och den schweiziska studien har också justerats för möjliga förväxlingsfaktorer (confounding).

Nya studier av samband mellan användning av mobiltelefon och spermakvalitet är av låg vetenskaplig kvalitet och kan inte användas för att utvärdera ett möjligt samband med exponering för radiofrekventa fält. Någon korrigering för möjliga förväxlingsfaktorer gjordes inte i dessa studier. Detta är ett återkommande problem eftersom många studier inom detta ämne har publicerats, men ingen har försökt att göra en rimlig uppskattning av exponeringen till testiklarna.

Under det senaste året har flera tvärsnittsstudier samstämmigt rapporterat ett samband mellan användning av mobiltelefon hos ungdomar och förekomsten av symtom. Det är emellertid fortfarande oklart om symtomen kan vara orsakade av exponering för radiofrekventa fält, confounding (t.ex. typ av personlighet) eller användning av mobiltelefon eller andra elektroniska apparater i sig.

När det gäller exponering från mobilbasstationer eller andra radiosändare så har ingen ny evidens blivit tillgänglig som skulle antyda ett orsakssamband mellan exponering och symtom eller egenrapporterad elöverkänslighet.

Preamble

In this preamble we explain the principles and methods that the Council uses to achieve its goals. Relevant research for electromagnetic fields (EMF) health risk assessment can be divided into broad sectors such as epidemiologic studies, experimental studies in humans, experimental studies in animals, and in vitro studies. Studies on biophysical mechanisms, dosimetry, and exposure assessment are also considered as integrated parts in these broad sectors. A health risk assessment evaluates the evidence within each of these sectors and then weighs together the evidence across the sectors to a combined assessment. This combined assessment should address the question of whether or not a hazard exists, i.e. if a causal relation exists between exposure and some adverse health effect. The answer to this question is not necessarily a definitive yes or no, but may express the likelihood for the existence of a hazard. If such a hazard is judged to be present, the risk assessment should also address the magnitude of the effect and the shape of the exposure response function, i.e. the magnitude of the risk for various exposure levels and exposure patterns.

As a general rule, only articles that are published in English language peer-reviewed scientific journals since the previous report are considered by the Council. A main task is to evaluate and assess these articles and the scientific weight that is to be given to each of them. However, some of the studies are not included in the Council report either because the scope is not relevant, or because their scientific quality is insufficient. For example, poorly described exposures and missing (sham) controls are reasons for exclusion. Such studies are normally not commented upon in the annual Council reports (and not included in the reference list of the report). Major review articles and reports are briefly mentioned but not evaluated.

The Council considers it to be of importance to evaluate both positive and negative studies, i.e. studies indicating that EMF has an effect and studies not indicating the existence of such an effect. In the case of positive studies the evaluation focuses on alternative factors that may explain the positive result. For instance in epidemiological studies it is assessed with what degree of certainty it can be ruled out that an observed positive result is the result of bias, e.g. confounding or selection bias, or chance. In the case of negative studies it is assessed whether the lack of an observed effect might be the result of (masking) bias, e.g. because of too small exposure contrasts or too crude exposure measurements. It also has to be evaluated whether the lack of an observed effect is the result of chance, a possibility that is a particular problem in small studies with low statistical power. Obviously, the presence or absence of statistical significance is only one of many factors in this evaluation. Indeed, the evaluation considers a number of characteristics of the study. Some of these characteristics are rather general, such as study size, assessment of participation rate, level of exposure, and quality of exposure assessment. Particularly important aspects are the observed strength of the association and the internal consistency of the results including aspects such as exposure-response relation. Other characteristics are specific to the study in question and may involve aspects such as dosimetry, method for assessment of biological or health endpoint, the relevance of any experimental biological model used.[1]

It should be noted that the result of this process is not an assessment that a specific study is unequivocally negative or positive or whether it is accepted or rejected. Rather, the assessment will result in a weight that is given to the findings of a study. The evaluation of the individual studies within a sector of research is followed by the assessment of the overall strength of evidence from that sector with respect to a given outcome. This implies integrating the results from all relevant individual studies into a total assessment taking into account the observed magnitude of the effect and the quality of the studies.

In the final overall evaluation phase, the available evidence is integrated over the various sectors of research. This involves combining the existing relevant evidence on a particular endpoint from studies in humans, from animal models, from in vitro studies, and from other relevant areas. In this final integrative stage of evaluation the plausibility of the observed or hypothetical mechanism(s) of action and the evidence for that mechanism(s) have to be considered. The overall result of the integrative phase of evaluation, combining the degree of evidence from across epidemiology, human and animal experimental studies, in vitro and other data depends on how much weight is given on each line of evidence from different categories. Human epidemiology is, by definition, an essential and primordial source of evidence since it deals with real-life exposures under realistic conditions in the species of interest. The epidemiological data are, therefore, given the greatest weight in the overall evaluation stage. However, epidemiological data has to be supported by experimental studies to establish a causal link between exposure and health.

An example demonstrating some of the difficulties in making an overall assessment is the evaluation of ELF magnetic fields and their possible causal association with childhood leukaemia. It is widely agreed that epidemiology consistently demonstrates an association between ELF magnetic fields and an increased occurrence of childhood leukaemia. However, there is lack of support for a causal relation from observations in experimental models and a plausible biophysical mechanism of action is missing. This had led IARC to the overall evaluation of ELF magnetic fields as “possibly carcinogenic to humans” (Group 2B).

[1] For a further discussion of aspects of study quality, see for example the Preamble of the IARC (International Agency for Research on Cancer) Monograph Series (IARC, 2002).

1. Static fields

1.1 Cell studies

Three papers are described in this section, related to the effect of static fields on oxidative stress, protein expression and apoptosis. Moreover, two more studies deal with the effect of magnetic resonance imaging (MRI) scans, and are presented in a separate section. Other papers have been recognized but are not presented due to the lack of sham-exposed controls or because they refer to biomedical applications.

1.1.1 Oxidative stress

Rat pulmonary arterial smooth muscle cells (rPASMC) were employed by Usselman et al. (2014) to investigate the effects of magnetic fields on the production of reactive oxygen species (ROS) from intracellular superoxide and extracellular hydrogen peroxide (H_2O_2). The authors considered the combination of a static magnetic field (SMF) of 45 µT and a RF magnetic field (7 MHz). A first experimental run was carried out for the simultaneous exposure of three 6-well cell culture plates as a control to the 45 µT SMF. The second set served to expose cells to the SMF and to perpendicularly-applied RF magnetic fields. In both cases, the 45 µT SMF was oriented perpendicular to the plane of growth of the cells. Sham exposures were conducted only for SMF, since the other cases posed a significant challenge, according to the authors. The experimental exposure included both groups placed within separate tri-axial coils containing a single Helmholtz loop in separate incubators. The RF coil was not energized for the control SMF and was energized for the RF group. The exposure duration was 24 and 48 h long, starting 24 h after cell seeding.

The results of three independent experiments, carried out in blind conditions, indicated an enhanced cell proliferation with continuously applied 45 µT SMF and a10 mT RMS RF magnetic fields (40 % and 45 % after 24 and 48 h exposure, respectively, compared to the 45 µT SMF control group). No effects were detected on cell viability.

Moreover, cultures exposed to RF magnetic fields produced 50 % more H_2O_2 compared to the SMF control for both exposure durations investigated, with a similar amount of H_2O_2 produced for each day. Catalase, added as a negative control, suppressed the RF magnetic field effects on H_2O_2 production. Electron paramagnetic resonance spectroscopy evidenced that RF magnetic fields significantly reduced the amount of superoxide concentration by 40 %, compared to SMF. According to the authors, the corresponding decrease in superoxide species with the accompanying increase in H_2O_2 implies a RF-induced modulation in the distribution of ROS products.

The results of some investigations seem to indicate that EMF, at least in certain experimental conditions, could enhance the level of reactive oxygen species (ROS). ROS include oxygen ions, free radicals and peroxides. They are highly unstable, chemically reactive molecules due to the presence of an unpaired electron and react with several cellular components, including proteins, lipids and DNA.

ROS are continuously produced during cellular metabolism (respiration and substrate oxidation) in all aerobic organisms but exogenous factors such as gamma rays and chemical carcinogens can also generate oxygen radicals.

A number of primary antioxidant enzymes, such as different dismutases, catalases, reductases or peroxidases are known to neutralize the amounts of ROS. Moreover, several compounds, such as reduced glutathione (GSH) and its oxidized form (GSSG), scavenge free radicals. These molecules cooperate to maintain a cellular reducing environment (redox state).

Oxidative stress occurs when the production of ROS overrides the antioxidant capability of the target cell. It is involved in many pathological processes, among which are cancer, inflammation and neurodegenerative diseases (Alzheimer, Parkinson, multiple sclerosis etc.). It cannot be ruled out that the enhanced ROS levels that have been observed in some cells and animals after EMF exposure have a biological impact, but whether this is the case and, if so, what this impact is and whether it might result in health effects, is not known at present.

1.1.2 Protein expression

Expression of heat shock protein (HSP70) was evaluated by Laramee et al. (2014) in rat primary fibroblast cells (RAT1) transfected with a HSP70 promoter-linked luciferase reporter. Cell cultures were exposed/sham exposed to SMF of 1 to 440 mT for 16, 24 or 48 h starting at 24 and 48 h post transfection. HSP70 expression was followed for up to 96 h and showed a dependence on flux density, exposure duration, and start time post transfection. A nonlinear response in expression was observed for increasing flux density with a maximum of a 3.5-fold increase over control occurring at 48 h of exposure starting 48 h after transfection. As stated by the authors, it should be evaluated if the observed effect is consistent across different cell lines and other experimental models.

1.1.3 Apoptosis

Ben Yakir-Blumkin et al. (2014) evaluated the effect of SMFs on neuronal survival in rat primary cortical and hippocampal neurons. These cell types represent a suitable experimental system for modelling the neurodegenerative state *in vitro*. Different intensities of SMFs (from 0.4 to 5 mT) were achieved by placing the cultures at varying distances from magnets. Cultures exposed for up to 7 days in presence of etoposide or amyloid beta, two apoptotic inducers, exhibited an exposure- and time-dependent decrease in the percentage of apoptotic cells, with the maximum effect at 5.0 mT. Moreover, primary cortical neurons exposed to 5.0 mT for 7 days also showed a marked decrease in the expression of the pro-apoptotic markers, such as cleaved poly ADP ribose polymerase-1, cleaved caspase-3, active caspase-9 and the phosphohistone H2A variant, together with a reduction of etoposide induced mitochondrial membrane potential. Using the L-type voltage-gated Ca^{2+} channel inhibitor nifedipine, the authors found that the anti-apoptotic effect of SMFs was mediated by Ca^{2+} influx through these channels.

1.1.4 MRI

Szerencsi et al. (2013) investigated the effects of magnetic resonance imaging (MRI) scans on the DNA integrity of human leukocytes. Peripheral blood samples from three healthy donors were exposed to electromagnetic fields produced by 3T MRI equipment for 0, 22, 45, 67, and 89 min during the scanning procedure. To evaluate DNA damage, blood samples from each donor were processed to apply the alkaline comet assay and the micronucleus (MN) assay. No effects were detected in exposed cultures while in positive controls, exposed to 4 Gy gamma rays, a significant increase in the comet parameters and in MN frequency was induced. Unfortunately, this well done study lacks of sham controls.

Cho et al. (2014) also employed mitogen-stimulated human peripheral blood lymphocytes from healthy donors to investigate the effects of ELF-EMF generated by an MRI scanner on gadolinium (a contrast agents for enhanced magnetic resonance imaging) toxicity. Genotoxicity (strand breaks and MN induction) and cytotoxicity (cell viability, ROS and apoptosis) were investigated. Exposures/sham exposures (60 Hz, 0.8 mT) of different duration up to 48 h, based on the biological parameter investigated, were carried out concurrently with several doses of gadolinium (0.2-1.2 mM). The results of three experiments indicated that EMF exposure was able to enhance the gadolinium-induced cytotoxicity and genotoxicity in an exposure-dependent manner. In this study, the effect of ELF-EMF alone is not reported.

1.1.5 Conclusions on SMF cell studies

The new *in vitro* studies confirm the previous Council conclusions on the induction of variation of some biological endpoints, including oxidative stress, apoptosis and protein expression. These observations should be repeated by applying rigorous experimental protocols before firm conclusions can be drawn.

1.2 Animal studies

Effects of strong SMFs (1.5T -11.7T) produced by MRI systems were investigated in two studies using zebrafish or mice.

1.2.1 Brain and behaviour

Ward et al. (2014) investigated the swimming behaviour of adult (7.5 months old, 15 male / 15 female) zebrafish in strong magnetic fields. With a MRI-compatible video camera behaviour was recorded inside and outside the magnetic bore when fish had been individually introduced into the centre of a vertical 11.7 T magnetic field bore for 2 minutes. Two days later, heading preferences relative to a magnetic field were similarly recorded in a horizontally oriented 4.7 T magnet (1 min SMF exposure) and under infrared (IR) light which ensures lack of vision in zebrafish. One week later and after a gentamicin bath to ablate lateral line hair cell function in the inner ear, a sub-population of 10 zebrafish was tested again in the 11.7 T SMF. A second (not pre-treated) cohort of 10 fish underwent a repeat exposure and served as control. The SMF-exposed zebrafish exhibited markedly altered swimming behaviour independent of vision or lateral line function. After the short-term exposure to the vertically oriented 11.7 T SMF, 66% of fish showed increased swimming velocity or consistent looping/rolling behaviour. Altered swimming behaviour in the 4.7 T horizontally oriented SMF demonstrated “in most cases preferred swimming direction with respect to the field”. The data indicate that short-term exposures of strong SMF disturb orientation and locomotion in zebrafish. The effects support that they are mediated by the vestibular system.

1.2.2 Reproduction and development

Zaun et al. (2014) investigated the effect of daily exposure in utero to static magnetic fields during prenatal development on germ cell development and fertility of exposed offspring in C57BL/6J mice. Four groups of 29-33 eight weeks-old dams were in utero exposed (once daily, 75 min/d, day 1.5 – day 18.5 pc) to different static magnetic field strengths at the bore entrance or in the isocenter of 1.5 T and 7 T MRI systems. A fifth group was sham-exposed in a mock scanner, noise and light intensity were similar to that in the isocenter of the 7 T MRI. Group no. 6 served as a cage control. The offspring was mated at 8 weeks of age. In utero-exposed females were mated to one unexposed male; in utero-exposed males were mated to two unexposed females for 10 days. Pregnant dams were humanely killed on day 17.5 p.c., number of pups and resorption sites were determined. Of all mated males testis, epidymidis weight and sperm quality were investigated. Those in utero-exposed male mice revealed no effect of MF strength on weight of testes and epididymis or on sperm count, sperm morphology, or fertility. In exposed dams no reduced fertility (pregnancy rate, litter size) was seen. But a lowered placental weight in offspring of in utero exposed females correlated with a low embryonic weight in mice exposed at the strongest magnetic field (7 T isocenter). Summarizing, repetitive in utero exposure to SMF fields in mice did not impair fertility later in life but may have some effect on placental development and foetal growth. When comparing the experimental results to the situation in humans it should be considered that daily exposure during the entire pregnancy would be a non-realistic exposure of patients in a clinical setting.

1.2.3 Conclusions on SMF animal studies

The zebrafish study (Ward et al., 2014) supports observations (nystagmus, nausea) in humans being MRI-scanned in strong fields. The mouse study (Zaun et al., 2014) indicates that even strong static magnetic fields are mostly harmless on reproduction and development.

1.3 Human studies

Since the previous Council report (SSM, 2014) three human experimental studies of effects of a static magnetic field were published.

In two phases Theysohn et al. (2014) investigated vestibular effects of a 7 T MRI examination on body sway (Romberg’s test with eyes open and eyes closed) and Unterberger’s stepping test. In phase one 26 volunteers were exposed to a 7 T head MRI examination (lasting 30 min) and 13 of them took part in an additional exposure scenario with deactivated RF transmission (exposure to 7 T SMF and the fields of the gradient coil). Subjects were blind to the RF-exposure condition, for the other conditions blinding was not possible. 16 subjects of this sample were studied in a control situation with no fields at all while resting on a gurney in a dark and quiet room for 30 min. The investigated parameter for subjects in this phase was Romberg’s test on body sway before as well as 2 min and 15 min after exposure. The results indicate that the sway path length of the lumbar spine as indicator of postural (in)stability was significantly prolonged in the 2 min after exposure assessment in the 7 T and the 7 T no RF condition, but not in the sham condition. This was only observed in the eyes-closed condition. This difference in (in)stability was not present any more 15 min after the end of exposure.

In phase two twenty additional volunteers without previous MRI experience were recruited. They were exposed to the 7 T magnetic field only (no RF and gradient coil) and were tested after movement into the magnet with immediate removal (7 T in & out). An analogous design was used for a 1.5 T (no RF) exposure situation with randomly assigned exposure conditions. Additionally to Romberg's test in this phase Unterberger's stepping test was performed. Sway paths for all long-lasting 7 T scenarios (normal, no RF, only SMF) were significantly prolonged at the 2 min post assessment with eyes closed, they were normalized again in the 15 min post assessment. The brief exposure to 7 T (in & out SMF) as well as 30 min exposures to 1.5 T or 0 T did not show significant changes. Unterberger's test showed significant effects only in the three 7 T exposure conditions (no RF, only SMF, in & out SMF) with incomplete normalization after 15 min. No effects were observed in the 1.5 T condition. Sub group analyses by gender and age with small sample sizes revealed that the transient effects were seen to be significant in the young subjects and in men. These observations need to be confirmed by studies with appropriate sample sizes. In summary the results show that exposure to the 7 T static magnetic field causes only a temporary dysfunction of the vestibular system, not seen in the 1.5 and 0 T condition.

Van Nierop et al. (2014a) compared results of analyses of associations between two different measures of exposure to static and time-varying magnetic fields and neurocognitive test performance: a) using distance to the magnetic source and b) quantitative measurements with personal exposure dosimeters. They used the results of an earlier study with a test battery consisting of 12 neurocognitive tasks (van Nierop et al., 2012) to identify those tests, which in the original study (with distance as exposure parameter) showed significant effects: line bisection task (visual-spatial orientation), as well as simple, complex and inhibition reaction tasks. The 31 healthy volunteers (10 males and 21 females, age: 23.8 ± 6.4 years) were tested on three occasions with one week intervals between the tests. The subjects wore a dosimeter (Magnetic Field Dosimeter, University of Queensland, Australia) that was attached inside a plastic helmet. When exposure condition (high and low) was estimated based on time-weighted average personal exposure to static magnetic fields and time varying magnetic fields, the outcome of the experiments was not affected, indicating that in a controlled experimental setting distance to the bore is a good proxy for personal exposure when subjects are placed at fixed positions with standardized head movements in the magnetic stray fields of a 7 T MRI. Although this study is not directly analysing neurocognitive effects, it contributes to confirm earlier studies on exposure effects.

Another study by this Dutch group (van Nierop et al., 2014b) investigated whether a SMF alone and the combination of SMF and low-frequency movement-induced time-varying magnetic fields (TVMF) of a 7 T MRI scanner in stand-by-modus differentially affects neurocognitive outcomes. 36 healthy volunteers (6 males and 30 females, age range: 18 – 30 years) participated in the study. A training session on five neurocognitive tests was followed by four experimental sessions (lasting 15 min each) with a 30 min break between sessions on two consecutive days (time of day was kept constant). Each day consisted of two sessions: a real and a sham exposure (either sham alone or sham plus head movements), which were randomly assigned. The real exposure consisted of either a 1.0 T SMF or a 1.0 T SMF and a

2.4 T/s TVMF, the latter induced by standardized head movements. Exposure to SMF alone did not result in any effects on test results, while exposure to SMF in combination with TVMF led to a significantly decreased verbal memory performance and changed visual acuity.

1.3.1 Conclusions on SMF human studies

In summary these three studies, which are all related to exposure from a 7 T MRI with various exposures and exposure combinations, show that in experimental studies on neurocognitive effects distance from the bore is a good proxy for personal exposure. Furthermore an effect of exposure to an SMF alone was only observed in Unterberger's stepping test while effects are more frequently observed for a combined exposure with time-varying magnetic fields. Effects of the vestibular system which occur after longer exposure are only observed in the eyes-closed condition and are transient with regard to the results of Romberg's test. Unterberger's test results were partially normalized 15 min after the experiment.

As already stated in the previous report (SSM 2014:16), studies with MRI exposure are usually not restricted to pure static magnetic fields. While exposure of workers in an MRI environment usually also includes a time-varying component induced by movements in the field, exposure of subjects in a scanner always additionally includes switched gradient magnetic fields in the kHz frequency range and RF EMF components.

1.4 Epidemiological studies

The incidence of acute transient symptoms associated with occupational exposure to static magnetic stray fields from MRI scanners has been addressed in a cross-sectional study of 331 employees of 14 clinical and research MRI facilities in The Netherlands (Schaap et al., 2014). Participants reported their work activities during one or more work shifts inside and/or outside the MRI facility. In addition, they completed a symptom diary with a list of potentially MRI-related symptoms complemented with unrelated symptoms (negative controls). Based on their work activity, participants were assigned to a static magnetic field exposed group or to an unexposed group. Within the exposed group, five scanner categories were separately considered: 1.5 T closed bore, 3 T closed bore, 7 T closed bore, <1.5 T various types, and >4.7 T small bore. Data from 633 shifts were analysed using finite mixture models adjusted for gender, age, workload, use of solvents and alcohol consumption. Symptoms *a priori* considered to be related to static magnetic fields were associated with working at closed bore scanners in an exposure-response manner: The OR for any target symptom was 1.88 (95 % CI: 1.07–3.31) for 1.5 T closed bore, 2.14 (1.13–4.03) for 3 T closed bore, and 4.17 (1.30–13.35) for 7 T closed bore. Even stronger associations were found for the *a priori* defined core symptoms (sensation of dizziness or vertigo, nausea, tinnitus/sensation of head ringing, seeing light spots or light flashes, metallic taste). Absence of associations were observed for negative control symptoms such as seeing black spots or having a temporary loss of vision, itchy skin, watery or red eyes, earache or palpitation. No symptom increase was observed when working with <1.5 T scanners (various types) and >4.7 T small bore scanners. The authors concluded that this study indicates an exposure-response association between exposure to strong static magnetic fields (and associated motion-induced time-varying magnetic fields) and reporting of transient symptoms on the same day of exposure.

Movement of the workers through the static magnetic stray field around an MRI scanner can cause low-frequency time-varying magnetic fields. Thus, this observational study cannot resolve whether the observed associations are due to the static or the time-varying magnetic fields. However, the human experimental studies on neurocognitive effects discussed above suggest that static fields alone did not result in effect whereas combined exposure with time-varying magnetic fields did. The specificity of the symptom pattern and the exposure-response relationship strongly supports the hypothesis that the symptoms are related to MRI work. Job titles were not equally distributed over the exposure conditions but seem to produce no bias according to sensitivity analyses. Potential long term health consequences of these transient symptoms are not known and were not assessed in this study. Of note, 10% out of 103 exposed participants with symptoms indicated that their work practice had been affected by their symptoms, which indicates that these findings are relevant for the workers.

2. Extremely low frequency (ELF) fields

2.1 Cell studies

The studies published on the effect of ELF fields, in the period covering the current report, deal with several cell functions and are reported in the following. Moreover, other papers have been recognized but were not considered due to the lack of sham-exposed samples. Several studies investigated therapeutic applications of ELF fields (Bai et al., 2013, Chen et al., 2013, Corallo et al., 2014, Hilz et al., 2014, Kang et al., 2013, Sadoghi et al., 2013). These will not be discussed in the current report, but they are mentioned to indicate that also possible positive effects of ELF field exposure are being observed.

