Strål
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Research

2014:16

Recent Research on EMF and Health Risk

Ninth report from SSM's Scientific Council on Electromagnetic Fields, 2014

Report number: 2014:16 ISSN: 2000-0456
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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 nine in the series and covers studies published up to and including September 2013. 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 sec-tion covering other relevant expert reports published recently.

Project information

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Swedish Radiation Safety Authority

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Contents

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 nine in the series and covers studies published up to and including September 2013.

The composition of the Council that prepared this report is:

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

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

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

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Declarations of conflicts of interest are available at SSM.

Stockholm in March 2014
Leif Moberg
Chair

Update on key issues

ELF magnetic fields - childhood leukaemia and other health endpoints

Extremely low frequency magnetic fields, of the type that are generated from distribution and use of electricity, have been associated with an increased risk of acute lymphoblastic leukaemia in epidemiologic research. These were classified as a possible carcinogen to humans by WHO's International Agency for Research on Cancer (IARC) in 2002. 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. Further, there are 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 is unclear whether electric shocks rather than magnetic fields are involved in the development of ALS. Thus, the question whether extremely low frequency magnetic field exposure could cause Alzheimer's disease or ALS is still not resolved**.**

Effects from use of mobile phones

In 2011 IARC classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B) based on an increased risk for glioma and vestibular schwannoma (acoustic neuroma) associated with wireless phone use. However, in previous reports the Scientific Council of SSM has concluded that studies of brain tumours and other tumours of the head (vestibular schwannomas, 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 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 children and adolescents and risk for brain tumours, 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 more recent studies underline that this effect is variable, it is neither restricted to the spindle frequency range nor to the beginning of the night. The observed effects, however, are weak and do not seem to translate into behavioural or other health effects.

Health risks from transmitters

In line with previous studies, new research does not indicate any health risks for the general public related to exposure from radiofrequency electromagnetic fields from base stations for wireless networks, radio and TV transmitters, or wireless local data networks in schools or at home.

Self-reported electromagnetic hypersensitivity

While the symptoms experienced by patients with perceived electromagnetic hypersensitivity are real and some individuals suffer severely, studies so far have not provided evidence that exposure to electromagnetic fields is a causal factor. 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, but symptoms have not been more prevalent during real exposure than during sham exposure of the experimental groups. Several studies have indicated a nocebo effect, i.e. an adverse effect caused by an expectation that something is harmful. Little new research on the causality of EHS has been published since the last Council report.

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 source of exposure to strong static magnetic fields (> 1 T) is the use of magnetic resonance imaging (MRI) for medical diagnostic purposes. 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. Volunteer studies have confirmed these effects.

Cell studies

The previous Council report concluded that the results available were difficult to interpret due to the different exposure conditions applied and biological endpoints investigated. The recent in vitro studies indicate that sporadic effects could arise that are transient in most cases. However, the lack of sham-exposed controls in some studies limited the number of papers that could be considered.

Animal studies

The latest animal studies on the effects of exposure to static magnetic fields indicate that long-term exposure to fields in the millitesla range may invoke an adaptive response to stress, and that short-term exposures may result in pain reduction. These results indicate potential therapeutic applications of exposure to static magnetic fields rather than harmful effects. Repeated exposures of mice to fields in the tesla range showed some inconsistent evidence of possible effects on fertility and development. However, these exposure situations are not encountered in daily life by humans and have no bearing on human health risks.

Human studies

One experimental study in humans showed no effect of MRI exposure on male hormone levels related to reproduction. The study was not blinded, however, and therefore of limited value.

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 and the development of childhood leukaemia, the conclusion from previous Council reports still holds: a consistent association has been observed, but a causal relationship has not been established.

Cell studies

The conclusions on ELF in vitro studies in previous Council reports are still valid: there is a large variety of biological and electromagnetic parameters investigated; and few investigations aim to address the correlation between power frequency exposure and leukaemia. Moreover, as for static fields, several studies lack sham-exposed controls.

Animal studies

The exposure levels used in many studies are in the millitesla range and therefore considerably higher than those to which people can be exposed in daily life and higher than the current exposure limits. This means that there is no direct relevance of these experiments for human health. Several studies used exposure to levels equal to the 2010 ICNIRP exposure limits (i.e. 0.2 mT for the general public and 1 mT for workers). These studies are relevant for human exposures, although such exposure levels are seldom encountered.