2.1.1 Differentiation

Embryonic neural stem cells have the potential to differentiate to mature neurons upon proper stimulation. It has been suggested that magnetic field (MF) exposure can influence neuronal differentiation and the study by Ma et al. (2014) deals with this topic. They used embryonic neural stem cells from the telencephalon of embryonic day 13.5 BALB/c mice. All the experiments were performed at a frequency of 50 Hz sinusoidal magnetic field at intensities of 0.5, 1 and 2 mT for 3 days; or at 2 mT for 1 day, 2 days and 3 days, with an intermittent cycle of 5 min on/10 min off under double blind conditions. Sham and exposed groups were randomly selected by the computer. Cells were cultured under conditions that either promoted proliferation or differentiation, and a number of biological endpoints were studied (viability, DNA synthesis, neurosphere diameter, cell cycle progression, specific proteins and mRNA expression). No effects were detected for all the exposure conditions investigated, except for some of the gene expression profiles during intermittent exposure. In particular, some genes involved in early stages of neural differentiation were up-regulated, although this had no effect on the phenotype of the cells. These results are interesting since they suggest that continuous and intermittent exposure can induce different cell responses.

Differentiation from stem cells to nerve cells was investigated by Seong et al. (2014). Neuronal differentiation was induced in human bone marrow-mesenchymal and mouse embryonic stem cells by means of a 50 Hz 1 mT MF exposure (8 and 6 days, respectively). Neuronal molecular markers as well as morphology and electrophysiological properties supported that MF exposure led to neuronal differentiation. A transcriptome analysis was carried out and data from exposed cells were compared to sham-exposed samples. The results obtained showed that 57 genes expressed significant changes (>1.5 fold) following the exposure. Most of these genes were transcription factors, and in many cases associated to expression of the early growth response 1 (Egr1) gene. Moreover, the authors also reported that Egr1 protein, a strong early neurogenic transcription factor, is necessary but not sufficient for ELF-induced neuronal differentiation.

2.1.2 DNA damage, cell proliferation and cell cycle

Mihai et al. (2014) exposed fibroblast-like monkey kidney cells to evaluate the effects on DNA strand breaks (comet assay) and cell cycle progression. Exposures/sham exposures were carried out for 45 min, either continuous or intermittent (1 s on/3 s off), to 100 Hz magnetic field, 5.6 mT flux density, and analysis were performed 48 h after exposures. In three independent experiments, magnetic field exposure, either continuous and intermittent, resulted able to cause DNA strand breaks and a cell cycle arrest in the S stage of the cell cycle ($p<0.05$).

Human SH-SY5Y neuroblastoma cells were employed by Luukkonen et al. (2014) to investigate whether the MF-induced changes in DNA damage response can lead to genomic instability in the progeny of the exposed cells. Cell cultures were exposed/sham-exposed for 24 h to 50 Hz, 100 μT MF, followed by a 3-h treatment with menadione (an inducer of oxidative stress and DNA damage) at final concentration of 0, 1, and 20 μM. Cell cultures, treated with MF alone or co-exposed to menadione, were assayed 11 and 18 days after the end of the treatment for micronucleus (MN) frequency and 8 and 15 days after the end of the treatment for mitochondrial and cytosolic superoxide production, reactive oxygen species (ROS), production and reduced glutathione (GSH) level. Moreover, these endpoints were also measured immediately after the treatment. Methyl methanesulfonate for 24 h, diethyl maleate for 1 h and tertbutylhydroperoxide for 3 h were employed as positive controls for MN frequency, ROS production and lipid peroxidation, respectively. The results from 3 to 4 independent experiments did not show effects of MF alone. Treatments with menadione showed a slight increase (<2-fold in comparison with sham control) in MN, measured by flow cytometry, 11 and 18 days after the end of the treatment. The effect was statistically significant in a 3-way ANOVA where MF and menadione were fixed factors and replication a random factor. The authors interpreted this effect as induced genomic instability. Moreover, immediately after the co-exposure, ROS (DCFH-DA assay) and superoxide in mitochondria were increased, and a decrease in glutathione levels was observed. Superoxide in cytosol and mitochondrial activity were affected by menadione but not by MF. 8 days after the end of the treatment, MF increased mitochondrial activity without menadione but did not affect the levels of ROS, glutathione, lipid peroxidation, or superoxide. 15 days after the exposure, the only parameters reported to be significantly affected by co-exposures were lipid peroxidation (apparent also without menadione) and ROS production (only at 20 μM menadione). According to the authors, the results suggest that changes in oxidant/antioxidant balance induced by an initial effect of MF can lead to genomic instability. Even if the effect on MN frequency seemed to be rather small, a prolonged increase in the level of chromosome damage may be expected to have significance with respect to carcinogenesis.

Delle Monache et al. (2013) exposed human umbilical vein endothelial cells (HUVECs) and mouse endothelial transformed cell line (MS-1) for different times up to 24 h to a 50 Hz sinusoidal magnetic field at 1 and 2 mT field amplitude. Cell proliferation and cell cycle were assayed after a 24 h further incubation in both cell lines, while cell migration and tubule formation ability were tested in HUVECs. When exposed HUVECs were compared to their sham controls, 6, 9 and 10 h exposures at 1 mT resulted in increased cell proliferation, while a decrease was detected after 24 h exposure. MF exposures at 2 mT resulted in a decreased cell proliferation at all time-points (1, 3, 6, 9, 12 and 24 h), as assessed in three independent experiments. MS 1 cells also showed a decreased proliferation after MF exposure of 72 h at 2 mT field intensity. As stated by the authors, the results indicated that exposure of 1, 6, 12 and

24 h induced an arrest of HUVECs in G2/M stage of cell cycle that partially recovered at 24 h exposure. MS-1 cells exposed for 72 h also presented a slight increase of cells in G2/M stage. In addition, a reduced HUVECs cell migration and capillary tube formation after 1, 6 and 12 h exposure at 2 mT was also detected.

2.1.3 Oxidative stress

de Groot et al. (2014) investigated the effects of acute (30 min) and sub-chronic (48 h) exposure to 50 Hz on naıve and chemically stressed rat pheochromocytoma cells (PC12, a model of neuron-like cells) to evaluate Ca^{2+}-homeostasis, ROS production and membrane integrity, by means of Fura-2 single cell fluorescence microscopy, H2-DCFDA and CFDA assays, respectively. Stressed cells were obtained treating naive PC12 cells, prior to exposure, with Dexamethasone (DEX, a corticosteroid with immunosuppressant effects) for 3–5 days or with non-cytotoxic concentrations of L-DOPA (a direct precursor of dopamine) or with $FeSO_4$ for 24 h. Such treatments induced higher levels of iron and/or ROS and cells displayed increased vulnerability to environmental insults. The results from 3 to 9 independent experiments indicated that both acute and sub-chronic exposure of naive and chemically stressed PC12 cells up to 1000 mT failed to exert consistent effects on the endpoint investigated. The authors concluded that exposure to 50 Hz ELF-EMF up to 1000 mT, i.e. 10,000 times above background exposure, does not induce neurotoxic effects in vitro, neither in naive nor in chemically stressed PC12 cells.

2.1.4 Other endpoints

The role of voltage-gated T-type Ca^{2+}-channels in responses to ELF MF was investigated by Cui et al. (2014). The authors transfected T-type channels (Cav3.1, Cav3.2, Cav3.3) and measured the electrophysiological responses to sine wave 50 Hz MF (0.2 mT; 0.5-3 h exposure duration) in human embryonic kidney (HEK293) cells and in cortical neurons derived from the cerebral cortex of 15-day-old embryonic ICR mice. The exposure caused inhibition of preferentially the Cav3.2 channel type, which also was seen in experiments where native channels (in cortical neurons) were investigated. By using various types of receptor antagonists, the authors could show the probable involvement of increased arachidonic acid and subsequent increased leukotriene E4 levels in the MF response. In this investigation it is not clear if proper sham conditions have been employed.

2.1.5 Conclusions on ELF cell studies

As for the previous Council report, the conclusions on ELF in vitro studies can be summarized as follows: a) there is a large variety of biological and electromagnetic parameters investigated; b) few investigations aim to address the correlation between power frequency exposure and leukaemia. Moreover, as for static fields, several studies lack sham-controls and are therefore not interpretable.

2.2 Animal studies

Also in 2014, studies addressing the epidemiologically observed link between ELF exposure and childhood leukaemia are missing. The following studies mostly describe effects of ELF on brain and behaviour, reproduction and oxidative stress.

2.2.1 Brain and behavior

The influence of 12- and 18-kV/m electric fields (EF) on specific brain activities and on oxidative brain damage and apoptosis in male Wistar rats was investigated by Kantar Gok et al. (2014). The EF was generated in an exposure system using parallel plate capacitors. Groups of 15 three months old male rats were daily exposed to 0 (sham), 12 or 18 kV/m, 50 Hz EF for 1 h/d between 9 am and 5 pm over a period of 2 or 4 weeks, respectively. The maximum MF density was reported as 0.1 μT. Starting 24 hours after the last exposure, event related potentials (ERP) were tested in urethane-anesthetized rats that received stainless steel electrodes exactly positioned in the (auditory) brain region of interest. This enabled the researchers to investigate the mismatch negativity (MMN) component of ERPs which "is regarded as a bioelectric correlate of a result of the mismatch between a sensory memory trace and an incoming stimulus", in that case an (auditory) click stimulus. At the end of the ERP recordings, the animals were sacrificed and brain tissues frozen. As an indicator for lipid peroxidation 4-hydroxy-2-nonenal (4-HNE), and for ROS-mediated oxidation of sugar and membrane lipids CO-proteins were determined. 4- HNE and tissue carbonyl content (CO proteins) were increased in all exposed rats. Apoptotic brain cells (in hippocampus, auditory and frontal cortex layers) analysed by the TUNEL assay were not seen. According to the authors, "MMN systematically decreases with increasing ELF-EFs exposure duration as well as with exposure intensity". Such a clear conclusion is not supported by the study design (2 EFs, 2 exposure durations only) and data presented.

Alsaeed et al. (2014) studied in male BALB/c mice whether a perinatal ELF-MF exposure affects the social behaviour aiming to address "autism spectrum disorders (ASD)" in adult life. Sham-exposed controls (n=9) were compared to exposed mice (n=8, 50 Hz, 1 mT). The pups (from 4 mothers per group) were exposed during the last week of gestation till one week after birth. At an adult age of 8-11 weeks, all behavioural tests were conducted and scored blindly between 9 am and 6 pm. The ELF-MF exposed mice revealed a "lack of sociability and preference for social novelty" compared to controls. No significant differences were observed during testing for "anxiety-like behaviours, locomotion, olfaction, and motor coordination." Size and study design is too little (one exposure group, one species, one sex only) for a definite conclusion regarding ASD.

Obsessive compulsive disorder (OCD)-like activity was addressed by studying the marble-burying behaviour (MBB) and locomotor activity in 50 Hz 1 mT ELF-MF exposed male Swiss albino mice. Salunke et al. (2014) exposed groups of 6-8 male mice for 8 hours per day up to 120 days to a control handling and housing or ELF-MF. Further controls and 1 mT groups were concurrently treated once daily intraperitonally up to 120 days with the NO precursor L-Arginine (L-ARG) or the NOS inhibitors N^G-nitro-L-arginine methyl ester (L-NAME) or 7-nitroindazole (7-NI). Finally, a pure saline control and 3 dose groups each for testing a dose dependency of the 3 NO modulators were used. The 1 mT 50 Hz ELF-MF resulted in a "gradual increase in MBB" tested after 7, 30, 60, 90 and 120 days of exposure. No effect on locomotor activity was seen. After 120 days the levels of NO in brain tissue (cortex, hippocampus, hypothalamus; but not in striatum) were increased, dopamine and serotonin were not affected. L-ARG increased the number of marbles buried by the mice, whereas L-NAME and 7-NI dose dependently decreased that endpoint; the locomotor activity was not affected. After 120 days "subeffective doses" of the NO precursor L-Arg or the NOS inhibitors L-NAME and 7-NI concurrently administered to the ELF-MF exposure potentiated or attenuated "the OCD-like effect". The authors conclude: "the prolonged exposure of ELF-MF produced OCD-like behaviour in mice, resulting from the increase in nitric oxide levels in the cortex, hippocampus, and hypothalamus." That conclusion cannot be justified by the data presented. In addition, the study design is poorly described; observations of interim time points in the concurrently exposed groups are missing.

Frilot et al. (2014) tested the hypothesis that anaesthetic agents which antagonize glutamate neurotransmission should degrade EMF-evoked potentials (EEPs) to a greater extent than other pharmacologically active compounds. The group used ketamine which blocks N-methyl-d-aspartate (NMDA) receptors (NMDARs), and xylazine which is an α_2-adrenoreceptor agonist. 20 female 300 g Sprague Dawley rats were used in a very complex study design. A 60 Hz 25 µT ELF-MF was applied for 2 s with an inter-stimulus off period of 5 s to detect both onset and offset EEPs. Therefore, the EEG was divided into 7-s intervals (trials). Results were determined with data from at least 50 trials. Auditory evoked potentials (AEPs) served as positive controls. During wake and under xylazine anesthesia, EEPs and AEPs were detected. Despite the complicated experimental set-up the authors concluded that "the afferent signals triggered by the transduction of weak EMFs and detected as EEPs using recurrence analysis of the EEG were likely mediated by NMDA receptors in the trigeminal nucleus".

Xiong et al. (2013) investigated the effects of a 2- or 4-week-lasting 50 Hz 0.5 mT ELF-MF exposure on the dendritic spine density and shape in the superficial layers of the medial entorhinal cortex (MEC) in male Sprague Dawley rats. Five rats per group were used for the 2- and 4-week controls or 2- and 4-week ELF-MF exposures (4h/d). Golgi staining revealed the dendritic spines of the principal neurons. Spine density was expressed as the average number of spines per micron of dendrite length. Two and 4-week ELF-MF exposure resulted in a decrease of the spine density in the dendrites of stellate neurons and the basal dendrites of pyramidal neurons. Spines in the apical dendrites of pyramidal neurons were less sensitive to ELF-MF than those in the basal dendrites. The authors explain: "the changes in spine number and shape …involved in synaptic plasticity and the MEC …as part of neural network that is closely related to learning and memory".

In a study of the same department of the 3rd Military Medical University, Chonqing, China, Li et al. (2014a) compared in the brain of adult male Sprague Dawley rats, after 14 and 28 days of ELF-MF exposure the protein expression of subunits of the fast excitatory neurotransmitter receptors for NMDA (N-methyl-D-aspartate) and AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) with the rat spatial learning. [NMDA and AMPA are specific agonists for the NMDA and AMPA receptors (NMDAR, AMPAR), where these agonists mimic the effects of the neurotransmitter glutamate.] Four groups of 15 rats were exposed to 50 Hz 0.5 mT ELF-MF or sham-exposed for 4 h/d over a period of 14 or 28 days. After the exposure, hippocampus, entorhinal cortex and prefrontal cortex of 5-6 animals per group were subjected to protein detection by western blotting. 9-10 animals per group were tested in a water maze. The 2- and 4 week ELF-MF exposure differently altered the expression of the

AMPAR and NDMAR subunits in the 3 brain regions. No clear picture can be drawn looking at brain region and/or duration of exposure. Finally, both exposure durations did not affect the rat spatial reference learning and memory.

Li et al. (2014c) evaluated the effects of previous training and ELF-MF exposure on learning and memory using the Morris water maze (MWM). Forty 10-week-old male Sprague-Dawley rats were divided into groups of 10 animals: one group without training and without ELF-MF exposure served as sham control, the second group of rats without training was ELF-MF exposed, the third group was MWM-trained and not exposed, the fourth was trained and ELF-MF exposed. The ELF-MF groups continuously received a 100 µT (rms), 50 Hz alternating MF for 90 days. Training and test phases in the MWM were done with the same procedures for spatial acquisition and probe trial. The rats (of the training groups) were trained once daily for five days to locate the platform in the MWM. A probe test was done on day 6. Trained rats (with and without ELF-MF exposure) performed better on spatial acquisition when re-tested. No difference between training phase and the test phase was seen for the probe trial. The ELF-MF groups showed no significant differences when compared with the respective sham controls. Therefore, the study only confirms that previous training improves the spatial learning and memory capabilities tested in the MWM for at least 90 days. This improvement was not observed during the probe trial. Concluding, the described 100 µT MF exposure has no positive or negative effect on spatial memory.

In a small study with two groups (n=10) of 12 weeks old male Sprague Dawley rats, Zhang et al. (2014) investigated potential ELF-MF effects on memory impairment. Animals were exposed to 50 Hz 100 µT ELF-MF- or sham-exposed. After 12 weeks of continuous exposure, the Morris water maze was used for testing cognitive and memory ability. In addition, ELISA assays were applied for the measurement of amyloid-beta (Aβ) content in cortex, hippocampus and plasma. Finally, the hippocampal CA1 area and the cortical area above the hippocampus were microscopically observed in HE stains. Body weight was similar between ELF-MF- and sham-exposed rats. ELF-MF did not induce any cognitive and memory impairment. Aβ showed no significant change between the two groups. Histologically, there was no difference in the "density of normal cerebral corticular/hippocampal neurons". Summarizing, the described 50 Hz 0.5 mT ELF-MF exposure for 12 weeks in rats did not show any effect on cognition and memory, and did not alter the expression of Aβ and the neuron morphology.

In a paper that is difficult to understand, Podda et al. (2014), specifically assessed the influence of ELF-MFs on hippocampal new-born cell survival. This is based on their previous work which demonstrated "that in vivo exposure to ELF-MF promotes the proliferation and neuronal differentiation of hippocampal neural stem cells (NSCs)". Twenty 4-5 week old male C57BL/6 mice were injected intraperitonally with BrdU, and 9 days later [i.e. when the "most dramatic decrease in number of newly generated cells occurs"] exposed to 50 Hz 1 mT ELF-MF (n=10) or sham-exposed (n=10) for 3.5 h/d for 6 days. These 20 mice were used for immunohistochemical detection of neuronal differentiation and survival. Further 34 mice (17 sham- and 17 exposed for 3.5 h/d for 6d) underwent hippocampus memory tests (n=10+10), namely the novel object recognition (NOR) and Morris water maze (MWM) tests. For

Western immunoblot assay 4+4 animals, and finally for detecting apoptosis, 3 sham-exposed and 3 exposed mice were used. Immunohistochemical evaluation of BrdU pre-treated mice revealed a promoting effect of ELF-MF exposure on the survival of new-born neurons. In addition, NOR and MWM demonstrated an improvement in spatial learning and memory of ELF-MF-exposed mice. Compared with sham-exposed mice or NSCs, Western immunoblot assays revealed reduced expression of the pro-apoptotic protein Bax, and an increased one of the anti-apoptotic protein Bcl-2, in the hippocampi of ELF-MF-exposed mice as well as in ELF-MF-exposed NSC cultures. Overall, the implication of the study results is not obvious.

2.2.2 Reproduction and Development

Hafizi et al. (2014) investigated *in vitro* fertilization (IVF) success rate in 10 (5 control, 5 experimental) NMRI mice after a 5-hour *in vitro* exposure (control or 4 kHz pulsed 1.3 mT ELF-MF) of a culture medium containing metaphase II ovi and sperm. Fertilizing criterion was the identification of two-pronuclear zygotes (2PN). The total number of collected ovi in the control and ELF-MF groups was 191 and 173, respectively, from which 58 and 52 ovi were collected from metaphase II, respectively. IVF success rate was 77 % in the ELF-MF compared to 68 % for control group. Summarizing, between controls and exposed mice there was no statistically significant difference observed for the IVF success rate.

Li et al. (2013) studied effects of short-term (≤ 72 h) and long-term (312 h) ELF-MF exposure in male Drosophila melanogaster. Using a Helmholtz coil in an incubator, 50 Hz 3 mT ELF-MF was applied for up to 72 h (8, 16, 24, 48, 72 h) to adult male flies ("short-term exposure") and to all developmental stages (eggs, larvae, adults) of Drosophila for 312 h ("long-term exposure"). In addition, non-exposed flies were used as controls. Transcriptomics of 20 males per group showed 439 up-regulated and 874 down-regulated genes after 72 h short-term exposures whereas after 312 h long-term exposure 514 genes were up-regulated and 1 206 genes were down-regulated. For short-term exposure, the DEGs (differentially expressed genes) were identified to be involved in metabolic processes, cytoskeletal organization, mitotic spindle organization, cell death, protein modification and proteolysis. Long-term exposure changed the expression of genes involved in metabolic processes, response to stress, mitotic spindle organization, aging, cell death and cellular respiration. "In the intersection of short-term and long-term exposure, a series of DEGs were related to apoptosis, aging, immunological stress and reproduction." The experiments on male reproduction ability demonstrated a decrease after short-term ELF-MF exposure, but no effect after long-term exposures was detected. Finally, the authors discuss specific pathways and gene families to be responsible for the decrease in male reproduction (i.e., caspase pathway), or for inhibition of apoptosis and accelerated senescence. This study may influence basic research in developmental and reproduction science. The discussion is well-done but the link to a potential risk of ELF-EMF in mammals is not directly addressed.

2.2.3 (Cyto)Toxicity, Oxidative Stress

In a study that was difficult to understand, Raus Balind et al. (2014) looked at effects of ELF-MF (50 Hz, 0.5 mT) on oxidative stress in the brain of 3 months old male gerbils submitted to 10-min global cerebral ischemia by occluding both carotid arteries. Animals were continuously exposed to ELF-MF for 7 days. In groups of n=6-13 gerbils nitric oxide and superoxide anion production, superoxide dismutase activity and index of lipid peroxidation were examined in 3 regions of the animals' brain (forebrain cortex, striatum, hippocampus) on day 7 and 14 after reperfusion (delayed effect of ELF-MF). Ischemia increased oxidative stress in the brain on day 7 and 14. More than ischemia, ELF-MF increased oxidative stress, but only directly after the end of exposure. Ischemia plus ELF-MF increased oxidative stress also on day 7, but not as much as in ischemic or ELF-MF-exposed gerbils. On day 14, oxidative stress parameters were close to control levels. This small study addresses oxidative stress in a highly artificial animal model. On the basis of the demonstrated but transitory increased oxidative stress, the study is over-interpreted by the claimed indication for "a beneficial effect of ELF-MF (50 Hz, 0.5 mT) in the model of global cerebral ischemia".

Manikonda et al. (2014) (sham-)exposed three groups of 6 male 21 day-old Wistar rats to 50 Hz ELF-MF of 0, 50, and 100 µT for 90 days continuously (24 h/d). The hippocampal, cerebellar and cortical brain regions were analysed for ROS, metabolites indicating oxidative stress (TBARS [thiobarbituric acid reactive substances], GSH/GSSG [GSH=reduced & GSSG=oxidized glutathione]), and antioxidant enzymes (SOD [superoxide dismutase], GPx [glutathione peroxidase]). Body weight and histopathology of the brain did not reveal differences between the three groups. Oxidative stress and decreased GSH/GSSG ratios were dose-dependently affected in the three regions of the brain. Compared to sham-controls, accumulation of ROS, lipid peroxidation (TBARS) and SOD activity was dose-dependently elevated in different brain regions mostly in the descending order of cerebellum < hippocampus < cortex. The presented data show an ELF-MF caused oxidative stress in the brain which is more pronounced at 100 µT than at 50 µT. A more extensive study should confirm these results and test the potential impact on neuronal functions in the same animals.

2.2.4 Physiology

Taherianfard et al. (2013) investigated a potential modulation of $GABA_A$ receptors and ELF-MF on serum testosterone level of young adult male Sprague Dawley rats. The study consisted of 10 groups, n=5 per group. Animals of 5 groups (1, 3, 5, 7, and 9) were sham exposed while the rats of the other 5 groups 2, 4, 6, 8, and 10 were exposed to 50 Hz 0.5 mT ELF-MF for 30 days, 8 h/d. At the end of the study period, rats of groups 1 and 2 received saline intraperitonally, groups 3 and 4 were administered 1 mg/kg, groups 5 and 6, 3 mg/kg of bicuculline methiodide. Groups 7 and 8 were treated with 0.5 mg/kg of muscimol hydrobromide, groups 9 and 10 with 2 mg/kg muscimol hydrobromide. Serum testosterone level was assayed using RIA, in blood samples taken approximately 40 min after the intraperitonal injections. The $GABA_A$ receptor agonist muscimol hydrobromide at both doses significantly decreased serum testosterone in sham-exposed rats compared to saline-shams. Administration of the classical $GABA_A$ receptor antagonist bicuculline methiodide had no significant effect on the serum testosterone level of sham-exposed animals as compared to saline group 1. Serum testosterone levels between the 5 ELF-MF groups were statistically not different. In addition, serum testosterone of exposed versus sham-exposed rats in each treatment did not show significant differences. But there are inaccuracies in the corresponding figures. Therefore the author's conclusion: "No interactivity is present in modulatory effects of $GABA_A$ receptors and ELF-EMFs on serum testosterone of male rats" cannot be finally proven.

Tuncel et al. (2013) determined the influence of a 50 Hz, 5 mT ELF-MF on the expression level of P-selectin in rat colon tumours induced by MNU. Two month-old male Wistar rats were divided into group I (n=7, N-Methyl-N-Nitrosurea [MNU]), II (n=7, ELF-MF + MNU), III (n=9, ELF-MF) and IV (n=5, control). Once a week for 10 weeks 2 ml per animal of MNU/saline-solutions were administered intra-rectally (i.r.) to groups I and III, rats of groups II and IV received 2 ml/animal of a sterile isotonic solution [an exact dose of MNU was not given]. Following the MNU treatment, groups II and III were exposed to a sinusoidal ELF-MF (50 Hz, 5 mT) for 6 h/d for 8 months. P-selectin expression in rat colon tissues was determined by immunohistochemistry on paraffin sections. There was no statistically significant change in the expression level of P-selectin reported.

Tunik et al. (2013) described changes in kidney tissues of male Wistar rats after a 4-week exposure to extremely low frequency pulsed and sinusoidal EMFs. Groups of nine 4-month old male Wistar rats were allocated to 1) a control group, 2) sinusoidal electromagnetic field (SEMF), and 3) pulsed electromagnetic field (PEMF) group. The SEMF and PEMF groups (pulse time 25 µs, pulse frequency 50 Hz) were exposed to 1.5 mT for 6 h/d, 5 d/wk for 28 days in methacrylate boxes. Formalin-fixed, paraffin-embedded kidney tissue sections were stained with HE, Gomori and periodic acid-Schiff and evaluated histopathologically. Immunohistochemically, matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9), E-cadherin and collagen type IV expression levels were examined. Compared to normal histopathology of controls, thickening of glomerular basement membranes was described in both EMF groups 2 and 3. In addition, tubular degeneration and hemorrhages in kidneys the PEMF and hypertrophy of glomeruli, inflammatory cell infiltration and tubular degeneration was reported. Immunohistochemically, with both EMF exposures expression levels of E-cadherin were decreased and the expression level of MMP-9 increased, whereas MMP-2 and collagen type IV expression levels were not altered. A conclusion cannot be drawn since the histopathology and immunohistochemistry is qualitatively or semi-quantitatively presented only. Furthermore, a weight range of 150 – 230 g at study start and providing no data on water consumption describing changes in kidney gives not much confidence in this small study.

2.2.5 Immunology, Therapy

Nie et al. (2013) investigated immunological parameters in tumour-bearing BALB/c mice. At an age of 6-8 weeks 76 female BALB/c mice were subcutaneously inoculated with $1x10^6$ H22 hepatocarcinoma cell line. Four groups were used. 10 (non-tumour) mice each and 38 tumour-mice each were sham- or (7.5 Hz, 0.4 T) ELF-MF-exposed for 2 h/d and 30 days. 10 mice per group were sacrificed on day 33. Cardiac blood and serum was taken for flow cytometry and cytokine assays respectively, parts of each spleen also for flow cytometry or to isolate RNA for qPCR. The survival time and rate was observed in the remaining 28 plus 28 tumour-mice per sham- and ELF-MF-exposed group. 0.4 T MF treatment prolonged survival time and inhibited tumour growth. 0.4 T MF suppressed the cytokines IL-6, G-CSF and keratinocyte-derived chemokine (KC), which were shown to be tumour-induced. Other cytokines tested (IL-1, IL-2, IL-3, IL-4, Rantes, TNF-α) were not significantly different between the sham- and MF-exposed tumour group. Finally, EMF MF exposure activated macrophages and dendritic cells, CD4+ and CD8+ T lymphocytes, and the ratio of Th17/Treg were increased, whereas the inhibitory function of Treg cells was reduced. With these data the conclusion is plausible that "the inhibitory effect of MF on tumour growth was related to the improvement of immune function in the tumour-bearing mice."

2.2.6 Therapeutic Application

The study of Mahna et al. (2014) on the effect of ELF-MF in BALB/c mice on tumour growth after electrochemotherapy as well as the study of Mert et al. (2014) on pain-relieving effects of pulsed magnetic fields in a rat model are not discussed in this report since they mostly belong to the field of therapeutic application.

2.2.7 Conclusions on ELF animal studies

Most studies used exposure levels of 0.5 -1 mT. As stated in the previous report, these levels may be relevant for risk assessment, although exposures under real-life conditions are normally in the µT range.

Studies describing ELF-MF effects on brain function and physiology dominate this year. Single studies show in the cortex, hippocampus and hypothalamus an increase of NO, specific neurotransmitters and a subtle decrease of (new-born) nerve cell loss and spine density after ELF-MF exposure. Some further experiments are describing a negative effect on learning and memory ability, others do not.

With the exception of single studies, the quality of the experiments and their description did not substantially improve compared to the previous years. When investigating subtle changes in specific areas of an animal's brain or its learning and memory behaviour, all experimental details are of importance. E.g., presenting the daytime of animals' sacrifice / sample collection or of behavioural testing is a must. The same holds true for a detailed declaration of the animals' health status (including a list of specific pathogens). Furthermore, referring to direct DNA-damage due to "low doses" of ELF-MF or presenting "dose-dependencies" using two groups only is somehow doubtful.

Overall and similar to the previous SSM report, the results of the described studies are not very consistent.

2.3 Human studies

The previous Council report (SSM, 2014) concluded that ELF did not seem to have any effects on general physiology and that there was some evidence for effects on the EEG. Stimulation with various low frequencies did not lead to any resonance effects in the EEG activity. The report stressed that it was difficult to distinguish between statistically significant and physiologically meaningful effects.

Since the last report three studies investigating ELF effects in human experimental studies have been published. Two (Maestu et al., 2013, Rikk et al., 2013) investigated therapeutic applications, which is beyond the scope of this review.

One study (Shafiei et al., 2014), which according to the authors aims at developing specific protocols for the treatment of symptoms in psychology focused on brain electrophysiology investigated possible effects of ELF magnetic fields on the EEG power spectrum in 20 males

(23.5 ± 2.5 years). The subjects had simultaneous localized MF exposures at sites corresponding to EEG positions T3, T4, F3, F4, and Cz. In four sessions separated by a one-day interval the localized flux densities were 0, 100, 240 and 360 µT, respectively. EEG was considered at temporal, frontal and central sites. Baseline assessments were made by recording EEG for 2 min with eyes open and eyes closed each, before the electrodes were attached. The procedure comprised two assessments with 2 min recordings (2 min eyes open, 20 sec rest, 2 min eyes closed) without magnetic field followed by two assessments with field (2 min eyes open, 20 sec rest, 2 min eyes closed). Within the 2 min exposure blocks an intermittent exposure (2 s ON and 3 s OFF) was applied. After a 10 min rest the procedure was repeated four times. Each of the five iterations was done with one of the five MF frequencies: 45, 17, 10, 5 or 3 Hz. The session ended with a "post baseline" assessment, again 2 min recordings with eyes open and eyes closed separated by a 20 s break. EEG analysis was based on 2 s artefact-free segments selected from the 3 s OFF periods. Effects in this very complex exposure design were considered on the basis of five EEG frequency bands. The authors observed various statistically significant results with a trend that some exposure to MFs decreased alpha band in the eyes-closed state, however, resonance effects were neither observed in the eyes-open nor in the eyes-closed condition. Given the large number of statistical tests, the results should be interpreted with caution. Since there is no information about blinding of subjects and/or researchers in this paper nor about randomization of exposures this study is considered not to contribute to our knowledge on ELF effects on the EEG.

2.3.1 Conclusions on ELF human studies

There was no informative study on ELF effects in humans during the reporting period.

2.4 Epidemiological studies

In the previous Council report (SSM, 2014) it was concluded that from an epidemiological point of view, the most consistent association for ELF-MF exposure has been observed for childhood leukaemia, but a causal relationship has not been established in experimental research with cells or animals. Further, some studies indicated a possible association between neurodegenerative diseases (in particular Alzheimer's disease and amyotrophic lateral sclerosis, ALS) and ELF-MF exposure. However, data are not entirely consistent and confounding by electrical shocks may be an explanation for the observed increased risk of amyotrophic lateral sclerosis for workers in the electric occupations.

2.4.1 Pregnancy outcomes

Su et al. (2014) published a cross-sectional study conducted among pregnant women seeking abortion, their magnetic field exposure and embryonic development. Women were eligible if aged between 18 and 35, if the abortion was due to an unwanted pregnancy and not a medical reason, if the women had no known chronic disease or diseases of the reproductive system or if their lifestyle, working or living conditions had changed significantly over the 6 months prior to the abortion. 149 women (34 % of eligible) were included. Emdex Lite ELF-MF meters were used to collect a 24 h personal measurement of a typical workday within 4 weeks of the abortion. Three outcomes were assessed: Gestational sac length, embryonic bud length and apoptosis greyscale. Linear regression analysis was performed to assess the relationship between magnetic field exposure (arithmetic mean, median and 75 % percentile, log transformed) and the outcomes, as well as with logistic regression analysis, dichotomising the outcomes comparing the worst 25 % (shortest sac or bud length/higher greyscale) against the rest. Analyses were adjusted for women's age, gestational age and educational level. Other potential confounders were evaluated but found to not materially change the association between the outcomes and the magnetic field levels. The median of the average exposures of the women was around 0.09 µT with an interquartile range of 0.6-1.6. Associations were detected between higher magnetic field exposure and shorter embryonic bud length, but not with gestational sac length or apoptosis greyscale. For the dichotomised outcome analysis, this translated into an odds ratio of 3.95 (95 % CI 1.1-14.20) for women whose 75th percentile of daily ELF-MF measurements exceeded 0.08 µT compared to those whose 75th percentile of daily ELF-MF exposure was below that value (dichotomised at the median of these values). For the linear regression analysis, an increase in 0.1 µT (1 mG) translated into a coefficient of about -3, although it is unclear what this unit refers to (mm?).

The strength of the study was to perform measurements, and given that these measurements were performed in women who had undergone an abortion, it was less likely that women had adjusted their lifestyles, a concern in many other studies that addressed magnetic field exposures in pregnant women. The participation rate is on the low side, although it would be unclear in how far the results could have resulted from participation bias. Naturally, miscarriage could not be evaluated and it is unclear in how far growth of the embryo translates into an adverse pregnancy outcome.

A case-control study was reported by Shamsi Mahmoudabadi et al. (2013). 58 women who had a spontaneous abortion before 14 weeks gestation were enrolled, as were 58 women who presented at the same hospital at 14 weeks gestation. Non-smoking women in the age range 18-35 years, without chronic diseases, free of genetic disorders (including partner and first-degree relatives), having a 'spontaneous pregnancy' (so no assisted reproductive technology), and not vaginal bleeding in the first trimester were included. Women filled in a questionnaire providing information on potential confounders, and measurements of ELF-MF were performed with an ELF-828 meter in the homes of the women. Workplace measurements were not performed; 81 % of cases and 83 % of controls were housewives. Magnetic field levels among cases were higher than among controls with 0.4 µT (sd 3.1) versus 0.14 µT (sd 0.15). Logistic regression analysis adjusted for maternal and paternal age, history of abortion and 'relatives of the spouse' (unclear what this represented) yielded a statistically significant OR of 1.85 (95 % CI 1.38-2.47) for spontaneous abortion. Unfortunately, many questions remain open: What was the measurement procedure: e.g. did measurements get performed in the bedroom of the women, how long and when, what exposure metric was used in the analysis (e.g. arithmetic mean, a percentile, maximum,…)? It is further unclear what the OR refers to (OR per increase in 0.1 µT?). In addition, it was not reported how many women were approached and how many finally participated, so that a potential participation bias cannot be evaluated. Finally, it would have been interesting to learn what kind of sources contributed to the women's exposure. All these issues make this study uninformative.

Two publications by de Vocht et al. (de Vocht et al., 2014, de Vocht and Lee, 2014) were published in 2014, addressing the same data set of mothers living close to power lines at the time of birth. Birth outcomes that were evaluated were birth weight, sex, gestational age-adjusted z-scores of birth weight, and four adverse pregnancy outcomes: low birth weight, small for gestational age, spontaneous pre-term birth and pre-term birth. Maternal and perinatal information was collected at the time of delivery between 1990 and 2009 in 21 maternity units in the northwest of England. Only data between 2004 and 2008 were extracted, as these had some key additional information that was necessary for the analysis. This data set included then 265 926 singleton live births of which 23 % were excluded due to incorrect or missing postal code information. Residential proximity to high voltage cables, overhead power lines, electricity substations or towers was used as a proxy for ELF-MF exposure. Analyses were adjusted for maternal age, ethnicity, parity, socio-economic status of the postal code area, and, for a subgroup only, also for maternal smoking. All adverse pregnancy outcomes displayed elevated OR in the group of children whose mother had lived within 50 m of a power line, although none of these were statistically significant. In a statistically more powerful analysis when looking at birth weight in grams, a decreased birth weight was observed in the nearest-distance category, with on average -125 g (reduction of) weight (95 % CI -243 to -7), but no effect on gestational age became apparent. If adjusted for smoking, the estimate increased to -212 g, but the number of exposed cases dropped substantially due to missing smoking information (-62 %). Thus, it was not clear whether the change in effect estimates was due to (negative) confounding by smoking or to selection bias. In a sensitivity analysis published in a second paper, the author used multiple imputation to address problems of missing data on important potential confounders, such as maternal smoking (missing for 62 % of the data set) or BMI (missing for 45 % of the data set). In addition, propensity score matching was performed, which is a method that uses a prediction model to assess the conditional probability of living close to a high-voltage power line, taking the potential confounders into account – the propensity score. It was found that effect estimates were not heavily affected by the considered confounders. This indicates that confounders such as smoking do not play an important role and the above mentioned discrepant results for smoking adjusted results are the consequences of selection bias.

Wang et al. (2013) performed a 2-year prospective cohort study on residential exposure to ELF-MF from power lines and miscarriage risk. The study was performed in China, where women were required to register every pregnancy. Participants filled in a questionnaire to assess a range of potential confounders. Subsequently, spot measurements were performed at the front door as well as in the streets in the vicinity of the places of residence of the women. 552 women were included into the study, but the response rate was not reported. Over the duration of the study, 37 women miscarried. The average exposure to magnetic fields was low (median of 0.1 µT), but nearly 5 % of the sample were exposed to levels exceeding 1 µT. It was not reported what kind of sources generated these higher exposures, but the authors report that they had a study area with a relatively dense net of high-voltage power lines. Per increase in exposure of 1 µT, a HR of 1.67 (95 % CI 0.25-11.11) for front-door exposure, and 1.72 (95 % CI 1.10-2.69) for street exposure was observed. The analysis was adjusted for a range of potential confounders, including a history of abnormal pregnancy, which might represent over-adjustment if indeed there was an association between exposure to ELF-MF and miscarriage. It is not entirely clear if the street exposure has relevance for the personal exposure of the women, although the paper discusses that 30 % of the sample had no employment and spent much of their time with the neighbours on the streets.

2.4.2 Childhood cancer

Selection bias has been previously discussed as an alternative explanation for the consistently observed epidemiological association between ELF-MF and childhood leukaemia. This issue was addressed in the Northern California Childhood Leukaemia Study (NCCLS), Slusky et al. (2014). Since the calculation of residential wire codes is based on place of residence only, it does not require cases' or controls' consent to participate, and therefore, eligible but non-participating subjects of the NCCLS study could be compared to participating subjects in this study. The authors reported that overall, participating subjects had a slightly higher socioeconomic status (SES) compared to non-participating subjects, with higher levels of education of the mothers, older mothers at child's birth, and a higher likelihood to live in a single-family home or in a neighbourhood with higher SES. Lower magnetic field exposure (assessed by wire codes) was observed for Non-Hispanic-White people, highly educated people, apartments and rural environment. For the neighbourhood SES the picture was mixed across the various categories. An analysis of all ideal cases (n=376) and ideal controls (n=426) was very similar to the analysis of the actually participating cases and controls with a very slightly increased, although statistically non-significant, odds ratio of 1.18 (95 % CI 0.85, 1.64) and 1.21 (95 % CI 0.85, 1.72), respectively. These results indicate that the results of the NCCLS study are not likely to be strongly affected by selection bias. Nevertheless, magnetic field exposure was associated with various factors that were related to the participation probability.

The availability of wire codes in this study represented a good opportunity to address potential selection bias that might have affected previous epidemiological studies on childhood leukaemia and ELF-MF. Exposure classification using wire codes have been used also in earlier studies that observed an association with childhood leukaemia e.g. Wertheimer and Leeper (1979). The sample size of the NCCLS study is however somewhat small to draw firm conclusions whether observed differences in various analyses are due to chance or not. However, the overall conclusion that selection bias is unlikely to play a relevant role in NCCLS was fairly robust.

Bunch et al. (2014) published a case-control study analysing the risk of childhood leukaemia based on cases and controls from England, Wales and Scotland. Cases from 1962 until 2008 were included, as were one or two controls per case, matched on approximate date of birth, sex and birth registration sub-district. Mothers' residential address at birth was obtained for 53 515 children as well as for 66 204 controls. After excluding children where the residential address could not be geo-coded, about 94 % of the children were included in the final data set. Distance of place of residence at birth to power lines (132-400 kV) was evaluated in categories of 0-199 m, 200-599 m, and 600-999 m and compared to living further than 1 km away. The authors separately analysed three groups of cancers: Leukaemia (total of 16 630 cases), Central Nervous System (CNS) tumours or brain tumours (11 968 cases), or other cancers (21 985 cases). Cancer risk was reported for the years 1962-1969, 1970-1979, 1980-1989, 1990-1999 and for 2000-2008. Analyses adjusted per census ward using the Carstairs deprivation index were similar to the unadjusted analysis. Increased risks for childhood leukaemia for the 275/400 kV lines were observed in the distance categories 0-199 m and to some extent also for the 200-599 m distance category for childhood leukaemia, but only in the time frame between 1962 -1989. Analyses for 1990 onwards resulted in odds ratios below unity and the combined analysis reported an odds ratio for childhood leukaemia of 1.00 for the 0-199 m-distance group. Results including lower voltage level lines were similar. Given the pattern of decreasing risks over time as well as the distance category over which increased risks were observed, the authors conclude that the reported risks are unlikely to be associated with the magnetic fields emanating from the power lines. As alternative explanation, changing population characteristics of persons living in the vicinity to power lines are named. It is unclear, however, what kind of changing characteristic would have occurred in that time frame. Population mixing has been hypothesized to be associated with childhood leukaemia, as has a higher socio-economic position of the parents. However, these factors are not established risk factors for childhood leukaemia. It is therefore unclear how these characteristics, or any other potential confounder for that matter, could possibly induce odds ratios of 4-5 in children being born in close proximity to power lines, even if these risks were confined to earlier time periods.

Previous case-control studies addressing magnetic field exposures and the risk of childhood leukaemia were meta-analysed by Zhao et al. (2014b). Nine case-control studies were included, corresponding to 11 699 cases and 13 194 controls. Results are in line with previous meta-analyses (Greenland et al., 2000) as well as with two previous pooled analysis (Ahlbom et al., 2000, Kheifets et al., 2010), showing a somewhat increased risk for children exposed to levels above 0.4 µT compared to background levels (>0.1µT) with a summary OR of 1.57 (95 % CI 1.03-2.4) for all leukaemia, and 2.43 (95 % CI 1.3-4.55) for acute lymphocytic leukaemia. Unfortunately, excluded studies were not listed, and it is unclear why several studies were left out e.g. (Bianchi et al., 2000, Wunsch-Filho et al., 2011).

Pedersen et al. (2014b) evaluated distance from birth address to the next power line in Denmark and childhood leukaemia. The authors evaluated distance categories up to 600 m of place of residence to the nearest overhead power line, a distance for which a large study from England and Wales had previously observed an increased risk of childhood leukaemia (Draper et al., 2005). All children diagnosed with any leukaemia until age 15 between 1968 and 2006 were identified and two controls per case were matched by gender and year of birth. This resulted in 1 698 cases and 3 396 controls. Address at birth was geo-coded and distance to the nearest power line was calculated. All power lines of 132-400 kV were included, and geo-coding and distance calculation was successful for 94 % of the included children. The final analysis included 1 577 cases and 3 191 controls. Risk of childhood leukaemia was presented for distance categories of 0-199, 200-599 and more than 600 m from a power line and adjusted for socio-economic status of the municipality. No increased risk emerged for children living within 200 m of a 132-400 kV power line (OR 0.76, 95 % CI 0.40-1.45), for children living 200-599 m the OR was 0.92 (95 % CI 0.67-1.25). The OR for living within 600 m of a highest voltage power line of 220-400 kV was 1.24 (95 % CI 0.61-2.50) with no cases occurring within 200 m of a highest voltage power line. Magnetic field exposure was also calculated, but exposure was not presented by cases and controls, presumably because only 12 children in total were exposed to levels above 0.1 μT, including 8 children who were exposed to levels above 0.2 and 5 children to levels above 0.4 μT. Given these very low numbers, the observed lack of association had to be expected. In another publication from the same study, restricted to the analysis of 879 cases diagnosed between 1968 and 1991, potential confounding and interactions with other risk factors were evaluated using 1 621 randomly selected population-based controls, individually matched by gender and age (Pedersen et al., 2014a). For children living within 200 m of a power line a relative risk of 1.68 (95 % CI: 0.72–3.92) was reported compared to those living ≥600 m from the nearest power line. The confidence intervals of the two analyses overlap and are described to be two versions of the same null-result. Little indications for confounding or effect modification were found except an increased risk for children being exposed to both radon and power lines. However, this result is based on 9 cases only and is most likely a chance finding.