In general, the results of the studies are not very consistent and need to be replicated. Replication studies should address potential association to childhood leukaemia.

Human studies

A study on physiological parameters underlines the conclusion from the previous Council report that ELF magnetic fields do not seem to have any effects on general physiology. Two recent electrophysiological studies add to the conclusion that effects on the EEG have been observed which is in line with the results of an Italian expert working group review. It is, however, difficult to distinguish between statistically significant and physiologically meaningful effects. At least the latest studies indicate that stimulation with various low frequencies did not lead to any resonance effects in EEG activity.

Epidemiology

New epidemiological studies on ELF magnetic field exposure and cancer tend to confirm previous results. One large French study found some indications for an increased childhood leukaemia risk whereas small studies on this topic had too little power to be informative. Interestingly, a large pooled analysis found no evidence that survival rate of childhood leukaemia patients was affected by ELF magnetic field exposure, but the study might have been affected by exposure misclassification. With respect to adult cancer, absence of risk was confirmed in most studies. In particular, with respect to breast cancer, evidence of absence of risk has increased with a large, well conducted cohort study of 267,000 workers. Similarly, a large Dutch general population cohort study confirmed the absence of risk for cardiovascular diseases in workers exposed to ELF magnetic fields.

The main result of a Danish cohort study on ELF magnetic field exposure from power lines and Alzheimer's disease did not indicate an increased risk for people living within 50 m of a high voltage power line. However, the power of the study was too small to address risk related to the lines with the highest voltages and one subgroup analysis pointed to an increased risk for people aged 65 to 75 years. A comprehensive meta-analysis found an increased risk for Alzheimer's disease and the Motor Neuron Disease Amyotrophic Lateral Sclerosis (ALS) mostly based on occupational studies. However, publication bias is of concern for the occupational studies and, as discussed in the previous Council report, it is unclear whether electric shocks and not magnetic fields are involved in the development of ALS. Thus, the question whether ELF magnetic field exposure causes Alzheimer's disease or ALS is still not resolved and might be further investigated.

Intermediate frequency (IF) fields

The intermediate frequency region of the EMF spectrum is defined as being between the ELF and RF ranges. Exposure from such fields can arise from the use of induction cooking, anti-theft devices or some industrial applications. Very few experimental studies are available on (health) effects of intermediate frequency 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 surveillance systems. Studies on possible effects associated with chronic exposure at low exposure levels are particularly relevant for confirming adequacy of current exposure limits.

Radiofrequency (RF) fields

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

Cell studies

Although some repetition studies have been carried out, most of the studies reported do not support an effect of RF EMF on DNA damage or cell death, and only minimal effects on protein expression.

Animal studies

The majority of the recent RF animal studies still lack a clear working hypothesis and adequate study design. Often the exposure systems and dosimetry are poorly described. If any international recommendations for description of laboratory animal experiments are taken into consideration they are only partly followed.

Overall, the animal studies provide weak indications of possible effects on oxidative stress and brain function including behaviour and emotionality. The reported effects on genotoxicity, hormones, glucose, male fertility and reproduction are mostly originating from single studies and need well-designed replication.

Human studies

Two of the three studies on cognition underline the conclusion from the previous Council report that there is no demonstrable effect on cognitive functions; the third study indicates a better performance under exposure. In the reporting period, effects of exposure to radiofrequency fields on waking EEG were investigated in two studies with regard to young adolescents and patients (epileptic). While no effect was observed in the adolescent group, patients showed an effect in the alpha frequency band. These results suggest that (i) age-related variations in EMF effects on the central nervous system should be considered (so far there are no studies in elderly subjects), and (ii) effects may be different in patients which CNS-related pathologies. Two sleep studies with different ELF pulsed radiofrequency and ELF magnetic field exposure underlined that effects on the sleep EEG are neither restricted to the spindle frequency range nor to NREM sleep. Both studies also found isolated effects on the macrostructure of sleep. The probability of finding effects seems to increase with the duration of exposure. No exposure-related effects in other physiological parameters have been observed. Effects of radiofrequency field exposure on temperature regulation and pain desensitization have been observed in single studies, and need confirmation.