In summary the Danish analysis was limited in the ability to estimate risk for children living in closer distances to power lines and to power lines of higher voltages (e.g. 50 m). For instance a previous analysis from France showed an increased risk of acute leukaemia only for children living within 50 m of a power line of 225-400 kV, no increased risk was seen for lower voltage lines (Sermage-Faure et al., 2013). Draper et al. in 2005 observed an increased risk of childhood leukaemia in England and Wales primarily up to 200 m, but risks were still slightly elevated up to 600 m from power lines of mostly 272-400 kV. For living within 600 m of a power line, an OR of 1.3 (95 % CI 1.1-1.6) was observed, which is not contradictory to the findings from the Danish group. In conclusion, only five study participants were exposed above 0.4 μT and thus the power of the study was too small to interpret the absence of an association as evidence against causation. At least, the very low number of cases and controls that lived close to power lines over a time period of 39 years suggests that any public health impact, at least for Denmark, appears to be limited.

Grellier et al. (2014) performed a calculation of the proportion of childhood leukaemia cases attributable to current non-occupational ELF-MF exposure levels in 27 European Union member states. This calculation is based on the assumption of a causal association between the exposure to ELF-MF and childhood leukaemia. Data were extracted from the literature. For this analysis, an exposure-response function was extracted from the literature; the most recent of these was regarded as the most up-to-date (Kheifets et al 2010). Exposure distribution of populations from studies performed in Finland, UK, Denmark, Germany, Belgium, Austria, France and Italy were summarised. The attributable number of cases per year for the whole EU region varied between 10 and 61, depending on whether a categorical threshold model was calculated (assuming risk only at levels exceeding 0.4 μT), or whether a continuous non-threshold model was calculated. The latter was regarded by the authors as better representing the epidemiological evidence. The presented numbers correspond roughly to 1.5-2 % of the annually occurring cases of childhood leukaemia in the EU.

2.4.3 Adult cancer

In The Netherlands, Koeman et al. (2014) performed a case-cohort study on the association between occupational exposure to ELF-MF and several selected cancer outcomes. The study was based on the Netherlands Cohort Study on diet and cancer, where around 58 000 men and 63 000 women in the age group 55-69 years were enrolled in September 1986. The participants completed a questionnaire on occupational history, dietary habits and other potential risk factors for cancer. For the occupational history, subjects reported their job title, type of job, type and name of industry and period of employment for up to five jobs during their lifetime. Of a randomly selected subgroup of 5 000 persons, all questionnaires were entered fully into the digital database.

After enrolment, the cohort was followed up for cause-specific mortality and cancer incidence until December 2003, covering a period of 17.3 years. Cases were obtained by record linkage with the Netherlands Cancer Registry and the Netherlands Pathological Registry. For each occurring case, all questionnaire information was entered as well. This procedure led to 2 336 men and 2 438 women that were included into the analysis. Based on the information from the occupational history, a job exposure matrix was used to assign exposure to job titles as background, low or high. Next to the highest exposure a person had ever had, the authors also evaluated the duration of exposure and cumulative exposure. The authors investigated breast and brain cancers, and hemato-lymphoproliferative malignancies, lung cancer was used as a "negative control". Cox regression analyses were adjusted for potential confounders depending on the outcome of interest. For breast cancer, no significant increased risk was observed in any of the exposure categories, except in the lowest exposure category for cumulative exposure, where a small increase was observed. For brain cancer, no statistically significant increased risk was found in any of the exposure categories. Regarding lung cancer, a significantly increased hazard ratio (HR) was observed among ever high ELF-MF exposed men (HR 1.33, 95 % CI 1.01-1.75), but this finding was not confirmed when analysing duration of exposure or cumulative exposure. HR for all types of leukaemia combined tended to be above unity for exposed men. In a subgroup analysis, an increased HR for acute myeloid leukaemia (AML) was observed for both ever low exposed (HR 1.84 95 % CI 1.18-2.85, n=52) and ever high exposed (HR 2.15, 95 % CI 1.06-4.35, n=10) men as compared to background exposure. The analyses of cumulative exposure did not provide evidence of an exposure-response relationship, as the lowest risk estimate was found in the highest exposure category. For follicular lymphoma (FL), increased risks were reported for ever-high exposed workers based on 7 cases, and in addition, there was a statistically significant exposure-response pattern for cumulative exposure. Increased risks were only observed in men, but exposure cut-offs were sex-specific. Due to the lower prevalence of occupational ELF-MF exposure in women, this means that the highest category of exposure in women corresponded to a much lower exposure level of men.

Overall, no associations were observed among women. The somewhat increased risk in subgroup analyses of AML and FL require a cautious interpretation of the results. On one hand the number of high exposed cases was low and residual confounding by smoking cannot be ruled out as indicated by the increased lung cancer risk among ever high exposed men, even though risk estimates were adjusted for smoking status. The recent paper by Sorahan (2014b) did not provide evidence for an increased risk of AML in utility workers, but follicular lymphoma has not been previously evaluated.

Occupational exposure to extremely-low frequency magnetic field exposure and risk of brain cancer was evaluated in a case-control study published by Turner et al. (2014). The study analysed a subset of countries that had collected data for the Interphone study (INTERPHONE, 2010). Data of cases and controls from Australia, Canada, France, Germany, New Zealand, UK and Israel were analysed. 1 939 gliomas and 1 822 meningioma cases, as well as 5 404 controls were included in the final data set. Occupational histories for jobs held for at least 6 months were assessed; persons who reported never having had a job were excluded from the analysis. Exposures were assigned to occupations with help of a job exposure matrix (JEM). A one-year lag was applied to all lifetime exposures, and separate exposure-time windows were evaluated: 1-4, 5-9 and 10 years or more prior to diagnosis, defined *a priori*. Overall, glioma risk was not associated with any of the explored magnetic field exposure metrics (average or maximum exposure or exposure duration). Increased risks emerged for the time window of 1-4 years' time-lag, with an increased risk in the highest 10 % compared to the lowest 25 % exposed persons with an OR of 1.67 (95 % CI 1.36-2.07). In contrast, for the same distributional exposure cut-offs, risks were somewhat decreased in the longest exposure lag of 10 or more years (OR 0.77, 95 % CI 0.6-0.99). For meningioma, there was a weak increase of risk in the 1-4 year time-lag, with an OR of 1.23 (95 % CI 0.97-1.57) with a statistically significant trend (p-value 0.02) of increasing risk over increasing exposure categories.

Zhao et al. (2014a) performed a second meta-analysis, this time on breast cancer and ELF-MF exposure. 40 papers were found on the topic, but studies with fewer than 100 subjects per group, as well as studies of lower quality were excluded and after the selection, 13 publications were retained for the meta-analysis. Stratified analyses were performed for a subset of 4 and 5 studies that reported on risks of ELF-MF exposure in premenopausal and postmenopausal women, respectively. The overall summary OR of the meta-analysis was 1.10 (95 % CI 1.01-3.09). Within the subgroup analysis, summary ORs of 1.25 (95 % CI 1.05-1.49) and 1.04 (95 % CI 0.93-1.18) were observed for premenopausal and postmenopausal women, respectively. Funnel plot asymmetry appeared to be indicative of some small study effects, although the statistics on the funnel plot (e.g. Egger test) were not reported. The authors interpret the slightly increased OR in premenopausal women as evidence for an effect of the exposure of ELF-MF on the risk of developing breast cancer.

Several questions remain open, in particular the chosen cut-off of sample size and the use of the quality rating to exclude studies. Residential as well as occupational exposures, or exposures to sources at home (in particular the use of electric blankets) were included, but this is not further explained in the publication. A previous meta-analysis published by Chen et al. (2010) (summarised in the SSM report 2010:44) yielded a summary risk estimate for premenopausal women of 1.07 (95 % CI 0.81–1.40). Meta-analysis is sensitive to the comprehensive inclusion of studies, which might have led to the slightly different risk estimate observed here.

Three publications on the same cohort were published by Sorahan (2014a), one on brain tumour risk, one on leukaemia and a last one on neurodegenerative diseases (discussed in the following chapter). The publication links also to a previous paper by the same author on the same cohort (Sorahan, 2012), which was discussed in the previous SSM report. In brief, the cohort consisted of over 80 000 employees of the former Central Electricity Generating Board. All employees were included who had worked for the company for at least 6 months during 1973-1982. Persons with a detailed work history from 1971-1993 were analysed for the current study. Exposures were evaluated as cumulative lifetime exposure, as well as cumulative exposure received more than 10 years ago, and also as those received in the past 10 years. This last step is somewhat unclear, given that the cohort member's occupational histories were evaluated up to 1993, but follow-up lasted until 2008. Date of diagnosis-information was available, and the author evaluated both total brain cancer mortality, as well as astrocytoma/glioma and meningioma incidence, which was done for the period 1973-2008. In the first paper, brain tumours combined, astrocytoma/glioma and meningioma were analysed separately. Risk estimates of all brain tumours as well as astrocytoma/glioma were close to 1 for cumulative live-time exposure and exposure received >10 years before diagnosis. Interestingly, results were consistently below unity for exposures received in the last 10 years, which is in contrast to the results reported by Turner et al 2014. For meningioma, the highest three exposure categories (between 5 and more than 20 µT years) were elevated, although not statistically significantly. Analyses were repeated for a sub-cohort of 48 768 persons who were first employed in power stations and for whom a more detailed exposure assessment was available. In this sub-cohort, RRs seemed to be closer to unity than in the original analysis. In the second publication (Sorahan, 2014b), evaluated leukaemia, acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), acute lymphocytic leukaemia (ALL) as well as chronic lymphocytic leukaemia (CLL). Analyses for AML, CML and CLL did not provide evidence of an exposure-response relationship. Based on only 14 cases of ALL, significantly elevated risks emerged from the analysis for exposed workers, with a RR in the highest cumulative exposure category of 7.70 (95 % CI 1.22–48.5), corresponding to a risk increase per 10 µT years of 1.52 (95 % CI 1.03-2.25). However, the author argued whether this result may have been due to either unusually high risks among exposed, or unusually low risks among the unexposed. A comparison of the total cohort with national cancer registration rates resulted in standardised registration ratios (SRRs) for ALL of 0.82 (95 % CI 0.42-1.44), which speaks against higher risks in the cohort.

The question is whether such a comparison to external data is not problematic. This can occur due to the "healthy worker effect" which means that people who are employed (i.e. who were included in the study) are often healthier on average than the whole population (i.e. who were in the registry). In this case, the internal analysis would be correct, the comparison to external data not. This does, however, not exclude that by chance exceptionally few people had developed ALL in the unexposed group, resulting in apparent higher risks of exposed workers. All in all, the strength of this study is its prospective design, the relatively large size and the observed contrast in exposure. It is unclear, however, how exposure was operationalised for the 15-years' time gap between the end of assessing the occupational histories and the end of follow up for all cancer outcomes, which might have affected the categorisation of cumulative exposures in which case less weight should be given to the presence or absence of a clear exposure-response function across increasing cumulative exposure categories.

2.4.4 Neurodegenerative diseases

In the same cohort as the previously discussed two publications by Sorahan (2014a) and Sorahan (2014b), Sorahan also published an analysis on neurodegenerative disease mortality (Sorahan and Mohammed, 2014). Alzheimer's disease (AD), amyotrophic lateral sclerosis (motor neuron disease, MND) and Parkinson's disease (PD) mortality were analysed. RRs for AD and PD varied around unity for the different exposure categories. For ALS, all RRs were elevated, but only statistically significant for the 2^{nd} lowest exposure category. All in all, this study provides no evidence for an association of occupational exposure to ELF-MF and Parkinson's disease or Alzheimer's disease. For amyotrophic lateral sclerosis, the results remain unclear.

In The Netherlands, van der Mark et al. (2014) performed a case-control study to evaluate the association between exposure to ELF and electric shock and Parkinson`s disease. 448 cases and 876 controls recruited during 2010 and 2012 from neurology departments in five hospitals in the Netherlands were included in the analyses. Participation rates for cases and controls were 45 % and 35 %, respectively. Information regarding residential and occupational history, number of self-reported experienced electrical shocks, dietary items, smoking history, medical history, etc. was collected via computer-assisted telephone interviews. In addition, information about use of several household appliances that could substantially contribute to ELF-exposure to the head was also collected. All jobs were coded into an international occupational coding system (ISCO88) and subsequently linked to job-exposure matrices (JEMs) that assign exposure levels for ELF-MF and risk of electrical shocks. The JEMs classify exposure into low, medium and high exposure. Several exposure metrics were explored: ever medium or high exposure, duration of exposure and cumulative exposure.

The exposure from household appliances were also modeled, and expressed in µT-years. When using low ELF-MF exposure as reference, the OR for ever-high exposure was 0.78 (95 % CI 0.50-1.20). The same pattern with non-significant reduced risk estimates was found in all the exposure categories except in the highest exposure group from household appliances, which had an OR of 1.13 (95 % CI 0.67-1.90). Unadjusted and adjusted results were similar. The analyses for electrical shocks showed the same pattern as for ELF-MF, with an OR of 0.85 (95 % CI 0.59-1.21) among ever high exposed persons. The low participation rate among cases and controls always raises the concern that possibly results were biased, although it is unclear why in this case more higher exposed controls than cases would have been triggered to participate in the study. The result of no increased risk of Parkinson's disease in exposed workers is well in line with previous reports.

In the Swiss National Cohort the association between amyotrophic lateral sclerosis (ALS) with respect to occupational exposure to magnetic fields and electric shocks was addressed (Huss et al., 2014). In this study death certificates, immigration and emigration records were probabilistically linked with nationwide censuses carried out in 1990 and 2000. ALS mortality between 2000 and 2008 was analysed in a cohort of all adults registered in the 2000 census with an age of >30 years or older. Magnetic field and electric shock exposure was assigned based on job titles that persons had reported in the census 2000 and if available also in the census of 1990. Exposures were assigned using a modified version of an established ELF-MF job-exposure matrix. Data was analysed by means of Cox proportional hazard models adjusted for gender and nationality (Swiss, other). Educational level, civil status, language region, degree of urbanization of the municipality where persons lived and a neighbourhood index of socioeconomic position was not related to ALS mortality risk and thus not considered. Separate analyses were performed for the job title of 2000 and 1990. Of 1 349 eligible ALS deaths, 792 were included in the analysis of occupational exposure in 1990 and 299 in the analysis of occupational exposure in 2000. A total of 2 167 046 persons (278 cases) contributed data for the analysis of both censuses. The main reason for exclusion from analysis was missing job title (pensioners). Magnetic field, electric shock exposure and electrical occupation were not associated with ALS mortality in the 1990 and in the 2000 census cohort. However, in the combined census analysis an increased risk was seen for those being in the medium (0.19 µT) or high (0.52 µT) magnetic field exposure category in both censes, 1990 and 2000 (HR=1.55, 95 % CI: 1.11-2.15). For those who had been exposed only once (either 1990 or 2000) the risk was not increased. Risk of electric shock was not associated with ALS in the combined census analysis. When both exposures were included in the same model, the HR for ELF-MF changed little. Sensitivity analyses considering magnetic field and electric shock exposure in vocational training and full-time working load yielded slightly higher ALS mortality risks for ELF-MF exposure.

This study indicates that exposure duration may be critical to observe an association between occupational ELF-MF exposure and ALS. Interestingly, no association was seen with working in an electrical occupation, which is in contrast to previous reports in the literature (Vergara et al., 2014). Also, no association was observed with electric shocks, as was previously suggested (WHO, 2007). A limitation of the study is that the combined census analysis is based on only approximately 20 % of all eligible cases and selection bias or chance is an alternative explanation for the observed pattern. In total, 46 ALS cases were observed in the group of people who were exposed to ELF-MF in 1990 and 2000. Thus, the observed 55 percent risk increase is due to approximately 15 additional cases only. Of note, the combined census analysis and the 1990 census analysis did not include people who died between 1990 and 2000 and thus, competing risks may have influenced the results: if magnetic fields or electric shocks were a strong risk (or protective factor) for ALS with a relatively short latency (<10 years), it would affect the likelihood to enter the cohort which could produce an under or overestimation of the risk. However, no evidence from the previous literature exists that this would be the case. In summary, this study addresses the open issue whether previously observed associations between ALS and electrical occupations were due to magnetic field exposure or electric shocks. Overall, the results suggest that longer duration occupational exposures to magnetic fields, rather than electric shocks, may be associated with the risk of dying from ALS.

Davanipour et al. (2014) performed a study in 3 050 elderly Mexican persons living in five south-western States in the USA to determine whether occupational MF exposure might be a risk factor for cognitive dysfunction. This study was embedded in the Hispanic Established Population for Epidemiologic Studies of the Elderly (H-EPESE); persons older than 65 years were included in the study. Although the H-EPESE is a longitudinal study, for this analysis cross-sectionally collected data from 1993 and 1994 were analysed. The primary occupation a person had had during most of his or her life was collected by means of interviews, as was information regarding smoking, alcohol consumption, stroke or heart attacks as well as socio-demographic characteristics. Information from 6 % of the population was obtained by interviewing surrogate-respondents. The primary outcome was a mini-mental test score of less than 10 points, which was the case for about 1.6 % of the total population. Occupations were classified regarding their occupational exposure, about 5 % were classified as medium-exposed, and about 4 % as high-exposed, which translated into 5 high-exposed cases and only one medium-exposed case. Medium exposure was reported to range between 0.2-1 μT and high exposure above 1 μT on average, classification was based on task description and job title, in line with previous publications of the same author. High compared to low magnetic field exposed persons had an OR of 3.4 (95 % CI 1.3-8.9) for cognitive dysfunction, and adjusted for age group and stroke an OR of 3.7 (95 % CI 1.3-10.1). Comparing medium-together with high-exposed persons vs. low-exposed resulted in the same OR.

In principle, this is a well-conducted study. Morbidity (mini-mental test scores) instead of mortality information (e.g. dementia on the death certificate) was used for assessing the primary outcome. The classification of medium or high exposed jobs was performed based on occupational and task information and blinded to outcome status. Only a relatively low percentage of persons were classified as high-exposed. More recent publications have used so-called job exposure matrices based on measurements, to assign average magnetic field exposures to occupations, usually this resulted in higher percentages of persons classified as high exposed. It would have been interesting for the interpretation of this work by Davanipour (and other studies) to see if applying a JEM in parallel to the analysis performed here would have resulted in a different outcome of the study. Another problem is the low threshold of the mini-mental test score that was used to determine cognitive impairment and which does not correspond to conventionally used cut-points. On the one hand this made the outcome very rare (and the power of the study low), on the other hand the selection of this threshold may have been data driven.

A case-control study on occupational exposure to electric shocks and magnetic fields from amyotrophic lateral sclerosis (ALS) in the US was performed by Vergara et al. (2014). Cases and controls were based on death certificate data from those US states that included an occupational code on the death certificate. Data from 1991-1999 were included. Causes of death that have previously been discussed to be possibly linked to ELF-MF exposure (e.g. leukaemia or brain tumours) were an exclusion criterion to enter the study as a control; 10 controls were matched to cases on year of death, sex, 5-year age group and four major regions. Exposure was based on linking an ELF-MF, as well as an electric shock JEM to the job code that was provided as the “usual occupation” on the death certificate. In addition, electrical occupations and welding occupations were evaluated. Adjustment was done for educational level, ethnicity and race. Overall, 5 886 ALS cases and 57 667 controls were included into the study. Persons with medium exposure levels to magnetic fields had an adjusted OR of 1.09 (95 % CI 0.96-1.23) and persons with high magnetic field exposures also had an OR of 1.09 (95 % CI 1.00-1.19). For risks of electrical shocks at work, risk estimates were below unity in those at higher risk of shocks: For median shock risk, the OR was 0.90 (95 % CI 0.84-0.97) and for high risk of shocks, the OR was 0.73 (95 % CI 0.67-0.79). Very slightly increased risks were observed in electrical occupations with an OR of 1.23 (95 % CI 1.04-1.47), but in welders, a reduced OR was observed (OR 0.70, 95 % CI 0.55-0.89).

If anything, this very large study supports an association of ELF-MF exposures with ALS rather than an association with electric shocks. However, the observed protective effects for electric shocks and welders are difficult to interpret and prevent from drawing firm conclusions. A problem is the quality of occupational information registered on death certificates that has been previously assessed but found to be not suitable for epidemiological studies: "The limited quality of occupation and industry information on death certificates argues against relying on such information to evaluate modest associations with mortality" (Andrews and Savitz, 1999). If random errors occur, one would expect an underestimation of the risk, otherwise a bias is possible. It is therefore unclear to what extent the results are affected from misclassification of the exposure.

2.4.5 Symptoms

To investigate the possible correlation between exposure to ELF and sleep quality and general health, Monazzam et al. (2014) performed a survey in 40 workers. ELF-MF was measured in a control room and in high voltage substations of a petrochemical complex using a uniaxial HI-3604 ELF Survey Meter. The highest measured field strength was 49.90 µT. Maximum field levels in the control room were between 0.05 and 0.14 µT. Forty male workers working in 12-hour irregular shifts in these buildings were divided into an exposed (n=18) and an unexposed (n=22) group according to their place of work. Their sleep was assessed with the "Pittsburgh Sleep Quality Index" (PSQI) questionnaires and general health with the "General Health Quality (GHQ)". Scores for both outcomes tended to be worse in the exposed group but differences were not statistically significant according to t-test, Duncan and Chi-square tests. The small sample size and lack of adjusting for confounding variables are severe limitations and thus the study is not informative in terms of possible sleep and other health effects from the occupational exposure to ELF-MF.

2.4.6. Other outcomes

A survey in exposed and unexposed electric utility workers on neurobehaviour was performed by Li et al. (2014b). Initially, 710 workers were selected to conduct a neurobehavioral test battery on a laptop that included mental arithmetic, curve coincidence, simple visual reaction time, visual retention, auditory digit span and pursuit aiming. Workers who performed tour inspections close to transformers or distribution power lines were assumed to be exposed (n=364). Inspectors, working in offices (n=346), were assumed to be unexposed to magnetic field exposure. All exposed workers were reported to have an occupational history of 3-25 years in their respective job. After excluding persons with incomplete information or due to underlying medical reasons, neurobehavioral tests of 310 exposed and 300 unexposed workers were analysed. Spot measurements of ELF electric as well as magnetic fields were performed with a portable meter.

Of the spot measurements, median exposure was around 7-37 μT, depending on the subgroup of exposed workers. None of the spots exceeded 1mT. All neurobehavioral test outcomes were presented stratified first only by exposure status, and then additionally by age groups (<30, 30-40, ≥40 years), sex and in men, according to years worked (<5, ≥5 years). Final analyses of variance were conducted by adjusting for green tea and alcohol consumption. No statistically significant differences emerged from any of the analyses. EMF spot measurements were performed at those spots where tour inspectors would stop. However, it was not reported how many spots a tour inspector would check, only that a stop would take about 2-5 minutes. Therefore it is unclear in how far the reported ELF-EF and MF values translate into higher personal exposure levels. A problem of the study is that only the confounder green tea and alcohol was considered in the data analysis but not age, gender and work experience. Omitting these factors from the analyses and instead presenting results stratified by the potential confounders resulted in a loss of power.

2.4.7 Conclusions on ELF epidemiological studies

Over the last year, several publications appeared addressing pregnancy outcomes in relation to maternal ELF-MF exposure. Whereas two small studies observed an association between miscarriages and ELF-MF exposure, no effect on pre-term birth was seen in a large study from the UK with more than 250 000 singleton live births. However, this study found an association with decreased birth weights which warrants further investigation.

With respect to childhood leukaemia and distance to power lines, a striking pattern of decreasing risks over time between 1962 and 2008 was observed in a large study performed in the UK. Since ELF-MF exposure in proximity to power lines have most likely not heavily changed over time, this observation might indicate that a third factor is playing a role for the previously observed association. However, such a factor must be a very strong risk factor for childhood leukaemia to have such an impact and no obvious candidate can be proposed, given the limited number of strong known risk factors for childhood leukaemia, apart from genetics, which is unlikely to change over time.

New studies on adult cancers indicated associations for some tumours, but the consistency of these findings was not very high and no new ground-breaking methods haven been applied. Given the high number of similar papers already published in this area, the new studies do not change the view on the topic.

One new study on Parkinson's disease and occupational ELF-MF field exposure and electrical shock does not indicate an association for any of the exposure measures, which confirms the previously observed absence of an association with these exposures. Of note, two new studies on ALS rather support an association with ELF-MF exposure than with electric shocks, which was previously discussed to remain an open question in the research field. A Mexican study observed an association between ELF-MF exposure and impaired cognitive function, but suffered from low statistical power. In conclusion, similar to previous research, recent studies suggest that an association between ELF-MF exposure and ALS or Alzheimer's diseases may exist, which warrants further investigation.

3. Intermediate frequency (IF) fields

3.1 Cell studies

Only one *in vitro* investigation was conducted in the reference period. Shi et al. (2014) evaluated the effects of intermediate frequency magnetic fields (IFMF) generated by wireless power transmission based on magnetic resonance on cultured human lens epithelial cells. The 90 kHz exposure was carried out at 93.36 mT for 2 and 4 h to evaluate cell viability and induction of apoptosis and DNA damage. Viability was measured with a colorimetric assay 72 h post exposure. Apoptosis was evaluated 12, 24 and 48 h after exposure (Annexin V/PI staining). DNA damage was assessed by applying both the comet assay and the phosphorylated histone H2Ax foci (gamma-H2Ax). The authors did not detect any effect for any of the endpoints investigated, as assessed in three independent experiments, carried out blinded, while positive controls (treatments with 2 Gy x-rays, staurosporine and 4-nitroquinoline-1-oxide for viability, apoptosis and comet and gamma-H2Ax, respectively) gave positive findings, as expected. The authors stressed that the flux density employed in this study is about 3.5 times higher than the reference level in the ICNIRP guidelines.

3.2 Animal studies

Nishimura et al. (2013) addressed a potential health risk of induction cookers where the MF source is close to the abdomen of a person cooking. In case of a pregnant woman developmental effects may be a concern. The potential direct physical effect of MF on the development of chicken embryos was investigated. For this, fertile White Leghorn eggs (60/group) were either exposed to 20 kHz, 1.1 mT (rms) or 60 kHz, 0.11 mT (rms) sinusoidal MFs for 19 days during entire embryogenesis. Further, 60 fertile eggs were used as controls. The experiments were triplicated for both frequencies and corresponding controls. The frequencies chosen are typical primary frequencies used for induction heating cookers. Furthermore, for testing the equality between exposure and control facility a sham-sham experiment was conducted. After exposure, embryos were examined in a blinded manner for mortality rate, developmental stage, gross and skeletal anomalies. Mortality rate, stage, incidence of malformed embryos, and developmental variables in live embryos of the controls and IF-MF exposed groups were similar, including to those of historical controls. Also the data of exposure and control facility were comparable. Summarizing the data of this well performed and described study, exposure to 20 kHz or 60 kHz MF did not produce significant teratogenic developmental effects in chick embryos.

3.3 Conclusions on IF studies

Although well conducted, in the last year only two studies, one on human cell cultures and one on chicken embryos, have been published. Thus, as reported in the previous Council report, no general conclusions can be drawn on this frequency-range.

4. Radiofrequency (RF) fields

4.1 Cell studies

The number of cell studies on the effect of RF on several biological endpoints has been increased in the last years, with particular reference to frequencies and modulations employed in wireless communications and data transmission. Nevertheless, due to a large variety of experimental conditions tested, no firm conclusions have been drawn and this topic is still extensively investigated.

In the last year, several studies have been carried out to evaluate the effect of RF in human and animal cells. Most of them deal with oxidative stress, but gene and protein expression, DNA integrity, cell proliferation and differentiation and apoptosis have also been investigated. Since a number of studies lack sham samples, they do not allow a proper risk assessment evaluation, and they have not been considered in this report.

4.1.1 Oxidative stress

Ni et al. (2013) investigated the induction of oxidative stress in human lens epithelial B3 (HLE-B3) cells intermittently exposed (5 min on/10 min off cycles) to a 1800 MHz RF EMF GSM signal (average SAR=2, 3 and 4 W/kg). The Reactive Oxygen Species (ROS) levels were measured by flow cytometry (DCFH-DA assay) in cells exposed for 0.5, 1, and 1.5 h. Lipid peroxidation was detected by a malondialdehyde test (a member of a family of final products of lipid peroxidation) in cells exposed for 6, 12, and 24 h. The mRNA expression of SOD1, SOD2, CAT, and GPx1genes and the expression of SOD1, SOD2, CAT, and GPx1 proteins were measured by qRT-PCR and Western blot assays in the cells exposed for 1 h. For all the experimental conditions tested, in the RF exposed cultures ROS and MDA levels increased ($P<0.05$) and mRNA and protein expression significantly decreased ($p<0.05$) compared to sham-exposed samples; cell viability also resulted decreased (three independent experiments for each exposure condition/endpoint examined). Positive controls have not been included in the study design.

Epidermal reconstructs containing either only keratinocytes or a combination of keratinocytes and melanocytes grown on dead de-epidermized dermis, were exposed to a 900 MHz, GSM signal (SAR = 2 W/kg) for 6 hours by Simon et al. (2013). Cell cultures were analysed 2, 6, 18 and 24 h post exposure to evaluate ROS production and induction of apoptosis. In a set of 2 to 20 experiments, no effects were detected at any examined time point, evaluated by looking at global protein oxidation and by morphological (Hematoxylin and Eosin staining) and biochemical (cleaved caspase-3 expression) techniques for ROS production and apoptosis, respectively. Moreover, the authors also evaluate the expression and localization of various markers of keratinocyte and melanocyte differentiation using histology, immunohistochemistry and Western blot. No noticeable changes were found in the localization of basal markers (cytokeratins 5, 14) and late markers of differentiation (loricrin, filaggrin), but the rate of epidermal proliferation, was transiently decreased 2 h post-exposure. Overall, the main effect of the RF exposure was a subtle alteration of differentiation markers level without alteration of localization of such markers and no detectable induction of apoptosis.

In a study conducted by Kang et al. (2014) the effect on intracellular ROS formation of combined RF exposure, such as 837 MHz CDMA plus 1950 MHz WCDMA, was investigated. Three different neuronal cells, U87, PC12 and SH-SY5Y, were exposed for 2 h at a SAR of 2 W/kg and ROS formation was measured at different time points (1, 3, 6 and 12 h) after exposure. Results indicated an absence of effects in all the cell types for all conditions tested, except for 6 h post exposure in U87 cells and 12 h post exposure in PC12 cells, in which a slight but statistically significant increase was detected. Measurement of ROS levels in neuronal cells after 2 h co-exposure to multiple RF signals and 100 μM H_2O_2 were also carried out at 1, 3, 6 and 12 h post exposure and no significant changes were detected. Absence of cooperative effects was also detected when co-exposures were carried out with 100 and 200 μM menadione and ROS analysed after 0.5, 1 and 3 h. These findings indicate that neither combined RF alone nor combined RF with menadione or H_2O_2 influences the intracellular ROS level in the neuronal cells investigated.

In a study by Sefidbakht et al. (2014) RF exposure was reported to induce oxidative stress. Human embryonic kidney cells (HEK293T) were exposed for 15, 30, 45, 60 and 90 min to 940 MHz RF field at an average SAR of 0.09 W/kg. In three independent experiments, an increase in ROS formation after 30 min exposure was detected, followed by a sharp rise in catalase and superoxide dismutase activities and elevation of glutathione content during the 45 min exposure with a concomitant decrease in lipid peroxidation. The authors concluded that RF exposure is capable of activate the stress response by an immediate increase in ROS levels.

4.1.2 Gene and protein expression

Bourthoumieu et al. (2013) investigated the expression of p53 (a tumor suppressor protein, regulator of cell cycle) and its activation in human amniotic cells exposed for 24 h to 900 MHz RF EMF, GSM modulation (SAR = 0.25, 1, 2 and 4 W/kg). The results of three independent experiments performed using three different donors showed no effect in p53 expression (Western blot assay) by comparing sham-exposed to RF-exposed cultures. Bleomycin-exposed cells were used as a positive control and showed an increased expression of p53, as expected.

Valbonesi et al. (2014) exposed rat pheochromocytoma (PC12) cells for 4, 16 and 24 h to 1800 MHz CW or to two different GSM modulation schemes, GSM-217 Hz and GSM-Talk. Intermittent exposures (5 min on/10 min off cycles) at an average SAR level of 2 ±0.4 W/kg were carried out, and HSP70 and HSC70 mRNA levels and protein expression were evaluated. A significant enhancement in the transcription of HSP70 gene was recorded in cells exposed to GSM-217 Hz signal for 16 or 24 h with respect to sham, with no effect after 4 h exposure. No variation of HSC70 mRNA expression was detected in any of the exposure conditions. Absence of effect was also detected in either HSC70 or HSP70 protein expression in RF- exposed cultures with respect to sham-exposed ones. The authors stressed that the enhancement in the transcription of HSP70 gene observed in cells exposed to the GSM-217 Hz signal is a confirmation of their previous results reported in human trophoblast cells (Franzellitti et al., 2008).

A study was conducted at higher frequencies by Alexandrov et al. (2013). They exposed mouse mesenchymal stem cells (MSC) to either broadband THz radiation (centred at ~ 10 THz, 1 mJ, pulse width 35 fs duration, i.e., high peak power per pulse 30 MW) for 2 or 12 hours, or to single-frequency (2.52 THz) for 2 hours only. Each scenario was applied in three independent experiments and the reported results were averaged. In each experiment, the MSC cultures were synchronized to be at the same differentiation time point immediately before the irradiation. It is reported that prolonged (12 hours) broad-spectrum THz irradiation of MSCs resulted in overexpression of transcription factor peroxisome proliferator-activated receptor gamma (PPARG, that is known to be required for adipocyte differentiation), adiponectin, glucose transporter type 4 (GLUT4), and fatty acid binding protein 4 (FABP4) ($p<0.05$) with dependence on the level of stem cell differentiation, while 2 hour exposures did not have significant effects on gene expression. Taken together, the results showed that the effect of THz exposure on adipocyte differentiation depended on irradiation parameters such as the duration and type of THz source, and on the degree of stem cell differentiation.

4.1.3 DNA damage

The phenomenon of RF-induced adaptive response (AR), already reported in previous studies by Sannino and co-workers, was further studied by the same research group in a more recent investigation (Sannino et al., 2014). The authors demonstrated that human peripheral blood lymphocytes from four healthy male non-smoking donors which were pre-exposed in blinded conditions for 20 h to 1950 MHz, UMTS (SAR = 0.3 W/Kg), exhibit a decreased DNA damage induced by a subsequent exposure to 1.5 Gy X rays, evaluated as micronucleus frequency. But after a (subsequent) exposure to 1.0 Gy X rays only in two (of four) donors such a decrease was observed. In previous studies, it was reported that RF exposure was able to induce AR in lymphocytes treated with a chemical mutagen, Mitomycin-C. Since X rays and mitomycin-C induce different kinds of lesions in cellular DNA, these results suggest that the capability of pre-exposures to RF to induce AR is independent from the mutagen investigated.

Human skin cells (HDF and HaCaT) were exposed in vitro to THz radiation by Hintzsche et al. (2013). The exposure was for 2 and 8 h at the specific frequencies of 0.380 and 2.520 THz, with power density ranging from 0.3-9 W/m^2. Chromosomal damage (micronucleus assay) and DNA migration (comet assay) were not induced in the different cell types investigated after exposure both frequencies. In addition, cell proliferation was quantified and was unaffected by the exposure.

4.1.4 Cell proliferation and differentiation

Chen et al. (2014) carried out a blind study to evaluate the effect of 1800 MHz fields on embryonic mouse neural stem cells (eNSCs). Cell cultures were exposed at SAR values of 1, 2, and 4 W/kg for 1, 2, and 3 days. Apoptosis, proliferation, cell cycle and the mRNA expressions of related genes were not affected, as assessed by comparing exposed and sham exposed samples. Moreover, RF exposure also did not alter the ratio of eNSC differentiated neurons and astrocytes. However, after 4 W/kg RF-EMF exposure for 3 days, neurite outgrowth of eNSC differentiated neurons was inhibited; the mRNA and protein expression of the proneural genes Ngn1 and NeuroD, crucial for neurite outgrowth, were also decreased and the expression of their inhibitor Hes1 was upregulated. Exposure at 1 and 2 W/kg had no significant effect. The authors concluded that these results suggest that RF exposure at high SAR levels could have a potential adverse effect on brain development.

Different results on the basis of the exposure conditions employed were reported by Ozgur et al. (2014) who employed human hepatocellular carcinoma cells to evaluate the effects of GSM EDGE signals at 900 and 1800 MHz. Exposures were carried out blinded for 1, 2, 3 and 4 h in intermittent mode (15 min on/15 min off) at an average SAR of 2 W/kg. For each experimental condition 8 independent experiments were carried out. When compared with their respective sham-exposed controls, an increase in cell proliferation after 1 h exposure to 1800 MHz and a decrease in both the 900 and 1800 MHz exposed cells after 4 h exposure was observed ($p<0.05$). In the other experimental conditions tested, no effects were detected. Moreover, a significant increase in LDH and glucose levels released into the medium were observed after 4 h exposure to either 900 and 1800 MHz, associated with the presence of morphological changes characteristic of apoptosis.

4.1.5 Apoptosis

The investigation by Canseven et al. (2014) deals with the effect of exposure to a 1800 MHz, GSM signal on apoptosis and viability of Burkitt's lymphoma (Raji) cells with or without Gemcitabine, an inhibition of DNA synthesis and apoptosis inducer. Cell cultures were exposed to RF for 24 h at a SAR value of 0.35 W/kg. For co-exposure experiments, Gemcitabine was given 24 h before RF exposure. Apoptosis, measured using Annexin V-FITC and propidium iodide staining, was significantly increased, with a decrease in viability, in cells exposed to RF alone, compared to sham-exposed cultures. Co-exposures showed a significant increase in apoptotic cells and a decrease in viability compared to cultures exposed to RF alone (five independent experiments). In this investigation, cultures treated with Gemcitabine alone have not been included in the study design.

4.1.6 Other endpoints

Autophagy acts as a survival mechanism under conditions of environmental stress, maintaining cellular homeostasis. In a double-blind study by Liu et al. (2014b), mouse spermatocyte-derived cells (GC-2) were exposed double blind to 1800 MHz GSM signals, at SAR values of 1 to 4 W/kg for 24 h to investigate the induction of autophagy. The results of three independent experiments indicated that the expression of the autophagic marker LC3-II increased in a dose- and time-dependent manner with RF exposure, and showed a significant change at 4 W/kg ($p<0.05$). The occurrence of autophagy was further confirmed by GFP-LC3 transient transfection assay and transmission electron microscopy. Furthermore, the conversion of LC3-I to LC3-II was enhanced by co-treatment with Chloroquine (CQ). Intracellular ROS levels significantly increased in a dose- and time-dependent manner after

RF exposure. Phosphorylated extracellular-signal-regulated kinase (ERK) significantly increased after RF exposure at SAR values of 2 and 4 W/kg. Moreover, RF exposure did not increase the percentage of apoptotic cells. The authors concluded that the autophagy flux could be enhanced by RF exposure (4 W/kg), which is mediated by ROS generation (Liu et al., 2014).

Ahlers and Ammermuller (2013) focused on the acute effects of RF-EMF onto the light responses of the retinal ganglion cells under constant temperature conditions. They exposed isolated mouse retinae, in double blind conditions, to GSM-900, GSM-1800, and UMTS RF-EMF at SAR values of 0.02, 0.2, 2, and 20 W/kg. They recorded the responses of ganglion cells to light stimuli of three different intensities (0.5, 16 and 445 lx) before, during and up to 35 min post exposure. Several experiments were carried out for each condition, and experiments with unstable cell light responses were discarded. The results on a remaining number of experiments varying between 11 and 4 indicated no effects for any of the conditions tested, compared to sham-exposed retinae.

Moretti et al. (2013) investigated the effect of 1800 MHz (GSM signal, SAR 3.2 W/kg) exposure on neuronal activity in primary neuronal cell cultures obtained from the cerebral cortex of embryonic rats. The results from 16 independent experiments performed between 15 and 21 days *in vitro* by extracellular microelectrode array (MEA) recording show a decrease in both spontaneous spiking activity and bursting rate during 3 min of exposure. The effect was reversible: it lasted through the whole exposure period but ended with the exposure. Temperature elevation at the end of the 3 min exposure was about 0.06 °C.

A study was carried out on non-mammalian cells, regarded as a model system by Samsonov and Popov (2013). They investigated the influence of 94 GHz EMF on the assembly/disassembly of neuronal microtubules in *Xenopus* spinal cord neurons. Since the microtubule array is regulated by a large number of intracellular signalling cascades, it may serve as a sensitive reporter for the biochemical status of neuronal cytoplasm. They found that exposure for up to 60 min increased the rate of microtubule assembly ($p<0.01$; 24 experiments), and concluded that the effect was entirely attributable to the rapid EMF-elicited temperature jump. They reported that the intensity of the incident beam was measured with a power-calibrated crystal detector, and that each 1 mW of the forward radiation launched a wave with a nominal power density of 310 W/m^2 into the cell layer under the waveguide aperture. Positive controls were not included in the study design.

4.1.7 Conclusions on RF cell studies

A large number of *in vitro* studies dealing with several biological endpoints have been carried out, including studies on combined exposures to RF and chemical agents. Most of them do not indicate an effect of the exposure. Nevertheless, in some investigations effects on parameters related to oxidative stress are reported and in a few cases some slight and transient variations relative to to sham-controls have been recorded. Moreover, the ability of RF exposure to induce adaptive response has been confirmed. These results should be repeated by independent investigators to draw firm conclusions.

4.2 Animal studies

The 2014 SSM Council report concluded on the animal studies involving exposure to RF electromagnetic fields that they provided weak indications of possible effects on oxidative stress and brain function including behaviour and emotionality. Single studies gave indications for genotoxicity, effects on hormones, glucose, male fertility and reproduction, and needed replication. The studies published in the past year do not fulfil this requirement.

4.2.1 Brain function and behaviour

Maaroufi et al. (2014) exposed or sham exposed groups of 6 Long-Evans rats to 900 MHz RF EMF for 1 hour per day during 21 days. The rats were free roaming and the calculated whole-body SAR levels varied from 0.05–0.18 W/kg. There were two exposed groups. In the first one, EMF exposure was combined with an iron overload by daily intraperitoneal (ip) injection of ferrous sulphate in physiological saline during the exposure days. Iron overload was suggested to be linked with neurodegenerative disorders, including Parkinson's and Alzheimer's diseases. The second group received daily ip injections of physiological saline only. On days 1–8 after treatment, the reference memory was tested in a Morris water maze. On days 14–20, the working memory was assessed in an eight-arm radial maze and on day 21, 22 or 23 an object recognition task was performed. After this, the animals were killed and the brains removed for analysis of monoamines and oxidative stress parameters that were hypothesized to be increased due to the iron overload. No effect of any treatment was observed on reference or working memory. Spatial and non-spatial changes in the object recognition test were impaired in the EMF-only group ($p<0.05$), while in the EMF plus iron overload group only spatial changes were impaired ($p<0.05$). The monoamine levels and oxidative stress parameters were affected in both groups, with the direction and size of the changes depending on the brain region and treatment. In general, the changes in monoamines were larger in the EMF-only group, but this was not obvious for the oxidative stress parameters. No clear overall effect was observed for any of these parameters. The iron overload did not interact with the EMF exposure.

Shirai et al. (2014) exposed three generations of Sprague Dawley rats to a 2.14 GHz mobile phone signal used in Japan. The animals were exposed for 20 hours per day at SAR levels of not more than 0.24 W/kg (high), not more than 0.08 W/kg (low) or 0 W/kg (sham). The exposure levels varied over the duration of the study, since the animals were exposed in utero, as pups and as juveniles. Pregnant animals (4 per group) were exposed from gestational day 7 to weaning and then their offspring (4 males and 4 females per dam, respectively) were continuously exposed until 6 weeks of age. At an age of 11 weeks the offspring was mated and the procedure repeated. This was also done in another cycle with the next (third) generation. The whole experiment was performed in duplicate. All pups were tested at 6–12 days after birth for surface righting and negative geotaxis reflexes and at 13–19 days for the mid-air righting reflex (both developmental parameters). At an age of 7 weeks an open field test (testing for anxiety) was performed on the animals not used for further breeding, while at 9 weeks they were subjected to a water maze test of memory. No effect of exposure was observed on any of the investigated parameters in any of the three successive generations.

Several other studies also investigated effects of RF EMF on the brain, but cannot be interpreted due to missing or incomplete dosimetry. Yilmaz et al. (2014), Junior et al. (2014), Saikhedkar et al. (2014)

4.2.2 Hearing

Seckin et al. (2014) investigated the effect of exposure to 900 or 1800 MHz mobile phone signals during pregnancy and after birth on cochlear development in Wistar rats. The dams were exposed for 1 hour per day starting on the 12th day of pregnancy until delivery and this schedule was continued on the new-born animals for 21 days. The electric field levels in the cages of the free roaming animals varied for 900 MHz from 9–25 V/m [0.08–0.6 W/kg] for the dams and 19–25 V/m [0.35–0.6 W/kg] for the new-borns. For 1800 MHz these values were 9–18 [0.08–0.31 W/kg] and 10–18 V/m [0.1–0.31 W/kg], respectively. After the exposures [interval not mentioned] the function of the inner ear was determined by measuring distortion product otoacoustic emissions. No differences between exposed and sham-exposed groups were observed. However, electron microscopic evaluation of the middle segment of each cochlear turn revealed a decreased number of normal cells and an increased number of apoptotic and necrotic cells in animals exposed to 1800 MHz ($p=0.002$) and an increased number of apoptotic ($p=0.019$) and necrotic cells ($p=0.03$) after 900 MHz exposure. [It is not clear whether the control group was sham-exposed; therefore this study cannot be used in health risk assessment.]

Maskey et al. (2014) exposed male ICR mice to an 835 MHz Korean mobile phone signal at a whole-body SAR of 4.0 W/kg for 8 hours per day during 3 months. Immediately after the exposure period, auditory-evoked brainstem responses (ABR) were recorded. After that, the brains were removed and immunohistologically tested for glycine receptor (GlyR) activity under the assumption that a decrease in the number of GlyR immunoreactive cells in the auditory system is associated with hearing loss. The threshold for ABR was significantly increased in the exposed group ($p<0.001$), while in most brain sections the number of GlyR was reduced ($p<0.05$–0.0001). [Exposure to an SAR of 4.0 W/kg is a significant systemic challenge to a mouse with a metabolic rate of 4–7 W/kg under thermal neutral conditions. It cannot be excluded that the observed effects are the result of heating.]

4.2.3 Genotoxicity, oxidative stress

Akbari et al. (2014) exposed Sprague Dawley rats to a 900 MHz mobile phone base station signal at a power density of 0.68 mW/cm^2 (6.8 W/m^2) with or without concomitant administration of vitamin C. The RF exposure was for 4 h per day during 45 days. Immediately after the last exposure the brain was removed and processed for biochemical analysis. Exposure to RF alone resulted in decreased activities of superoxide dismutase, glutathione peroxidase and catalase, and an increase in lipid peroxidation. When vitamin C was administered before each exposure, the levels were not different from those in sham-exposed animals. The authors conclude that the RF exposures lead to an increase in oxidative stress in the rat brain.