Epidemiology

Most epidemiological studies in relation to mobile phone use addressed tumours in the head region. The Hardell group reported an increased risk for glioma but not for meningioma based on a new study including cases that were diagnosed between 2007 and 2009. The glioma results showed a clear exposure-response association in terms of duration and amount of exposure ranging from a 60% increase in risk for people using mobile phones for at least one year to a 190% risk increase for people with mobile phone use of more than 25 years. However, the results are in contradiction with recent and previous time-trend studies, which do not indicate a strong increase of glioma cases in the last decade. A strong increase in numbers would be expected if risk was indeed increasing by 60% after one year of mobile phone use, which applies almost to the whole population nowadays. In a recent study, no increase of salivary gland tumours was observed in Sweden between 1979 and 2009. The skin is the highest exposed part of the body from mobile phone use but the Danish cohort study did not find an increased risk for melanoma or other types of skin cancer in the head and neck region in relation to mobile phone use. Many of the studies on non-cancer outcomes (e.g. regarding hearing loss or salivary flow) have considerable limitations and thus no firm conclusions can be drawn from these studies.

Self-reported electromagnetic hypersensitivity and symptoms

Since the last Council report only a few studies on symptoms and/or electromagnetic hypersensitivity (EHS) have been published. Most studies were surveys which did not aim to investigate a causal association between EHS and exposure to electromagnetic fields but rather aimed at describing the distribution of EHS in the population. Experimental studies did not find indications for acute effects from exposure to extremely low frequency or radiofrequency electromagnetic fields. Epidemiological studies addressing the association between exposure to electromagnetic fields and symptoms had severe limitations and thus the state of knowledge has not changed noticeably since the previous Council report. However, recent findings on the interaction between risk perception and EHS may be helpful for risk management.

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. Att röra sig i så starka statiska fält kan inducera elektriska fält i kroppen och orsaka yrsel och illamående hos en del människor. Tröskelvärdena för dessa effekter tycks dock variera avsevärt mellan olika individer. Studier på frivilliga försökspersoner har bekräftat dessa effekter.

Cellstudier

I Rådets föregående rapport konstaterades att tillgängliga resultat var svåra att tolka beroende på att en stor mängd olika exponeringssituationer och biologiska utfall hade undersökts. Cellstudier genomförda under senare tid antyder att sporadiska effekter kan förekomma men att dessa i de flesta fall var transienta, dvs. avtog med tiden. Ett antal studier saknade uppgifter om oexponerade kontroller vilket innebar att dessa studier inte kunde utvärderas.

Djurstudier

De senaste djurstudierna av effekter till följd av exponering för statiska magnetfält antyder att långtidsexponering för fält i millitesla-området skulle kunna framkalla en stressreaktion och att korttidsexponering skulle kunna resultera i minskad smärtupplevelse. Dessa resultat antyder snarare möjliga terapeutiska tillämpningar av statiska magnetiska fält än skadliga hälsoeffekter. Försök på möss som upprepade gånger exponerats för fält i tesla-området visade motstridiga tecken på möjliga effekter på reproduktion och utveckling. Inga av dessa exponeringssituationer är emellertid sådana som människor utsätts för i det dagliga livet och de har ingen koppling till hälsorisker för människor.

Studier på människa

En studie av manliga hormonnivåer visade inte på någon effekt av MRI-exponering. Studien var dock inte blindad och därför av begränsat värde.

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 är slutsatsen densamma som i tidigare rapporter från Rådet: ett robust samband har observerats men något orsakssamband har inte kunnat fastställas.

Cellstudier

Slutsatserna från Rådets tidigare rapporter gäller fortfarande: det är stor variation i de exponeringssituationer och biologiska utfall som studerats och få studier syftar till att försöka förklara det observerade sambandet mellan exponering för lågfrekventa magnetfält och barnleukemi. Liksom för statiska fält saknar dessutom många studier oexponerade kontroller.

Djurstudier

De exponeringsnivåer som använts i många studier är i milliteslaområdet och därmed avsevärt högre än vad människor kan exponeras för i det dagliga livet och högre än gällande exponeringsgränser. Det innebär att det inte finns någon direkt relevans mellan dessa experiment och människors hälsa. Flera studier har använt exponeringsnivåer jämförbara med exponeringsgränserna i ICNIRPs rekommendationer från 2010 (dvs. 0,2 mT för exponering av allmänheten och 1 mT för yrkesexponering). Dessa studier är relevanta för exponering av människor, även om sådana exponeringsnivåer sällan uppnås.