Cetin et al. (2014) exposed or sham exposed pregnant Wistar rats to 900 or 1800 MHz 217 Hz pulsed modulated RF EMF, for 1 h per day, 5 days per week during pregnancy. Following delivery, the offspring was exposed for up to another 6 weeks. The exposure was delivered by an antenna that the animals faced so the SAR level varied over the body. The mean whole-body SAR level was stated to be 0.15 ± 0.10 W/kg; the level in the brain was higher, but not stated. Also it is not clear whether corrections were made for the size of the animals, which is particularly relevant for the exposures of the new-born animals. At 4, 5 and 6 weeks of exposure of the new-born animals, groups of 8 animals were killed and their brain and liver tissues processed for biochemical analysis. The activity of lipid peroxidation in the brain in the exposed groups at all ages was not different from that in controls, while in the liver it was increased for both frequencies at all ages. Glutathione peroxidase in both brain and liver was decreased at 4 and 5 weeks, but not significantly at 6 weeks. Glutathione levels in brain and liver were not different between exposed and control groups. Vitamin A levels were increased in the brain and decreased in the liver at all ages and for both frequencies. The same was the case for β-carotene levels in both tissues, except that at 6 weeks in the brain there was no difference between exposed and controls. Vitamin E levels were not affected. These results indicate an increase in oxidative stress in the brain and liver of growing rats under these conditions of exposure.

Furtado-Filho et al. (2014) exposed rats during pregnancy and the offspring up to 30 days to a 950 MHz field. Exposure was for 30 min per day. The average whole-body SAR in the pregnant animals was stated to vary from 0.03 W/kg on the first day to 0.01 W/kg on the 21st day of pregnancy. In the new-born animals the SAR was calculated to be 0.88 W/kg, in the 6-day old ones 0.51 W/kg, in the 15-day old ones 0.15 W/kg and in the 30-day old rats 0.86 W/kg. After the last exposure the animals were killed and the liver was removed for biochemical analysis. Lipid peroxidation was lower in the new-born exposed group, but did not differ from the sham-exposed controls in the other age groups. Some fatty acids were reduced in the exposed group, but the age of the animals is not indicated so this result cannot be interpreted. No effect of exposure was observed on protein oxidation. The index for DNA damage was found to be reduced in the 15-day old group and increased in the 30-day old group. The expression of the antioxidant enzyme catalase in the liver was lower in the new-born animals, but did not differ between exposed and control groups at the other ages. So except for some minor transitory changes in new-born animals, no effect of this RF EMF exposure on oxidative stress was observed.

The following two studies are missing important information on exposure and experimental details Motawi et al. (2014), Ragy (2014).

4.2.4 Cardiovascular system

Sisodia et al. (2013) exposed or sham exposed Swiss albino mice (10 per group) for 2 hours per day during 30 days to a 10 GHz electromagnetic field at an SAR of 0.18 W/kg [it is likely that a significant variation of the SAR value was present, since the cage containing the animals was exposed from one side]. A third group received the same 10 GHz exposure but was also orally given Prunus avium (wild cherry) fruit extract 1 hour before each daily exposure. After the exposure period, blood was collected and a number of haematological parameters assessed. In the animals exposed to RF only, a decrease in haemoglobin, monocytes, packed cell volume, red blood cells and mean corpuscular haemoglobin concentration was observed ($p \leq 0.01$), whereas white blood cells, lymphocytes, erythrocyte sedimentation rate and mean corpuscular volume were increased ($p \leq 0.01$) compared to the sham control group. Blood cholesterol, alkaline phosphatase and lipid peroxidation were also increased ($p \leq 0.01$), whereas blood glucose, total protein, acid phosphatase and glutathione levels were decreased ($p \leq 0.01$). Also histopathological alterations in blood cells were observed. Administration of the Prunus extract resulted for most parameters in a reduction of the difference between the RF and sham-exposed groups, but the difference generally remained significant.

A study by Meral et al. (2014) is missing important information on exposure.

4.2.5 Physiology

Taberski et al. (2014) used 16 Djungarian hamsters to investigate the effects of RF exposure using non-invasive methods. The animals were whole-body exposed continuously to a 900 MHz GSM signal at a SAR of 0 (sham), 0.08, 0.4 or 4 W/kg. A week of exposure was followed by a week of sham-exposure; the order of SAR levels in the weeks of exposure was random. Once per day, an infrared photograph was taken of the animals in their cage. This was used to determine the average temperature of the fur of the back of the animals as a surrogate for skin temperature, and that of the cornea of the eye as a surrogate for body temperature. Oxygen, carbon dioxide and humidity were measured continuously in the ambient and exhaled air. Food and water consumption, as well as body weight were recorded once per week. No effects on any parameter were observed for the lower SAR values. Only with a SAR of 4 W/kg the fur temperature was increased on average by approximately 0.5 °C ($p<0.001$), while the temperature of the cornea was not affected. Food consumption was lowered ($p<0.05$), while water consumption and body weight were not affected. The production of carbon dioxide was decreased only during the day ($p<0.01$), while no effect was observed on oxygen consumption. The results show that even at a whole-body SAR of 4 W/kg the body core temperature is being kept constant. The energy uptake from the RF-EMF exposure is compensated by a reduction in metabolism (or vice-versa, as the authors suggest).

In a study that received considerable media attention, but that is less relevant for human health, Engels et al. (2014) studied the orientation behaviour of migratory robins. They kept the animals in cages and registered the compass direction in which they wanted to fly. When the wooden hut in which the cages were kept was not screened from environmental broadband electromagnetic fields, the direction of flight showed a larger variability than when the EMF was screened by two orders of magnitude. Introducing an artificial EMF in the screened environment resulted in a similar variability as in the unscreened situation. Similar experiments were performed in a rural environment with lower environmental EMF levels than in the urban environment used in the initial experiments. In this rural environment no effect on magnetic orientation was observed. The fact that the effect only occurs in environments with relatively high background EMF levels might explain why in general migration of birds is not affected by this phenomenon, since they tend to be at enough distance from the higher EMF levels not to be influenced by them. But the experiments show that in principle the behaviour of birds may be influenced by external EMF. [Since humans do not have similar magnetic field orientation capabilities, the effect has no meaning for human health risk assessment.]

A study by Cam et al. (2014) is not included since it is missing important information on exposure and has severe weaknesses in the design.

4.2.6 Fertility

Shahin et al. (2014) exposed or sham-exposed groups of 20 Swiss mice to continuous-wave 2450 MHz EMF for 2 hours per day during 30 days. The average whole-body SAR was 0.018 W/kg. One day after the last exposure, blood samples were taken and the testes removed. A significant decrease in sperm count ($p<0.001$) and sperm viability ($p<0.01$), a decrease in seminiferous tubule diameter and degeneration of seminiferous tubules were observed in the exposed group. Also a reduction in the activity of testicular 3β-hydroxysteroid dehydrogenase (3β-HSD, a crucial enzyme in the steroid biosynthesis pathway) and plasma testosterone levels as well as an increased expression of testicular nitric oxide synthase were observed. Total reactive oxygen species (ROS) production in various tissues including testis ($p<0.001$) was increased, as was the level of nitric oxide and malondialdehyde ($p<0.01$). The levels of various antioxidant enzymes were decreased. This indicates an increased oxidative stress in the testis.

Dasdag et al. (2014) exposed Wistar rats to 2450 MHz EMF for 24 hour per day during 12 months. The average SAR_{10g} to the testes was calculated to be 0.001 W/kg. [The RF signal was stated to be representing exposure to a Wi-Fi signal, but it is not the same.] Immediately after the last exposure, the rats were sacrificed and the reproductive organs were removed. Some parameters were found to be significantly different from the sham exposed group: head defects in spermatozoa were increased ($p<0.05$), while weight of the epididymis and seminal vesicles, seminiferous tubules diameter and tunica albuginea thickness were decreased ($p<0.01$, $p<0.001$, $p<0.0001$). No differences were observed in other parameters: sperm motility, concentration, tail defects and total morphological defect, and weight of testes and prostate.

Trosic et al. (2013) investigated exposure to 915 MHz RF EMF on the reproductive organs of male Wistar rats. The animals were exposed or sham-exposed for 1 h day during 14 days at a whole-body SAR of 0.6 W/kg. After the last exposure, the testes were removed and the quality of the spermatozoa and the morphology of the tissue examined. No significant differences were observed for any parameter between the exposed and sham-exposed groups.

The study by Kumar et al. (2014) is missing important information on exposure and is therefore not included.

4.2.7 Conclusions on RF animal studies

In previous reports increased oxidative stress has been reported in brain and other tissues (SSM, 2013, SSM, 2014), but a significant number of studies could not be interpreted due to missing or incomplete dosimetry or problems in the study design. Both trends continue in this year’s review. So it seems that exposure to RF electromagnetic fields is capable of inducing increased oxidative stress under various circumstances in several tissues, but it is not a ubiquitous phenomenon and there is no obvious exposure-response effect. Why this is the case is not clear.

A general trend in all the different assays is that of mixed results. Two studies on effects on memory were contradictory. In the first, exposure for 1 h per day to SARs of 0.05–0.18 W/kg resulted in some effect on spatial memory (but not in reference and working memory), while in the second, lifetime exposure for 20 h per day to SARs up to 0.25 W/kg did not result in any effects on reflexes, mood and memory in three successive generations.

Studies into the effect of RF EMF on the testes and the quality of sperm also provided mixed results. Two studies with low exposure levels (SARs of 0.018 and 0.001 W/kg) show effects, while one study with a significantly higher level (SAR of 0.6 W/kg) does not.

Finally a study into metabolism and temperature regulation showed that even with exposure to whole-body SARs of 4 W/kg, Djungarian hamsters are capable of maintaining a constant body temperature by adjusting their metabolism.

4.3 Human studies

The previous report (SSM, 2014) concluded that the results published in 2012/2013 were inconclusive with regard to cognitive effects and that effects of RF – EMF on the central nervous system as measured by the waking EEG should take into account that effects might vary with age and might be different in patients with CNS-related pathologies. Furthermore, sleep studies revealed that RF – EMF effects are neither limited to the spindle frequency range nor to NREM sleep. No effects of RF exposure on physiological parameters have been observed. Effects of exposure on temperature regulation and pain desensitization have been observed in single studies, and need confirmation.

Since then 13 papers have been published addressing effects on different outcomes: sleep, resting state, waking, brain activity, event-related potentials, cortical excitability, heart rate variability, symptoms, skin blood flow and heat perception.

4.3.1 Sleep

Nakatani-Enomoto et al. (2013) investigated possible effects of W-CDMA exposure on subjective perception of sleep quality, sleep structure and the EEG power spectrum during sleep. Exposure lasted for three hours and started 5 hours prior to sleep. The sample comprised of 19 subjects (12 males and 7 females) aged 22-39 years. Exposure (sham or real) was applied in a double-blind, counterbalanced design in two consecutive nights immediately following an adaptation night. The exposure consisted of three 1h-blocks separated by 5 min breaks, in which batteries were replaced. A not further specified phone controlled by a base station generator was used for exposure. Peak spatial SAR10g values were calculated for a Japanese human head model resulting in 1.52 W/kg for the head and 0.13 W/kg for the brain. The location of the maximum was not specified. In this study none of the investigated endpoints: sleep stages and derived variables, EEG power spectra (calculated for six locations) of stages wake and NREM2 (analysed for frequency bands, not for narrow frequency bins), spindles as well as subjective ratings on sleep quality was affected.

4.3.2 Resting state brain activity: electroencephalography and fMRI

The impact of RF-EMF electromagnetic fields on the resting state brain activity was investigated in two studies with EEG as method and in one fMRI study.

In a comparatively large sample of 72 healthy subjects (35 females and 37 males, mean age 24.5 ± 5.4 years), Perentos et al. (2013) investigated the impact of pulsing of a GSM900-like RF signal on the resting EEG. In one single recording session participants received four 30 min intervals with 5 exposure-free min at the beginning and at the end and 20 min of exposure: sham, continuous RF, DTX pulsed RF, and DTX pulsed low-frequency magnetic fields with 4 min breaks between exposure 30 min intervals. The order of exposures was counterbalanced and randomly assigned in a double-blind cross-over design. The EEG was recorded continuously during the 2-h session. The recording device was protected against RF interference by shielding and filters. Exposure was applied by a specially constructed handset mimicking the spatial exposure characteristics of GSM phones. Peak spatial SAR10g was measured in a phantom: 1.95 W/kg for the continuous wave condition. The DTX signal used the same amplitude resulting in much lower SAR values. The peak magnetic induction was 25 µT at the surface of the handset. The authors exclusively looked at the alpha-band (8 – 12.75 Hz) in the EEG recorded with eyes open and observed a significant decrease in the power spectra during pulse modulated RF exposure, which is not in line with previous observations indicating an increase in alpha power under RF exposure. Since the EEG spectral power with pulse modulated RF exposure was not different from continuous wave RF exposure the authors concluded that their results do not support the hypothesis that “pulsed” RF is required to produce EEG effects. DTX-like ELF magnetic exposure did not affect alpha power. No significant pairwise differences in alpha power between exposure conditions have been observed in the post exposure period.

Suhhova et al. (2013) investigated effects of a 450 MHz exposure modulated at 40 Hz on the resting state waking EEG with eyes closed in a sample of 15 subjects (6 females and 9 males, 23 – 32 years). Following a baseline assessment two randomly assigned exposure levels were considered in a single-blind design: psSAR1g = 0.303 W/kg (field strength 24.5 V/m) and SAR_{1g} = 0.003 W/kg (field strength 2.45 V/m. This set-up (session) was repeated on the same day after a 15 min break with a reversed order of the two real exposures. Exposure was delivered by a signal generator, a modulator, an amplifier and a quarter-wave antenna located 10 cm from the left side of the head. Each exposure condition consisted of five 2 min cycles with 1 min exposure off and 1 min exposure on. The first 30 s of the 1 min segments were used for calculating deviations between on/off as percentages. The same segmentation was done for the reference condition. (Note: This methodological approach leads to an increase between on and off also in the reference condition amounting to a “change” of at least 10 %). Results showed a statistically significant increase in the EEG power in three of four EEG frequency bands: beta2, beta1, and alpha frequency bands at the higher SAR level, and in the beta2 frequency band at the lower SAR level. In a phantom measurement artefacts from RF exposure were identified in the EEG signal. Although the disturbing 40 Hz component was removed from the EEG by filtering it is not clear whether parameter shifts or other interference with the EEG recording system may account for at least a part of the differences observed in this single-blind study.

Lv et al. (2014) used resting state BOLD fMRI signals (BOLD: blood oxygen level dependent) to analyse possible effects of a 30-min RF-EMF exposure to an LTE signal (2.573 GHz) on spontaneous low frequency oscillations. The study design was double-blind, cross-over, randomized and counter-balanced. Assessments of spontaneous low frequency oscillations were made prior to and after 30-min of exposure. Eighteen subjects (6 females and 12 males) in the age range from 19 to 35 years (mean age: 24.9 ± 3.9 years) participated in the study. Subjects had test sessions on two consecutive days with the following assessments: structural MRI, pre-exposure resting state fMRI, RF-EMF exposure (real or sham) and post-exposure resting state fMRI. Exposure was delivered by a signal generator, amplifier, and a dipole antenna located on the right hand side of the head. Structural MRI data were used to model and calculate individual SAR distributions. The delivered power of the antenna was measured and adjusted to produce a mean spatial peak SAR_{10g} of approximately 1W/kg. Outcome parameters were the ALFF, which indicates the absolute strength of spontaneous fluctuations within a specific frequency range (typically 0.01 – 0.1 Hz), and fALFF, which represents the relative contribution of this specific frequency range to the whole detectable frequency range (0 – 0.25 Hz). Both parameters were individually standardized to reduce variability between subjects. A comparison of pre-post differences did not reveal significant differences in the sham exposure condition. In the real exposure condition three brain regions showed significantly decreased ALFF values (after correction of the alpha level for multiple testing). No region showed an increased ALFF or fALFF after correction. The study provided other than EEG-based evidence that RF-EMF may modulate resting state neural activity. However, deviating from EEG, it has to be kept in mind that the MRI scans involve stronger electromagnetic fields than the experimental ones.

4.3.3 Event-related potentials

Trunk et al. (2014) investigated possible effects of electromagnetic fields (duration of exposure 15 min) on event related potentials (ERP) in an oddball paradigm with 80 % frequent and 20 % rare target stimuli, with and without caffeine (co-)exposure (3 mg/kg). UMTS signals were delivered by a mobile phone controlled by test software provided by the phone manufacturer. For exposure an RF amplifier and a patch antenna mounted on a plastic headset were used. SAR values were measured in a phantom to be peak spatial SAR_{1g} = 1.75 W/kg and peak spatial SAR_{10g} = 0.73 W/kg, respectively. The study was performed in a sample of 25 healthy subjects (9 females and 16 males, mean age: 21.1 ± 3.6 years) following a double-blind 4-way cross-over design. The experimental conditions: 1) no caffeine and no mobile phone, 2) caffeine only, 3) mobile phone only, and 4) caffeine and mobile phone. While the area under the curve of the ERP and the reaction time were significantly decreased under caffeine exposure, no effects of mobile phone exposure alone or in combination with caffeine were observed for the four parameters characterizing the P300 of the ERP and the reaction time.

4.3.4 Cortical excitability

Cortical excitability was investigated in small samples of patients with epilepsy in two studies applying different methods.

Tombini et al. (2013) used paired-pulse transcranial magnetic stimulation (TMS) to analyse possible effects of a 45 min GSM-exposure on cortical excitability in 10 patients (5 females and 5 males, age range 19 – 67 years, mean: 39.9 ± 18.1 years, two women were in menopause, for the other three assessments were made during the early follicular phase) with cryptogenic focal epilepsy originating outside the primary motor area (M1). In a double-blind counterbalanced cross-over study three exposures (ipsilateral exposure (IH), contralateral exposure (CH) and sham) were applied 1 week apart. TMS was applied immediately before and following exposure. Exposure was delivered by a commercially available mobile phone equipped with a special card for test purposes. A typical GSM signal (carrier frequency 902.4 MHz, average power 0.25 W) was delivered resulting in a peak spatial SAR of 0.5 W/kg according to measurements in a phantom (Ferreri et al 2006). For weight balance and blinding an identical phone was placed at the other side of the head. Resting motor threshold (RMT) and amplitude of the motor-evoked potential (MEP) prior to exposure did not show inter-hemispheric differences. The MEP ratio for paired TMS showed the well-known inhibition-facilitation curve with inhibition at inter-stimulus intervals (ISI) of 1 and 3 ms, lack of inhibition/facilitation at ISIs 7, 9 and 11 ms and facilitation at ISI 13 ms. Differences between hemispheres were only observed for ISI 1 ms where inhibition at the ipsilateral hemisphere was lower than at the contralateral side. Following exposure there was no effect on RMT. The MEP amplitude revealed a significant hemisphere x condition x time interaction, which was due to a significant reduction of amplitude in the same hemisphere after EMF exposure of the contralateral side. The MEP ratio resulting from paired-pulses showed a significant increase at the contralateral hemisphere after exposure at the contralateral hemisphere as compared to the pre-exposure situation. These results indicate that EMF modulates cortical excitability in epileptic patients only when exposure was applied contralateral to the epileptic focus.

Curcio et al. (2014) used EEG to study the impact of a GSM-like signal on the spiking rate, power spectra and coherence data in a double-blind, crossover and counterbalanced design. Sessions were separated by one week. Before, during and after a 45 min real- or sham-exposure EEG was recorded in 12 patients (7 males and 5 females in the age range 21 – 79 years, mean age: 50.8 ± 20.9 years) with focal epilepsy. There is no information on interference between exposure and the recording device and no information on time of the day. Exposure was delivered by a mobile phone configured to transmit a GSM signal (carrier frequency 902.4 MHz, 0.25 W mean power, modulation components 217 and 8.33 Hz) resulting in a maximum SAR of 0.5 W/kg. The phone was placed in a helmet at the hemisphere where the seizures occur. An identical, but not operating phone was placed at the opposite side. EEG was recorded with 19 electrodes positioned according to the 10-20 system. The results indicate that under real exposure the spiking activity (as measured by spikes count, a spike was defined by an amplitude at least 1/3 higher than background activity and a duration less than 75 ms) tended to be lower than under sham exposure (repeated ANOVA with condition (real and sham) and session (pre, during post: $p = 0.06$). Furthermore a significantly increased power of the gamma frequency band (31 – 60 Hz) has been observed under GSM exposure as compared to sham, mainly evident in parieto-occipital and temporal areas. Coherence in the beta frequency band was higher under exposure as compared to baseline. The authors conclude that in epileptic patients acute GSM exposure slightly affects the EEG without reaching any clinical relevance. Specifically, no increased risk of incoming seizures has been observed in these patients as consequence of mobile phone use.

4.3.5 Cognition

A study by Movvahedi et al. (2014) aimed to investigate whether short-term exposure (10 min) to GSM 900 MHz electromagnetic fields has an effect on reaction time in a simple reaction task and/or short-term memory. The study was performed in 60 school children from 8 to 10 years. There is, however, too little information in the publication to be considered here.

4.3.6 Other endpoints

In the reporting period several studies investigating heart rate variability and related variables have been published, one of them also looked at perception and subjective symptoms. Furthermore one study investigated skin blood flow and another one the ability to distinguish different exposure conditions on the basis of heat perception. One of the studies investigating heart rate variability (Havas and Marrongelle, 2013) is not considered here because the publication was retracted in October 2014.

In a sample 26 subjects (12 females and 14 males, mean age: 25.5 ± 1.5 years) without cardiac or nervous system disorders between 21 and 28 years, Parazzini et al. (2013) analysed the effect of GSM exposure on nonlinear dynamics of the heart rate variability. The study was double-blind and exposures were randomly assigned in a cross-over design. Subjects were exposed by a commercial mobile phone controlled by manufacturer's test software to generate a GSM signal at 900 MHz (peak power 2 W which corresponds to an average of 0.25 W). Subjects had two test sessions (sham and real exposure) at least one day apart. Exposure is described in more detail in a previous paper (Parazzini et al., 2007). The sham condition was realized by using an identical phone, but with a resistive load on the external antenna connector resulting in no transmission. Local SAR was measured in a head phantom; the only information reported is that the local maximum SAR in the area of interest (hypothalamus and brainstem) was lower than 0.02 W/kg. All assessments were done in the morning to minimize circadian variation. No effect of exposure on nonlinear dynamics of heart rate was observed in this study.

In a double-blind randomized cross-over study Choi et al. (2014) investigated possible effects of a 32 min exposure to WCDMA on perception, eight subjective symptoms, heart rate, respiration rate and heart rate variability. The sample comprised two groups: a) 26 adults (13 females and 13 males, 28.4 ± 5.1 years), and b) 26 teenagers (13 females and 13 males, 15.3 ± 0.7 years). Exposure was delivered by a WCDMA module placed in a dummy phone, and controlled by a laptop. Double-blinding was assured by remote control of the laptop. Peak spatial SAR_{1g} was measured to be 1.57 W/kg at the left cheek. Assessment of physiological parameters was performed for a duration of 5 min at four times: pre-exposure, after 11 and 27 min of exposure, and post exposure. Data analysis is based on a comparison of changes from baseline (pre-exposure measure) by exposure separately for the two age groups. WCDMA exposure did neither in adults nor in teenagers significantly affect the autonomous system, subjective symptoms or perception.