Sammanfattningsvis visar studierna inte särskilt samstämmiga resultat och behöver upprepas. Nya studier bör inriktas på möjliga samband med barnleukemi.

Studier på människa

En studie av fysiologiska parametrar understryker slutsatsen från Rådets föregående rapport att exponering för lågfrekventa magnetfält inte tycks påverka den allmänna fysiologin. Två nya elektrofysiologiska studier styrker slutsatsen att effekter på EEG har observerats vilket ligger i linje med resultaten från en sammanställning av en italiensk expertgrupp. Det är dock svårt att skilja mellan statistiskt signifikanta och fysiologiskt meningsfulla effekter. Åtminstone de senaste studierna antyder att stimulering med olika låga frekvenser inte leder till några resonanseffekter i EEG-aktiviteten.

Epidemiologi

Nya epidemiologiska studier rörande exponering för lågfrekventa (ELF) magnetfält tenderar att bekräfta tidigare resultat. En stor fransk studie fann antydningar till en ökad risk för barnleukemi medan mindre liknande studier hade för låg statistisk styrka för att ge någon information. En stor poolad studie fann, vilket är intressant, inga bevis för att överlevnaden för barnleukemipatienter skulle påverkas av exponering för lågfrekventa magnetfält. Studien kan dock ha varit påverkad av felklassificering vad gäller exponeringen. När det gäller cancer hos vuxna så bekräftar de flesta studier frånvaron av risk. En stor, väl genomförd, kohortstudie på 267 000 arbetare, har stärkt stödet för att det inte föreligger någon risk för bröstcancer. En stor holländsk studie bekräftar frånvaron av risk för hjärt-kärlsjukdomar hos arbetare som exponerats för lågfrekventa magnetfält.

Det viktigaste resultatet från en dansk kohortstudie av Alzheimers sjukdom och exponering för lågfrekventa magnetfält från kraftledningar tyder inte på någon ökad risk för personer som bodde inom 50 m från en högspänningsledning. Studien är emellertid för liten för att undersöka risken från kraftledningar med de högsta spänningarna och analysen av en undergrupp antydde en ökad risk för personer i åldern 65 till 75 år. En omfattande meta-analys fann en ökad risk för Alzheimers sjukdom och amyotrofisk lateral skleros (ALS) vilket till största delen baseras på studier rörande yrkesexponering. Snedfördelning av publikationer (studier som visar effekter publiceras oftare än studier som inte visar effekter) är dock ett problem vid arbetslivsstudier och, vilket diskuterades i Rådets föregående rapport, det är oklart om det är kraftiga elektriska stötar och inte magnetfälten som skulle kunna vara orsak till utvecklingen av ALS. Frågan om lågfrekventa magnetfält kan orsaka Alzheimers sjukdom och ALS är ännu inte klargjord och bör utredas ytterligare.

Intermediära (IF) fält

Det intermediära frekvensområdet av EMF-spektret ligger definitionsmässigt mellan ELF- och RF-områdena och exponering kan uppkomma t.ex. vid användning av induktionsspisar, vid larmbågar i butiker och i samband med vissa industriella tillämpningar. Endast ett fåtal experimentella studier rörande hälsoeffekter från exponering för IF-fält finns tillgängliga, och slutsatser om eventuella hälsoeffekter är svåra att dra. Ytterligare studier skulle vara värdefulla eftersom människor exponeras för sådana fält i ökande grad, till exempel från elektroniska övervakningssystem. Studier om möjliga effekter av kronisk exponering för låga exponeringsnivåer är särskilt betydelsefulla för att bekräfta storleken på gällande rikt- och gränsvärden.

Radiofrekventa (RF) fält

Allmänheten exponeras för radiofrekventa fält från en mängd olika källor: från radio- och TV-sändare, trådlösa telefoner och mobiltelefoner och deras respektive basstationer samt mängder av andra källor som t.ex. trådlösa datornätverk. Delar av allmänheten är orolig 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

Trots att en del studier har upprepats ger flertalet rapporterade resultat inte något stöd för en effekt av exponering för radiofrekventa fält på DNA-skador eller celldöd och endast mycket små effekter på proteinuttryck.

Djurstudier

Flertalet av nyligen publicerade djurstudier för radiofrekventa fält saknar en klar arbetshypotes och en adekvat försöksutformning. Ofta är exponeringssystemen och dosimetrin dåligt beskrivna. Internationella riktlinjer för beskrivning av laboratorieförsök med djur har, i de fall de iakttagits, endast följts delvis.

Sammanfattningsvis ger djurstudierna svaga indikationer på effekter på oxidativ stress och hjärnfunktioner som beteende och känsloläge. De rapporterade effekterna på genotoxicitet, hormoner, glukos och manlig fortplantningsförmåga härstammar ofta från enstaka studier och kräver upprepade studier som är välgjorda.

Studier på människa

Två av de tre studierna av kognitivitet styrker slutsatsen från förra årets rapport från Rådet att det inte går att visa några effekter på kognitiva funktioner, den tredje studien antyder en förbättrad funktion under exponering. Under rapporteringsperioden har effekter av exponering för radiofrekventa fält på vaken-EEG undersökts i två studier: på ungdomar och på patienter (epilepsi). Medan inte några effekter observerades i ungdomsgruppen så visade patienterna en effekt i alfafrekvensbandet. Resultaten antyder dels att hänsyn bör tas till åldersrelaterade variationer (hittills har inte några studier genomförts på äldre personer), dels att effekterna kan variera för patienter med CNS-relaterade sjukdomar. Två sömnstudier med exponering för olika pulsade radiofrekventa fält och lågfrekventa magnetfält understryker att effekter på sömn-EEG är begränsade till områden med sömnspolar (korta utbrott av väldigt snabba rytmiska hjärnvågor från thalamus) eller till NREM-sömn (icke dröm-sömn). Båda studierna fann också isolerade effekter på sömnens makrostruktur. Sannolikheten att finna effekter tycks öka med exponeringens längd. Inga exponeringsrelaterade effekter har observerats för andra fysiologiska parametrar. Effekter av exponering för radiofrekventa fält har observerats på temperaturreglering och som minskad smärtkänslighet. Dessa observationer har gjorts i enstaka studier och behöver upprepas

Epidemiologi

De flesta epidemiologiska studier rörande användning av mobiltelefon har gällt tumörer i huvudområdet. Hardell och medarbetare har rapporterat en förhöjd risk för gliom, men inte för meningiom, baserat på en ny studie med fall som diagnosticerats mellan 2007 och 2009. Resultaten för gliom visade ett klart samband mellan exponering och respons vad gäller antal år mobiltelefonen använts och total samtalstid. Från en 60-procentig riskökning för människor som använt mobiltelefon i minst ett år till en 190-procentig ökning för människor som använt mobiltelefon i mer än 25 år. Resultaten motsägs emellertid av nya och tidigare incidensstudier som inte indikerar någon stark ökning av antalet fall av gliom under det senaste årtiondet. Man skulle förvänta sig en kraftig ökning av antalet fall om risken skulle öka med 60 procent efter ett års användning av mobiltelefon vilket skulle omfatta nästan hela befolkningen idag. I en nyligen genomförd studie kunde ingen ökning av spottkörteltumörer observeras i Sverige mellan 1979 och 2009. Huden är den kroppsdel som är högst exponerad vid användning av mobiltelefon men i en dansk kohortstudie observerades inte någon ökad risk för melanom eller andra typer av hudcancer i huvud-halsregionen kopplad till användning av mobiltelefon. Många av studierna av andra sjukdomar än cancer (t.ex. hörselnedsättning eller salivavsöndring) har avsevärda begränsningar och inga säkra slutsatser kan dras från dessa studier.

Egenrapporterad elkänslighet och symptom

Endast ett fåtal studier av symtom och/eller elkänslighet har publicerats sedan Rådets föregående rapport. De flesta studierna har varit översiktsstudier som inte avsett att undersöka ett orsakssamband mellan exponering för elektromagnetiska fält och elkänslighet utan snarare försökt beskriva hur elkänslighet fördelas i befolkningen. Experimentella studier fann inga indikationer på akuta effekter av exponering för lågfrekventa eller radiofrekventa fält. De epidemiologiska studier som undersökt samband mellan exponering för elektromagnetiska fält och symtom hade allvarliga begränsningar och kunskapsläget har inte förändrats nämnvärt sedan Rådets föregående rapport. Nyligen gjorda fynd rörande samband mellan riskuppfattning och elkänslighet kan eventuellt underlätta riskhanteringen.

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. 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 there exists a causal relation 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. 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, animal 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.

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).