Given that mobile phone contact increases skin blood flow (SkBF) by heating, Loos et al. (2013) investigated whether there is an additional RF-EMF specific effect on SkBF. The sample consisted of 20 healthy, young Caucasian subjects (12 females and 8 males, mean age: 25 ± 3.9 years). In two test sessions, performed at the same time of the day under constant ambient conditions, SkBF and skin temperature (Tsk) were measured by a laser Doppler system. Exposures were randomly assigned and the study was double-blind. Exposure was delivered by a commercial phone controlled by manufacturer's test software to deliver a peak 2 W (mean 0.25 W) 900 MHz GSM signal. The SAR was measured in a phantom resulting in a peak spatial SAR_{10g} = 0.49 W/kg. The sham condition was achieved by a resistive load as described above for the Parazzini et al. (2013) study. Following a 30 min rest period to stabilize Tsk, a five min baseline assessment was made. During the 20 min exposure (real or sham) measurements were made after 1, 5, 10, 15 and 20 min as well as 1, 5, 10, 15 and 20 after the exposure had been stopped and the phone had been removed. Furthermore, a heat challenge was applied 25 min after the end of exposure by locally heating both sides of the face to 44°C for one minute. During real exposure the SkBF on the exposed side was significantly higher than during sham exposure, while temperature was not significantly different between conditions. The heat challenge led to a significantly greater early peak value for SkBF at the exposed side following real exposure as compared to sham. These differences were not observed at the unexposed (contralateral) side of the face. The authors conclude that they identified specific, athermal modifications of the skin blood flow during mobile phone radiofrequency exposure.

It is well documented that RF experiments lead to a warming of the skin. If subjects are able to perceive the differential warming of real and sham exposure this severely challenges the blinding of experiments. Dorn et al. (2014) exposed subjects (15 healthy males, age range: 23 to 36 years; mean age: 28.4 ± 3.7 years) to three different exposure conditions: sham, Terrestrial Trunked Radio (TETRA, 385 MHz, pulse length 14.17 ms and a pulse period of 56.67 ms; i.e. duty cycle 25%; 17.65 Hz pulse modulation) with maximum SAR_{10g} values of 1.5 and 6.0 W/kg. Exposure was delivered by a body worn antenna fixed at the left ear: Each exposure was applied three times resulting in 9 test sessions on different days at a fixed time of the day. Skin temperature was measured at two locations close to the radiating element of the antenna. The measurements revealed a temperature rise, which was proportional to the supplied RF power with an average temperature increase of 0.8 °C (mean of two locations) for the 6 W/kg exposure condition. However, subjects were not able to distinguish between exposure conditions based on the subjective warmth perception, ensuring double-blind conditions in such an experiment.

4.3.7 Conclusions on RF human studies

The papers published since the last Council report are very heterogeneous with regard to investigated outcomes and methods. There is just one sleep study, which with a deviating method of analysis did not observe effects from RF-EMF on the power spectra during sleep. Studies on heart rate variability did also not observe exposure effects. The studies investigating neurophysiological parameters during wake showed some effects, partly with contradictory results.

4.4 Epidemiological studies

Most previous epidemiological research on RF-EMF focussed on intracranial tumours in relation to mobile phone use. In the previous report it was concluded that uncertainties remain for regular mobile phone use for more than 13-15 years and for brain tumours in children and adolescents. Several recent studies that observed an association between child development and mobile phone use do not allow differentiating between effects from RF-EMF exposure and effects from mobile phone use per se (e.g. social interaction, cognitive training). Many epidemiological studies reporting an association between chronic EMF exposure and symptoms had severe limitations, such as relying on self-estimated exposure or applying a cross-sectional design with none or minor confounding adjustment. Better designed studies relying on exposure modelling and more sophisticated design and analyses rather indicate the absence of a risk from RF EMF exposure on health-related quality of life. Nevertheless, some uncertainties remain regarding mainly high exposure levels from wireless phone use and longer follow-up times than one year. Many of the studies on other outcomes had considerable limitations and thus no firm conclusions could be drawn from these studies. In addition, the number of studies per outcome was relatively small, and consistency of findings between various studies could not be addressed.

4.4.1 Pregnancy outcomes

A systematic review of adverse reproductive outcomes in physiotherapists working with shortwave and microwave diathermy devices concluded that effects on delayed time to pregnancy (>6 months), still birth, altered gender ratio (low ratio of boys to girls), congenital malformations and low birth weight (<2500 g) have been observed, although inconsistently (Shah and Farrow, 2014).

Mortazavi et al. (2013) performed a survey aimed at evaluating the effects of maternal exposures to ionizing and non-ionizing radiation on birth weight in their offspring. They interviewed mothers after birth of their first singleton child whose new-borns' history had been registered in the neonates' screening program in Shiraz, Iran. Not included were mothers who had a chronic illness (chronic blood pressure (undefined whether high or low blood pressure), diabetes, heart diseases, chronic anaemia, renal diseases, chronic pulmonary diseases, rheumatologic diseases, or hyperthyroidism), smoking and/or drinking alcohol, other addiction, non-singleton pregnancy, congenital anomalies of the mother, placenta abnormalities, mother's age less than 20 and more than 40 and mother's weight less than 45 kg and more than 70 kg. It was not reported how many women were excluded from the analysis based on these criteria. Data were analysed using t-tests and ANOVA without consideration of any covariates. No associations between any use of mobile phone or cordless phone during pregnancy or use of cathode ray tube monitors at home and birth weight of the children were observed. Ionizing radiation sources (dental and non-dental radiography) were also not associated with birth weight.

Relevant information was not provided about who participated in the screening program and during what time period study participants were recruited. The very restrictive inclusion criteria are problematic for the generalizability of the results. While the authors describe that 1 200 new-borns were divided into exposed and non-exposed groups, it was not reported how exactly the exposure information was operationalised. In addition, the two groups were matched on age of pregnancy, sex of the new-borns and the BMI of the mother. This is a very uncommon procedure and likely to introduce selection bias in the analysis. It would be preferable to analyse the results using multiple regression modelling in a way that all relevant confounders can be considered. In conclusion, the study is not informative despite the large sample size. The observed lack of association may be true but may also be the consequence of too stringent inclusion criteria and/or lack of confounding adjustment. Further, collection of self-reported exposure data postnatally is a limitation of this study even though this procedure would be more likely to introduce reporting bias, which would be expected to result in false positive results.

4.4.2 Childhood cancer

In the UK, Feltbower et al. (2014) performed a pilot case-control study for a future investigation of brain tumours among children and adolescents aged 0-24 years. The aim of the study was to establish procedures for optimal participant ascertainment, to pilot the questionnaire and to develop the study protocol. The study was performed between 2007 and 2010. The use of mobile phones was one of several evaluated risk factors, together with breastfeeding, caesarean section, birth weight, number of siblings and contact with animals. Cases were identified through the UK Principal Treatment Centres in Leeds and Manchester. Controls were selected from general practice lists in Leeds and from friend controls in Manchester. Study participants were asked whether they had ever spoken on a mobile phone more than 20 times. 49 cases and 78 controls were interviewed (participation rate 52 % and 32 %, respectively). Logistic regression analysis was performed, adjusted for age, sex and an area deprivation index of the residential address of the child (Townsend score). The OR was 0.9 (CI 0.2-3.3) for participants answering "yes" to the mobile phone related question. Given the amount of available knowledge on mobile phone usage and exposure to RF-EMF in general in children and adolescents, it is unclear why the authors performed such a small and imprecise study in the first place, even if the purpose was to pilot the questionnaire. Also, other sources contribute to RF-EMF exposure (e.g. the use of cordless phones, if one is interested in exposure to the head), which was not assessed in this study. All in all, the study does not contribute strongly to the overall assessment of a presence or absence of a brain tumour risk in children using mobile phones. The authors claim to have applied frequency matching for age and gender but older children and females were clearly more common among controls than cases. The large age range with strong age-related increase in exposure is a challenge for the analysis and it is not clear why children aged between 0-4 years have been included in the study, since they are unlikely to use mobile phones often. The low participation rate in this study clearly demonstrates challenges for such studies with case-control design, with selection bias as a possible result. Selection bias occurs when there is a difference between the characteristics of the participants and those invited but not participated. Thus, the information and results from this study might not be representative for the population of interest.

In Switzerland, Hauri et al. (2014) conducted a cohort study to investigate the association between RF-EMF exposure from broadcast transmitters and childhood cancer with a special focus on central nervous system (CNS) tumours and leukaemia. The study was based on data from the Swiss Childhood Cancer Registry (SCCR). Information of the cancer registry was linked to the Swiss National Cohort, which contains data on all buildings, households and persons. Two strategies were used to analyse the data. First, a "time-to-event analysis" was performed. This analysis included children under the age of 16 living in Switzerland on the date of the census 2000. Incident cancer cases from SCCR were linked to the Swiss National Cohort, resulting in a data set containing date of diagnosis and potential confounders such as sex, birth order and socioeconomic status. In addition, information about potential confounding factors benzene, natural background ionizing γ (gamma) radiation, distance to a power line and degree of urbanization at the place of residence were available and could be accounted for in the analysis. Approximately 1.3 million children, including 997 cancer cases, contributed 7.6 million person years to the analysis. RF-EMF exposure from broadcast transmitters was modelled for each study participant at the place of residence. Three exposure categories were evaluated, exposure level at home <0.05 V/m, between 0.05 and 0.2 V/m, and >0.2 V/m, based on the modelled exposure values. Compared to the lowest exposure group, hazard ratios (HR) adjusted for sex, period effects, age and the environmental factors mentioned above for the exposure category >0.2 V/m were 1.03 (95 % CI 0.74-1.43) for all cancers, 0.55 (95 % CI 0.26-1.19) for leukaemia, and 1.68 (95 % CI 0.98-2.91) for CNS-tumours. For CNS-tumours, the analysis resulted in a linear increase in risk of 1.05 (95 % CI 1.00-1.10) per increase in 0.1 V/m. Sensitivity analysis taking the additional environmental exposures into account indicated that adjusting for these factors did not have material effects on the hazard ratios.

The second analysis was an incidence density cohort analysis, including 30 million person-years at risk with 4 246 cancer cases obtained from SCCR during the periods 1985- 1995, 1996-2008, and the entire period 1985-2008. This analysis used the same age group and exposure categories as the first analysis, but was only adjusted for the basic confounders age, calendar year and sex. These analyses showed approximately the same risk estimates for all cancers and leukemia as the "time to event analysis". Interestingly, for CNS-tumours, a somewhat increased risk emerged for the highest transmitter-exposed group in the time period 1985-1995 with a HR of 1.60 (95 % CI 0.98-2.61), but not for the later period of 1996-2008, where it showed a reduced HR of 0.75 (95 % CI 0.45-1.23). Over the whole time period, the HR was 1.03 (95 % CI 0.73-1.76), indicating no effect.

The main advantage for registry-based studies such as the one by Hauri et al. is that contact to study participants not is required and therefore, results cannot be biased by differential participation of cases and controls into the study. A challenge inherent of such registry-based studies is, however, that information regarding potentially confounding factors on lifestyle or residential history is usually limited. However, only very few risk factors for tumours in children are known and therefore, it is unlikely that e.g. lifestyle could represent a major confounding factor in the analysis. In line with that, all evaluated geographic confounding factors had little impact on the results. A weakness of the study is exposure misclassification since more than just broadcast transmitters will contribute to the RF-EMF exposure for children. However, the analyses for the period 1985-1995 cover a period where use of mobile and cordless phones was less prevalent. All in all, both analyses provided by Hauri et al did not provide strong evidence for an increased risk of CNS tumours in children exposed to RF-EMF from broadcast transmitters.

4.4.3 Adult cancer

Lagorio and Roosli (2014) conducted a consistency analysis to review the use of mobile phones and risk of meningioma, glioma and vestibular schwannoma (acoustic neuroma). The purpose of the systematic review and meta-analysis was to evaluate the consistency of findings across studies, to assess the sensitivity of the meta-analysis to inclusion or exclusion of studies, and to identify potential sources of heterogeneity. 47 epidemiological studies published by the end of 2012 were included into the study. For meningioma, the combined relative risks (RRs) of long-term mobile phone users ranged between 0.98 (95 % CI 0.75-1.28) and 1.11 (95 % CI 0.86-1.64) with little heterogeneity across studies. Analyses of glioma and vestibular schwannoma showed higher heterogeneity among long term users, with combined relative risks ranging between 1.19 (95 % CI 0.86-1.64) and 1.40 (95 % CI 0.96-2.04) for glioma, and 1.14 (95 % CI 0.65-1.99) to 1.33 (95 % CI 0.65-2.73 for vestibular schwannoma. According to the authors, the larger heterogeneity across estimates of glioma- and acoustic neuroma risks was due to the studies from the Hardell group. The overall conclusion was that no causal association between mobile phone use and incidence of brain tumours was found, but uncertainties regarding risk among children and long-time users warranted further investigation.

Hardell and Carlberg (2013) conducted a study that intended to use the Hill viewpoints for causality to evaluate strengths of evidence of the risk for brain tumours and use of mobile and cordless telephones. This study repeats what is already known; most analyses and discussions are mainly based on studies by Hardell et al. (Hardell and Carlberg, 2009, Hardell and Carlberg, 2013, Hardell et al., 2006a, Hardell et al., 2006b, Hardell et al., 2011, Hardell et al., 2013) and Interphone (2011, 2010). These studies were already evaluated in previous Council reports (SSI, 2007, SSM, 2010, SSM, 2013, SSM, 2014) and will not be considered any further in this report.

In France, Coureau et al. (2014) published a case-control study on the use of mobile phones and risk of gliomas and meningiomas in adults. This study, named CERENAT, included 596 (73 %) cases aged 16 years and older with a benign or malignant CNS tumour diagnosed between 2004 and 2006. The cases were identified from practitioners involved in diagnosis and therapeutic management, and from cancer registries. 1 192 (45 %) controls were randomly selected from the local electoral roll and matched on age, sex and department of residence. After exclusions of subjects for several reasons, such as acoustic neuromas, lymphomas, medullar tumours, unspecified brain tumours or missing data on regular mobile phone use, 1 339 subjects remained in the analysis; 253 cases and 504 controls for gliomas and 194 cases and 388 controls for meningioma. Data were collected as face-to-face interviews, and in addition to mobile phone use, the questionnaire covered socio-demographic characteristics, the medical history, lifestyle, and occupational and environmental data. Persons using their mobile phone for at least once a week for 6 months or more were considered to be regular users. Information concerning mobile phone model, average number and duration of calls per month, use of hands-free devices etc., were collected. Analyses were adjusted for level of education, smoking and alcohol consumption. The overall odds ratio (OR) for regular mobile phone use compared to never-use was 1.24 (95 % CI 0.86 -1.77) for glioma and 0.90 (95 % CI 0.61-1.34) for meningioma. For the category "average calling time per month" (in hours), an OR of 4.21 (95 % CI 2.00-8.87) was observed in the heaviest exposure group, corresponding to ≥15 hours call time per month. For cumulative number of calls in hours, an increase was observed in the 90th percentile, ≥896 hours (OR 2.89, 95 % CI 1.41-5.93). The same pattern was observed for cumulative number of calls, with a significant OR in the highest exposure group (OR 2.1, 95 % CI 1.03-4.31). This study has a design similar to that of the INTERPHONE study (Interphone 2010). In INTERPHONE, a pronounced increase in risk estimates was observed only in the highest exposure category. Recall bias has been regarded as the most plausible explanation for this observed pattern (Vrijheid et al., 2009), and the same might apply to the CERENAT study. In addition, the low participation rate in controls is a limitation as it may have introduced selection bias. Overall, the results of this study are in line with previous case-control studies on mobile phone usage and CNS tumours, which primarily highlight the methodological challenges when performing a case-control study on the issue. In particular, recall bias remains an issue, if cases with a disease are interviewed regarding their exposure in the past.

In Sweden, a case-control study of mobile phones and vestibular schwannoma (acoustic neuroma) was performed by Pettersson et al. (2014), using a self-administered postal questionnaire. 451 (response rate 83 %) cases aged between 20 and 69 years of age who were diagnosed between 2002 and 2007 were identified from hospitals, local acoustic neuroma registries and the Swedish Cancer registry. 710 (response rate 65 %) controls were selected from the Swedish population register, matched on age, sex and region of residence. The authors reported unadjusted ORs because of a negligible effect on the risk estimates when adjusting for several confounders such as smoking, education, marital status and parity. The odds ratio (OR) for regular mobile phone usage (defined as use of a mobile phone at least once per week during at least 6 months) compared to never or rarely usage was 1.18 (95 % CI 0.88-1.59). Analyses of cordless phone use showed an increased risk among regular users (OR 1.41 95 % CI 1.07-1.86). Exposure-response associations were observed for an increase in cumulative hours of use of any mobile phones or cordless phones. For all other investigated metrics (duration of regular use in years, time since first regular use in years, or cumulative number of calls) no consistent exposure-response pattern emerged. For instance, in terms of time since first regular use, effect estimates for long-term use (>10 years) were close to unity and highest risks were found for 5-9 years of use. Analyses restricted to histologically confirmed tumours, tended to produce lower effect estimates. Since vestibular schwannoma affects the hearing, detailed information about the history of laterality of phone use was collected. This allowed evaluating whether cases had adjusted their preferred side of phone use over time due to increasing hearing loss (reverse causality). Clear evidence for such a pattern was seen: a large proportion of cases and only a small proportion of controls have changed their preferred side of use. Consequently, ORs for ipsilateral use were 1.00 (95 % CI 0.69-1.49) for the time period of about 10 years before the diagnosis, but clearly below unity for time periods closer to the time of diagnosis. As a consequence, a reverse pattern was seen for contralateral use.

All in all, the results of this study indicate that mobile phone use may assist affected persons in the detection of the tumours (detection bias). Further reverse causality seems also to play a role for laterality analyses. For cordless phone use the results are also compatible with an increased risk although no indication for a risk increase was seen in long-term cordless phone users. Unfortunately, data on history of laterality was not collected for cordless phone use to evaluate potential detection bias. Maximum output power of cordless phones is considerably lower than for mobile phones. However, average output power of cordless phones is expected to be similar to UMTS phones. Further, cumulative duration for cordless phone use was found to be longer than for mobile phone use in the past (Lauer et al., 2013).

In a letter to the editor, Hardell and Carlberg (2014) express their concern regarding Pettersson et al`s use of reference category for regular users. Petterson et al. (2014) used "never or rarely" use as reference category separately for mobile and cordless phone use. When a person was defined as never or rarely user for cordless phones, one could not exclude the possibility of exposure from mobile phones and thus radiofrequency fields, and vice versa. Thus, Hardell and Carlberg suggest that never or rarely users both for mobile and cordless phone use should be used as reference category in the analyses to reduce misclassification. In a reply, Pettersson and Feychting (2014) performed these new analyses, which resulted in an OR of 1.04 (95 % CI 0.68-1.60) for regular mobile phone use and 1.22 (95 % CI 0.80-1.85) for cordless phone use, slightly lower than for the initial analyses. In addition, Hardell and Carlberg pointed out discrepancies regarding the number of cases and controls in the analyses of laterality. In their answer, Pettersson and Feychting explain this discrepancy by the use of a matched design, where incomplete case-control sets were excluded, which reduced the number of cases and controls in the stratified analyses as compared to the overall analyses.

In South Korea, Moon et al. (2014) conducted a case-control study to investigate the association between vestibular schwannomas and the use of mobile phones. 119 (89 %) patients with pathologically confirmed vestibular schwannomas, diagnosed between 1991 and 2010 were recruited from a hospital in Seoul. 238 controls who had visited the hospital for a routine medical check were recruited and matched to cases based on age, sex, general health condition and date of diagnosis (reference date). Information regarding participation rate among controls was not provided by the authors. Cases and controls were interviewed by telephone using a modified questionnaire based on the INTERPHONE study (2010). 54 % of cases were mobile phone users at the date of diagnosis, as were 85 % of controls. The amount of mobile phone use was categorised by duration in years, minutes per day and cumulative hours of use. The OR for duration of mobile phone use (in years) was 0.96 (95 % CI 0.91-1.01). Similar risk estimates were observed for the categories minutes per day and cumulative hours of use. In addition, a case-case analysis was performed to evaluate the association between tumour size and location, and amount of mobile phone use. The average tumour volume among regular users (defined as usage of mobile phones for at least once a week for 6 months) was significantly larger compared to non-regular users. When comparing tumour volume according to duration, daily use and cumulative number of hours, a statistically significant larger tumour size was observed among heavy users compared with light users for both daily use and cumulative number of times a mobile phone was used. No confounding factors such as age or gender were considered in this comparison.

The results of the case-control analysis appear improbable and are most likely erroneously calculated, because of the much higher proportion of mobile phone users among controls than among cases, one would expect risk estimates considerably below unity. In principle, the results of the case-case analysis could be interpreted as a potential effect of mobile phone use as a tumour-growth promoting factor. However, a prominent alternative explanation for this finding is reverse causation: Vestibular schwannomas are slow growing tumours that may be better detected by affected persons if they call more frequently, or longer. This is due to the fact that vestibular schwannomas typically affect hearing in one ear, and using a mobile phone may alert a person to changes in hearing capabilities between their ears. In this case, the increased risks would have resulted from detection bias. Evidence for such an effect emerged from the laterality analysis by Pettersson et al. (2014).

4.4.4 Reproduction

Since the last Council report (SSM, 2014), four meta-analyses and/or reviews regarding use of mobile phones and effect on sperm quality have been published (Adams et al., 2014, Barazani et al., 2014, Dama and Bhat, 2013, Liu et al., 2014a). Both *in vitro* and *in vivo* parameters were evaluated. With some exceptions, all the studies suggest mobile phone use or radiofrequency exposure to have negative effect on various semen parameters. However, several advisory groups do not support such a conclusion because of inherent weaknesses of these studies in terms of exposure assessment and study participant selection (AGNIR, 2012, FHI, 2012:3).

Semen quality might be affected by a number of environmental and lifestyle factors. Jurewicz et al. (2014) conducted a cross-sectional study to investigate several potential environmental factors, including the use of mobile phones, in relation to a number of semen parameters. The study population consisted of 344 men who were attending infertility clinics for diagnostic purposes. There was no information regarding non-participation. The authors assessed mobile phone use, BMI, smoking, alcohol consumption, use of loose underwear (boxer shorts), coffee intake, physical activity and use of sauna. Mobile phone use was categorised as year of use with 0-5 years as the lowest category and 11-25 years as the highest category. Sperm quality was evaluated as the volume, concentration, percentage of motile sperm cells, atypical sperm as head-, neck- and tail abnormalities, and DNA fragmentation index. Mobile phone use was reported to affect three out of the eight investigated outcomes. It is well known that the quality of semen is strongly influenced by age (Singh et al., 2003). Although age information was obtained, it was unfortunately not accounted for in the analysis (or any other potential lifestyle related confounders). The exposure assessment is also a problem, since there is no evidence that exposure of the testicles is correlated with self-reported mobile phone use.

These two limitations make this study uninformative regarding a potential effect of mobile phone use on sperm quality.

Rago et al. (2013) performed a cross-sectional study to evaluate sperm quality among mobile phone users. After examination of 250 men, 187 men were excluded due to various health or lifestyle related reasons that might alter sperm quality, such as endocrine diseases, being overweight or smoking. 63 healthy men with normal body weight in the age group 18-35 years were retained for the analysis. Semen analyses were performed for volume, density, total count, morphology motility, apoptosis, mitochondrial membrane potential, chromatin compaction and DNA fragmentation. Based on a questionnaire on use of mobile phones, the participants were divided into four exposure groups based on their average mobile phone use per day in hours (no use, <2 hours, 2-4 hours, >4 hours). Results were reported as mean ±SEM without any adjustment for potential confounders. The authors reported an effect on DNA fragmentation in a subgroup of men carrying the phone in the trousers, but none of the other evaluated sperm characteristics differed statistically significantly across the exposure categories.