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[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

To determine whether the achieved results reflect “true” biological response or if they are related to some unknown uncontrolled variable, inclusion of sham controls (cell cultures placed in an exposure device identical to the one employed for the exposure but with zero field) is mandatory since they allow to take into account the microenvironment in the exposure device that could affect the cellular endpoint under examination. 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.

Several endpoints have been evaluated to investigate the effects of static magnetic fields (SMF), such as oxidative stress, cell viability, proliferation, differentiation and orientation.

1.1.1 Oxidative stress

Kurzeja et al. (2013) exposed cultured mice fibroblasts to a SMF at different intensities (0.4, 0.6 or 0.7 T) for 4 days in presence of fluoride ions (F^-) at a concentration of 0.12 mM. To this purpose, a permanent magnet was employed. Sham-exposures were carried out employing steel instead of a permanent magnet. The oxidative stress induced by F^- was reduced by the concurrent exposure to the SMF, since the activities of some antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase) returned to normal values when cultures treated with F^- and exposed to a SMF were compared to cultures sham-exposed and treated with F^-. As stated by the authors, these results suggest that a SMF promotes the normalization of antioxidant enzyme activities and reduces ion-induced oxidative stress.

Sullivan et al. (2011) exposed several human cell types to a SMF ranging from 35 to 120 mT from 18 hours to 14 days. A sharp increase in ROS (Reactive Oxygen Species) production, together with a decreased cell attachment on the flask bottom and reduced cell growth was found in human embryonic lung fibroblasts exposed for 18 h with respect to sham-exposed cultures, but not in other cell types (adult skin fibroblasts, adult adipose stem cells, human melanoma cells). The effect was transient and reverted after 5 days of con-tinuous exposure.

1.1.2 Cell viability and proliferation

Gioia et al. (2013) evaluated the effects of chronic exposure (24-96 h) to a 2 mT SMF on cultured swine granulosa cells. No effects on cell viability ad orientation were detected. On the contrary, cell cycle kinetics was significantly reduced after 72 h exposure. Cell morphology (length and thickness) was also modified after 72 and 96 h exposure. Moreover, modifications on actin and α-tubulin cytoskeleton, together with a lower Ca^{2+} concentration and a reduction in mitochondrial activity were also detected. These results have been obtained by comparing control and SMF-exposed samples, although the authors stated that from preliminary results, obtained by comparing control and sham-exposed samples, influence of the experimental device on the environmental parameters (temperature and CO_2) can be excluded. However, the results of sham-exposed samples are not shown; therefore the validity of this study is questionable.

1.1.3 Other endpoints

Sakurai et al. (2012) evaluated the effect of strong static magnetic fields on myotube orientation of a mouse-derived myoblast cell line (C2C12). Cell cultures were exposed for 6 days to several conditions: maximum SMF of 10 T, 3T and 6 T with a magnetic field gradient of 41.7 T/m (6T-41.7) or 0 T/m (6T-0). Sham-exposed cultures were also set up. The results obtained indicated that the formation of oriented myotubes is dependent on the magnetic flux density and MF gradient and in the latter case a time-dependent increase in orientation was also detected. The myogenic differentiation and cell number were not affected for any of the experimental conditions tested.

1.2 Animal studies

In the previous Council report (SSM, 2013:19) the animal studies on SMF covered a period of several years. Most studies dealt with the issue of oxidative stress, which has also been studied in relation to exposure to extremely low frequency (ELF) and radiofrequency (RF) fields. In theory, oxidative stress may lead to increased damage to biomolecules, and thus may increase the risk of health effects. The 2013 report concluded that prolonged repeated exposures of animals to SMF in the millitesla range may lead to increased oxidative stress in various tissues, but that is has not been assessed whether this leads to health effects.

Other endpoints had been studied as well, such as behaviour and development. The report concluded that these animal studies did not provide indications of adverse health effects of SMF.

1.2.1 Reproduction and development

In the period covering the current report, several studies have been published that address reproduction and development.

In two associated papers, a group of German investigators describe experiments they performed with pregnant mice exposed in MRI scanners (Zahedi et al., 2013, Zaun et al., 2013). The animals received daily exposures for 75 minutes either in the bore entrance (representing the position of MRI workers) or at the bore isocenter (representing the position of patients) of a 1.5 T and a 7 T MRI scanner. The strength of the magnetic fields in the bore was homogeneous over the position of the cages, with mean field strengths of 1.495 and 6.979 T. At the entrance positions a clear field gradient was present over the bottom of the cages, varying from approximately 1–0.2 T for the 1.5 T scanner, and from approximately 1.4–0.6 T for the 7 T scanner. Sham-exposed animals were kept in a mock scanner under identical light and sound conditions as in a real 7 T scanner. The exposures took place for 18 days starting at day 1.5 of pregnancy. After delivery, the development of the offspring was monitored (Zahedi et al., 2013). No effects of any exposure were observed on duration of pregnancy and litter size, and in the sex distribution, malformations and development in the offspring. The only effects noticed were (a) a slight but significant delay in the opening of the eyes in all exposed groups compared to the sham and cage-control groups, and (b) a small delay in weight gain in the groups exposed at both positions in the 1.5 T scanner or at the entrance of the 7 T scanner. At an age of 8 weeks the offspring were mated with unexposed animals (Zaun et al., 2013). In male mice that had been exposed in utero no effect of exposure was measured on the weight of the testes and epididymis or on sperm count, sperm morphology, or fertility. In the in utero exposed female mice no effect on pregnancy rate and litter size was found. However, in the offspring of the females that had been exposed in the bore or at the entrance of a 7 T scanner, a reduced placental weight was observed. This correlated with a decrease in embryonic weight only in those animals exposed in the bore. Although these studies indicate possible effects of these repeated exposures on the fertility and development, the daily exposure of pregnant animals cannot be compared to exposures of humans in clinical situations.

1.2.2 Behaviour

Todorovic et al. (2013) exposed two species of mealworm beetles to 50 nT fields from a magnet for about 10 days during the pupal stage. They observed no difference in the time to develop from pupa to adult in either species, both in pupae exposed at the north and at the south pole of the magnet. After hatching, the adult beetles were replaced on the magnet for 24 h and their behaviour was monitored. In one species, *Tenebrio obscuris*, no significant effects on behaviour were observed. Beetles of the other species, *Teneb-*

rio molitor, showed increased movement when they had been exposed as pupae to the north pole of the magnet, whereas movement was reduced when they had been exposed to the south pole. No explanation of the difference can be provided, and these results have no bearing on human development or behaviour.

1.2.3 Analgesia

László and Hernádi (2012) exposed snails to either homogeneous or inhomogeneous SMF for 20–40 minutes. The strength of the homogeneous field was 147 mT, while the maximum strength of the inhomogeneous field was 578 mT with a gradient of 58 T/m over the 10 mm distance between neighbouring extremes. Directly following exposure, the response of the snails to a heat treatment (placement on a hot plate with a temperature of 43 °C) was determined by measuring the time to retract the foot. Exposure to the homogeneous field increased the response latency, i.e. it had an anti-nociceptive (pain-reducing) effect. This was maximal already after 20 minutes exposure. Exposure to the inhomogeneous field resulted after 20 minutes of exposure in an anti-nociceptive effect of approximately similar size of that following the homogeneous field exposure, but a stronger effect after 40 minutes exposure. It is not clear whether this is due to the inhomogeneous nature of the field, or by the higher maximum field strength. Application of the opioid receptor antagonist naloxone resulted in a decrease in response latency, i.e. the animals were more susceptible to the heat treatment. This effect was fully counteracted by exposure to the homogeneous field (the inhomogeneous field was not tested for this). These results show that SMF may have an analgesic effect that at least in part may involve opiod receptors.

1.2.4 Effects on blood

Using an array of small magnets that is used for magnetotherapy in patients, Djordjevich et al. (2012) exposed mice continuously for 28 days to either upward or downward oriented magnetic fields of maximum 16 mT at the bottom of the cage and a gradient of 10 mT/cm. At the end of the exposure period they assessed a number of parameters associated with blood and blood formation. They observed changes in several parameters, generally independent of the direction of the static magnetic field. They speculate that the observations are not indicative of an unspecified stress response, but more consistent with a specific adaptive response. This is also supported by the lack of effects on food consumption and body mass that would be expected to change when there would be a stress response.

1.2.5 Therapeutic applications

Several studies investigated therapeutic applications of SM fields (Bates et al., 2012, Bertolino et al., 2013, Ekici et al., 2012). These will not be discussed in the current report, but they are mentioned to indicate that also possible positive effects of SMF exposure are being studied and observed.