Exposure categorisation as performed in this study was poor, given that the exposure to the testes is very low when a person uses his or her mobile phone. Further, it is unclear whether exposure is relevant if the mobile phone is carried in the trouser pocket in stand-by mode since data transmission is minimal. Other sources also contribute to RF-EMF exposure but were not assessed here. In addition, the use of mobile phones as such may be related to a range of lifestyle factors (e.g. stress at work and sleep patterns), which in turn could have an impact on sperm quality. The fact that such potentially confounding factors were not accounted for in the analysis represents a major drawback of the study, which is essentially uninformative as to the effect of mobile phone use on sperm quality.

4.4.5 Self-reported electromagnetic hypersensitivity (EHS) and symptoms

In this chapter the two terms idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) and electromagnetic hypersensitivity (EHS) are used as synonyms according to the use of the terminology in the original papers.

In a Dutch survey, the symptom pattern of individuals suffering from IEI-EMF was compared with the symptom pattern as reported in a general population sample, and with people with general environmental sensitivity (GES) Baliatsas et al. (2014). Such other general sensitivities included for example chemical substances, smells, noise, light, colour, or changes in cold and warm environments. The study population was randomly selected from 21 practices of the primary care database of the Netherlands Institute for Health Services Research. A written questionnaire about various environmental sensitivities including those to mobile phones or other electrical devices-related exposure and a 23-item symptom list from the Symptoms and Perceptions scale was sent to 13 007 individuals. The 5 933 respondents were classified as non-sensitive (n=5,073), GES (514) and IEI-EMF (202). The GES and the IEI-EMF expressed considerably more symptoms than the non-sensitive group, but the symptom pattern was similar for both sensitive groups. IEI-EMF individuals scored also high on the GES score and approximately 40 % of the IEI-EMF group actually met the criteria of the GES group. The largest difference between the IEI-EMF group and the non-sensitive group was observed for pain/pressure in chest and heart region (OR=2.5, 95 % CI: 1.6–3.8), heart palpitations/awareness (2.3, 1.6-3.4), dizziness or feeling light-headed (2.3, 1.7–3.3) and sleep problems (2.2, 1.5–3.0). The higher prevalence of reporting of symptoms in sensitive groups compared to a control group as such is to be expected. The study confirms previous research that IEI-EMF is not associated with a specific symptom pattern. In addition, it indicates that different types of self-reported environmental sensitivities likely do not represent separate entities. The study did not address the question whether symptoms can indeed be caused by EMF exposure.

A similar research question was addressed in a Swedish survey that compared EHS individuals regarding their self-reported chemical sensitivity as well as noise sensitivity with a general population sample (Nordin et al., 2014). A total of 117 EHS participants were recruited by advertisement and age and gender matched to a sample of 48 controls, who were randomly selected from the population registry. Data collection took place between December 2005 and April 2006. The EHS individuals scored higher on both sensitivity scales, but the difference between the EHS and the control group was more pronounced for the Noise Sensitivity Scale. The two scales as well as various sensitivity subscales were highly correlated (Pearson correlation coefficient ≥0.6). In line with the study by Baliatsas et al (2014), this study also supports the idea that various self-reported environmental sensitivities have considerable overlap. However, it does not provide information whether EMF sources can indeed cause symptoms.

Gomez-Perretta et al. (2013) conducted a re-analysis of a previous study of (Navarro et al., 2003) by excluding additional 13 subjects from the original datasets, mainly because rainfall during the GSM mobile phone base station measurements for these subjects may have resulted in erroneous exposure estimates. Potential confounding factors were evaluated, but since none of the factors had an effect on the risk estimates for GSM mobile phone base station exposure, no confounder was considered in the analysis. Based on a total of 88 study participants, 17 out of 19 non-specific symptoms were associated with measured GSM exposure at the place of residence. The study suffers the same limitation as the original study (see summary in the second annual report from SSI's Independent Expert Group on Electromagnetic Fields, 2004). Recruitment of the participants was not described and may thus be subject to selection bias. In addition, the sample size was very small and the cross-sectional design did not allow evaluating whether the non-specific symptoms occurred after the exposure or before. Rainfall during the exposure measurement may have affected exposure assessment somewhat but is unlikely to have had a major effect, thus justifying a re-analysis (and re-publication) of these data.

To test the hypothesis that the duration of mobile phone use is an important determinant of psychological health in adolescents, a cross-sectional study was conducted in seven Japanese high schools (Ikeda and Nakamura, 2014). From 2 929 invited students, 2 698 students (participation rate 93.3 %) completed a questionnaire on their mobile phone use, which was defined as the cumulative time of using the phone for calling, e-mailing and browsing. In addition, they filled in a mood score ("Mood Inventory"), which evaluates five subscores:

tension and excitement, refreshing mood, fatigue, depressed mood and anxious mood. Mood scores were compared across quartiles of mobile phone usage, and data were analysed by means of ANCOVA adjusted for sex, school year, participation in sports club activities, number of hours spent sleeping, and school. In this collective, age was not reported, but since high school students of grade 1-3 were included, participants were most likely to be aged between 12 and 15 years. Mobile phone use for various activities added to about 24 hours per week on average. Higher usage of mobile phones was associated with tension and excitement, fatigue and depressed mood, but not with anxious mood and refreshing mood. The study had a high participation rate. RF-EMF exposure from various types of mobile phone use is very different, with virtually no exposure when using the phone for e-mailing. Thus no conclusion can be drawn whether the observed associations are due to RF-EMF exposure from mobile phones or due to other factors related to mobile phone use as such, but this was also not a goal of the investigators. The cross-sectional design of the study implies that it is impossible to exclude reverse causality, in that it is not clear what was first, extensive mobile phone use followed by symptoms; or the other way round, impaired well-being followed by increased mobile phone use.

A similar cross-sectional survey was conducted in adolescents living in New Zealand (Redmayne et al., 2013). A questionnaire about mobile phone and cordless phone use, presence of a Wi-Fi at home and symptoms was filled in during school hours between June and October 2009. In total, 373 adolescents took part in the survey (participation rate: 85 %) with a mean age of 12.3 years. Information on well-being included whether over the previous month, participants had experienced problems falling asleep, waking up at night, were tired during school, had had headaches, been feeling down or depressed, had experienced tinnitus or had had a painful texting thumb. Data were analysed using ordinal regression. Confounding variables were selected for each model separately. Considered variables were having a cold or flu, light-out time and being woken-up by a phone, SES, use of headphones when calling, age, sex, cordless phone use, use of earpiece. More than three quarters of the adolescents owned a cell phone and an additional 13 % reported to regularly use someone else's phone. Several symptoms were related to mobile phone use, such as increased headache in relation to number of long (>10 min) mobile phone calls per week (adjusted OR 2.40, CI 1.19-4.83) and duration of cordless phone calls per day (adjusted OR 1.74, CI 1.05-2.90) and use of wireless headsets (adjusted OR 2.23, CI 1.10-4.53), painful "texting" thumb with texting on the mobile phone and tinnitus with frequency of cordless phone use. Waking up during the night was less likely for those with Wi-Fi at home (adjusted OR 0.7, CI 0.4-0.99) but increased for those using headsets. Tiredness at school was strongly related to being woken at night by a mobile phone (OR 3.49, CI 1.97-6.2). This study used mobile phone and cordless phone call as proxy for RF-EMF exposure. No attempt was made to consider additional exposure relevant factors other than duration and frequency of mobile phone use and headset. Due to the cross-sectional design, no firm conclusions about causality can be drawn.

Szyjkowska et al. (2014) analysed data from a Polish survey on symptoms and mobile phone use conducted in 2005. The main inclusion criterion was being an owner of a mobile phone but no details about the recruitment process were provided. Out of 1 800 questionnaires that were distributed the response rate was 33% and 587 could be included in the analysis. Using a mobile phone for at least 30 minutes per day was significantly associated to headache, memory loss and warmth behind/on ear. This study does not provide sufficient detail about the recruitment process. A rationale for only including mobile phone owner in the study is not given and it is also not clear how this could be achieved in practice. To have non-exposed subjects would be preferred for such a cross-sectional survey to expand the exposure range.

The authors report that confounders were considered in the analysis, but unfortunately they did not state which ones. The relatively low participation rate and the cross-sectional design is a limitation for this study, and it cannot be excluded that selection and/or reporting bias strongly contributed to the results. In summary, the study is not informative regarding the generation of symptoms in mobile phone users.

In a recent paper by Byun et al. (2013), data from the Ten Cities Study of Korea on mobile phone use and symptoms in children (mean age 10 years) were presented. Out of 2 436 participants approximately 1 000 children who used a mobile phone and provided information about their usage were included in the analysis. Out of 11 symptoms, dry skin, impaired concentration and impaired memory were most consistently associated with mobile phone use. The main aim of the paper was to describe the mobile phone use among Korean children. Information regarding the analysis of symptoms was not well described. It remained unclear how the study participants were selected and it seems that no confounders were considered in the analysis. Thus, as the previous study, this one is not informative regarding a causal association between RF-EMF exposure from mobile phone use and the generation of symptoms.

4.4.6 Other outcomes

In a cross-sectional study performed in Amritsar, Punjab, India, DNA migration length, damage frequency (DF) and damage index (DI) were compared between 63 healthy individuals living between 50-300 m of a mobile phone base station and 28 healthy individuals not exposed to a mobile phone base station (Gandhi et al., 2014). Participants were interviewed regarding socio-demographic information, genetic, family and exposure history, life style and mobile phone usage (average daily use and duration of usage) and measurements of their RF-EMF exposure were performed. Exposed and unexposed persons were reported to be matched for gender, age, alcohol drinking and occupational subgroups, but apparently not successful, since differences between the groups are substantial. In addition, proportion of smokers and non-vegetarian diet was significantly higher in the exposed, compared to the non-exposed group. Also, participants were reported not to be exposed to any other agents, but it is unclear what other exposures were checked and how. Measured power density in the exposed sample ranged from 7.6 to 14.6 W/m^2 (corresponding to 53.5-234.6 V/m) and was relatively highly correlated with distance to the mobile phone mast (Pearson’s correlation of 0.5). Exposure in the unexposed group was reported to lie between 0.001-0.1W/m^2 (corresponding to 0.6-5.8V/m). DNA migration length, DF and DI were significantly higher in the exposed group compared to the non-exposed group. Within the exposed group no exposure-response pattern between these DNA damage parameters and various mobile phone base station exposure measures were observed despite the large exposure range within the exposed group. In an analysis of variance (ANOVA) of the sample group, DNA damages were related to duration of mobile phone use and power density but not to age, dietary pattern, smoking habits and alcohol drinking.

Little research on this topic has been published until now. A major drawback of the study is that detailed information on the measurement procedure was not provided (where exactly were measurements done, how long, how were these places selected, etc.). The measured exposures from mobile phone base stations at distances of >50 meters are extremely high compared to previous reports in the literature, where on average values closer to 0.2-0.5V/m are reported (Frei et al., 2010, Viel et al., 2009). Thus, one cannot exclude the possibility of either measurement error or a calculation error in the conversion of dB units into W/m^2. It is surprising that DNA damages were not related to well established risk factors such as age, alcohol drinking and smoking. Finally, the inclusion of many correlated base station exposure measures in the ANOVA represents a problem. In summary, the study results are difficult to interpret regarding their validity.

In Taiwan, Chiu et al. (2014) performed a cross-sectional study to examine the relation between use of mobile phones and symptoms in children. Parents of 2 042 (25 %) children in the age group 11-15 years were interviewed on behalf of the children. Identification of eligible participants in different areas was based on telephone numbers; random digit dialing was performed until the predetermined number of children was included into the study. Information was collected via computer assisted telephone interviews. Quantitative information about mobile phone usage was collected, but in the analysis it was only presented categorized crudely as ever/never usage. Information regarding symptoms such as daytime sleepiness, headache, insomnia and skin itches was also collected in the interviews. The authors performed logistic regression analysis on the presence or absence of symptoms, adjusted for grade, sex, residential area, type of school, parents education level and density of power lines with non-users as reference, statistically significant increased adjusted ORs were found among mobile phone users for headache (OR 1.42, 95 % CI 1.12-1.81) and skin itches (OR 1.84, 95 % CI 1.47-2.29). No statistically significant increased risk was observed for daytime sleepiness. Among mobile phone users, a statistically significant reduced risk for insomnia was observed. In addition, parents reported poorer general health among mobile phone users than non-users. Two things remain problematic for the causal interpretation of the reported results. First of all, exposure information was assessed simultaneously with the outcome, which means that concerned parents may have over-reported mobile phone usage. In addition, it cannot be excluded that reverse causality may be at play here, if children with more frequent occurrence of symptoms receive a mobile phone (and subsequently get called) from their parents in order to be reachable when they experience health problems.

A survey evaluating use of mobile phones and risk of erectile dysfunction was published as a short communication by Al-Ali et al. (2013). Mobile phone usage among 20 men with self-reported erectile dysfunction for at least six months was compared with 10 healthy men. There is no information how the participants were recruited. Clinical information was collected on all participants, including a measurement of testosterone levels; mobile phone use habits were assessed by means of a short questionnaire. The results indicated that men with erectile dysfunction used their mobile phone the same amount of time on average as the group of persons without erectile dysfunction; however they carried the mobile phone in standby position statistically significantly longer than men who did not have erectile dysfunction. This study has similar methodological challenges as the fertility studies described above. In particular, the small sample size, the lack of an informative exposure assessment, absence of control of potential confounding factors, and the simultaneous assessment of exposure and outcome render the study results uninformative.

4.4.7 Conclusions on RF epidemiological studies

New studies on mobile phone use and tumours in the brain using retrospective exposure assessment are in line with previous research, which means that increased risks were observed in some of the most extreme exposure categories. However, it is not clear to what extent these risk estimates are affected by recall bias. A Swedish study collecting history of laterality of mobile phone use provided convincing evidence that reverse causality and detection bias play a role in the observed association between mobile phone use and vestibular schwannoma. Since this slow growing tumour affects the hearing, mobile phone users might be more likely to notice the symptoms and obtain a diagnosis at an earlier stage of disease development.

A large Swiss study on childhood tumours and exposure to RF-EMF from broadcasting did not indicate an association, which is in line with two previous large case-control studies. These studies are more reliable than earlier ecological studies that found such associations in the 1990s because individual exposure assessment was conducted in the new case-control studies. Further, the case-control studies were based on substantially larger samples and the Swiss study also adjusted for potential confounders in its analysis.

New studies on associations between sperm quality and mobile phone use are of low quality and cannot be used to evaluate a potential association with RF-EMF exposure. Adjustment for potential confounders was not performed in these studies. This is a recurrent problem as many studies on this subject have been published, but none has tried to make a reasonable assessment of the exposure of the testicles.

It is striking that in the last year several papers appeared on symptoms in adolescents and use of mobile phones. Quite clearly, these cross-sectional studies are consistent in that they report an association between mobile phone use in adolescents and the occurrence of symptoms. What remains unclear, however, is whether this could be due to the exposure to RF-EMF or the usage of mobile phones or other electronic devices as such. From these cross-sectional studies, it remains unclear if the association could be due to reverse causation, which means that it cannot be concluded if mobile phone users are more likely to become symptomatic, or whether adolescents could start using mobile phones more because they are symptomatic. A further alternative explanation could be confounding. The likelihood of having symptoms may be associated with the extent of mobile phone use, e.g. if both was the consequence of being an extraverted personality type.

In terms of exposure from mobile phone base stations or other RF-EMF transmitters, no new evidence has become available indicating a causal link between exposure and symptoms or EHS.

5. Recent expert reports

This chapter briefly summarizes two expert reports published since the last Council report. The summaries from these reports are directly cited, but somewhat shortened. The Council does not evaluate or comment any of the reports.

5.1 A Review of Safety Code 6 (2013): Health Canada's Safety Limits for Exposure to Radiofrequency Fields

An Expert Panel Report prepared at the request of the Royal Society of Canada for Health Canada, The Royal Society of Canada, 2 April 2014

(https://rsc-src.ca/sites/default/files/pdf/SC6_Public%20Summary.pdf)

Public Summary

A large number of industrial and consumer technologies operate using radiofrequency (RF) energy, which consists of electric and magnetic fields. To protect the public from adverse health effects from exposure to radiofrequency fields, Health Canada established Safety Code 6 (SC6) in 1991. It sets recommended limits for safe human exposure to RF energy emitted from devices such as cellular telephones, Wi-Fi equipment, cellular phone towers, radar and radio/TV broadcast antennas. For the general public, by far the most frequent source of exposure is through personal use of cell phones.

Health Canada regularly reviews SC6 to ensure that it is based on the most up-to-date scientific knowledge. In 2013, it proposed several revisions to bring SC6 in line with current knowledge and other international standards and asked the Royal Society of Canada to form an Expert Panel to review the proposed changes to SC6. The Panel was asked to determine whether SC6 limits provide adequate protection from established adverse health effects, whether there are other potential health impacts that should be considered, and whether additional precautionary measures should be recommended. This report outlines the evidence considered by the Panel and presents their response to the questions posed by the Royal Society. In addition, the Panel identified where there are gaps in the current state of knowledge and where further research is warranted.

The Panel considered an "established adverse health effect" as an adverse effect that is observed consistently in several studies with strong methodology. With this definition in mind, the Panel reviewed the evidence for a wide variety of negative health impacts from exposure to RF energy, including cancer, cognitive and neurologic effects, male and female reproductive effects, developmental effects, cardiac function and heart rate variability, electromagnetic hypersensitivity, and adverse health effects in susceptible regions of the eye.

Many of the studies considered reached conflicting conclusions. For example, the Panel reviewed conflicting evidence about effects of exposure to RF energy on cancer, concluding that effects are possible but are not "established" in accordance with its definition of "established health effects". The Panel's conclusion on cancer is in agreement with a recent report from the International Agency for Research on Cancer (IARC, 2013). Similarly, while effects of exposure to RF energy on aspects of male reproductive function have been found, the evidence has not been established to indicate that these translate into fertility or health effects. Problems in study design and inadequate dosimetry make it difficult to interpret the results of many of these reproductive health studies.

Therefore, the Panel has concluded that the balance of evidence at this time does not indicate negative health effects from exposure to RF energy below the limits recommended in the Safety Code. However, research on many of these health effects is ongoing and it is possible that the findings of future studies may alter this balance of evidence. The Panel recommends that Health Canada should continue to monitor the literature for emerging evidence and that it aggressively pursue scientific research aimed at clarifying the RF energy-cancer issue and at further investigating the question of electromagnetic hypersensitivity, in particular.

Within the constraints of available resources and time, the Panel reviewed the scientific literature on biological effects of radiofrequency fields. This literature includes a number of reports of effects in various biological systems at exposure levels below recommended SC6 limits. In general, these reported low-level effects are often not consistent across similar studies and have no clear implications with respect to human health. Consequently they cannot presently be used to design safety standards. The Panel recommends that Health Canada continue to evaluate this literature as it develops.

Available studies suggest that the basic restrictions recommended in Safety Code 6 do provide adequate protection against known adverse health effects across the radiofrequency range. However, the science of exposure measurement is still developing and further research is required to not only examine the effects of exposure to new and emerging technologies, but also to compare the effectiveness of the recommended reference levels against the findings of new studies. In particular, the Panel recommends that Health Canada should consider studies in which additional data has been collected on child exposure, postured adult and postured child exposure, pregnant female and newborn exposure under grounded and isolated conditions.

During the public consultation, the Panel heard a number of significant concerns about the health effects of RF energy, the increasing levels of public exposure to RF energy, the process used to review the Safety Code, and the need for improved risk communication activities. While the Panel concluded that the human exposure limits in the Safety Code are science-based and do reflect the current state of knowledge regarding health effects, the Panel recommends that Health Canada continue to improve its efforts to inform the public regarding this issue and provide practical advice to concerned consumers on how to reduce their personal or their children's exposure. The Panel also urges Health Canada to investigate the problems of sensitive individuals with the aim of understanding their condition and finding ways to provide effective treatment, develop a procedure for the public to report suspected disease clusters and a protocol for investigating them, and encourage inclusion of basic education on non-ionizing radiation in the curriculum of Canadian medical schools.

5.2. Health Council of the Netherlands. Mobile phones and cancer: Part 2. Animal studies on carcinogenesis.

The Hague: Health Council of the Netherlands, 2014; publication no. 2014/22.

(http://www.gezondheidsraad.nl/sites/default/files/mobile_phones_and_cancer_part_2_animal_studies_on_carcinogenesis.pdf)

Summary

Systematic search

The systematic literature search performed by the Committee revealed a substantial body of 54 animal studies on the carcinogenesis of exposure to RF fields. In 23 studies the effect of exposure to RF EMF alone has been investigated. A variety of animal models and tumour types has been used, as well as a number of different types of RF signals, although the focus has been on the types of signals used in modern mobile telecommunication. Exposure has been from several weeks up to two years, and the follow-up time generally life-long. In addition, 24 studies investigated the modulating effects of RF exposure on carcinogenesis induced by various well-known carcinogenic compounds, and another seven studies on the effect of RF exposure on the growth of implanted tumours. These data cover a wide range of experimental situations and may thus provide a reasonably well insight into the effects of RF exposure on carcinogenesis in rodents.

No effect in most studies

The analysis of the quality of the studies, as reflected in the possibility that the internal or external validity of the studies could be affected, showed that most of the studies are of adequate design. However, in seven studies various issues resulted in a negative appraisal and these studies were consequently excluded from the overall analysis. Of the remaining 47 studies, five showed an increase in the incidence of several types of tumours. Four of these were closely linked and performed by the same research group. They used rather high exposure levels and could not exclude thermal effects. The fifth study found an increased incidence of chemically-induced lung tumours, but lacked a proper control group. The authors consider it to be a preliminary study that needs to be replicated. The Committee has given it a low weight in the overall analysis. A further three studies found a decreased rate of tumour growth in RF EMF exposed animals. There is no logical explanation for this, and therefore these are considered to be chance results. This might also be the case for the positive associations observed in the studies described above. In the majority of the studies, however, 39 in total, describing experiments on a range of tumour types and in different species, no effect on carcinogenesis has been observed.

Conclusions

This has led the Committee to conclude that, on the basis of the results of the animal studies presented in this systematic review, it is highly unlikely that long-term continuous or repeated exposure to RF EMF may have initiating or promoting effects on the development of cancer.

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The Swedish Radiation Safety Authority has a comprehensive responsibility to ensure that society is safe from the effects of radiation. The Authority works to achieve radiation safety in a number of areas: nuclear power, medical care as well as commercial products and services. The Authority also works to achieve protection from natural radiation and to increase the level of radiation safety internationally.

The Swedish Radiation Safety Authority works proactively and preventively to protect people and the environment from the harmful effects of radiation, now and in the future. The Authority issues regulations and supervises compliance, while also supporting research, providing training and information, and issuing advice. Often, activities involving radiation require licences issued by the Authority. The Swedish Radiation Safety Authority maintains emergency preparedness around the clock with the aim of limiting the aftermath of radiation accidents and the unintentional spreading of radioactive substances. The Authority participates in international co-operation in order to promote radiation safety and finances projects aiming to raise the level of radiation safety in certain Eastern European countries.

The Authority reports to the Ministry of the Environment and has around 300 employees with competencies in the fields of engineering, natural and behavioural sciences, law, economics and communications. We have received quality, environmental and working environment certification.

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