1.3 Human studies

Since the previous Council report (SSM, 2013:19) one human experimental study on effects of a SMF was published. Møllerløkken et al. (2012) investigated whether a 20 min standard MRI head scan with whole body exposure in a 1.5 T MRI scanner has an effect on hormones relevant for male reproduction. They used a randomized not blinded cross-over design (exposure condition was known to participants and investigators since the MRI locations were different) with real and sham exposure to study possible effects in a sample of 24 healthy male volunteers (18-40 years). Neither immediately after exposure nor 11 days later any exposure-related differences in hormone levels (inhibin B, testosterone, prolactine, thyreotropine, luteinizing hormone, follicle stimulating hormones, sex-hormone binding globuline, and estradiol) were observed. .

From a methodological point of view it has to be noted that studies with MRI exposure are 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

Gobba et al. (2012) published a case report based on three females with implanted copper intrauterine contraceptive devices (IUDs) working at a 1.5 T MRI unit. Some months after an increase of the working time these females developed prolonged and excessive uterine bleedings (menometrorrhagia), which progressively disappeared when the previous working conditions were re-established. The possible mechanism behind this observation is unknown, nevertheless, the authors conclude that given the progressive diffusion of more powerful MRI scanners, the possibility that MRI operators with implanted metallic IUDs can be included in the group of “workers at particular risk” according to the EU Directive 2004/40/EC should be considered.

1.5 Conclusions on static magnetic fields

The previous Council report concluded that the results available in vitro were difficult to interpret due to different exposure conditions applied and biological endpoints investigated. The recent in vitro studies indicate that sporadic effects could arise that in most cases are transient. However, the lack of sham-exposed controls restricted the number of papers to be considered.

The latest animal studies on the effects of exposure to SMF indicate that long-term exposure to fields in the millitesla range may invoke an adaptive response to stress, and that short term exposures may result in pain reduction. These results indicate more therapeutic purposes of SMF exposure than harmful effects. Repeated exposures of mice to fields in the tesla range showed some inconsistent evidence of possible effects on the fertility and development. All these exposure situations are not encountered in daily life by humans, however, so they have no bearing on human health risks.

One experimental study in humans showed no effect of MRI exposure on the levels of male hormones related to reproduction. However, the study was not blinded, therefore the results are of limited value.

2. Extremely low frequency (ELF) fields

2.1 Cell studies

2.1.1 Cell growth and viability

Several studies have been identified dealing with cell growth and viability after ELF EMF exposure. Some of them were not considered since sham-exposed cultures were not set up.

Bae et al. (2013) investigated the effect of three days exposure to 60 Hz, 1 mT on two human cancer cell lines. For this purpose, human prostate carcinoma (DV145) and T-lymphoblastoid (Jurkat) cells were employed and cell growth was measured by means of a tetrazolium assay (2-(4-lodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulphophenyl)-2H) and the trypan blue exclusion assay. The same frozen stock of cells was used to set up cultures over a period of five years. For each experimental run, four incubators of the same model were employed, one for control cultures and the other three for exposed/sham exposed cultures. The results obtained indicated that ELF field enhanced or reduced cell growth in the three incubators at many different time-points. Since sham-exposures also induced similar results, the authors suggested that changes in the geomagnetic field time-pattern could be responsible for the observed effects.

Cell growth and viability was evaluated by Trillo et al. (2013) by exposing human neuroblastoma NB69 cells to a 50 Hz (10 or 100 µT) intermittently (3 h on/3 h off cycles) for 42 h. They found a statistically significant increase in proliferation at both 10 and 100 µT, without influence on cell viability. The results obtained at 100 µT confirmed their previous results (Trillo et al., 2012). In a second set of experiments, the authors prolonged the exposure for an additional 48 h period (total exposure duration 90 h). In this case, the proliferative effect was not detected at any of the two flux densities tested. Moreover, differentiated cells (treated with retinoic acid) were also irresponsive to the magnetic field-induced cytoproliferative effect.

In another investigation, carried out by Zhang et al. (2013b), human epidermal stem cells were exposed 30 min/day for 7 days to a 1, 10 or 50 Hz sinusoidal ELF field (5 mT field intensity). Cell proliferation was enhanced by the exposure and 50 Hz resulted more effective than 10 and 1 Hz. These results also indicated that the ELF-induced effects are dependent on the electromagnetic parameters applied.

2.1.2 Other endpoints

Gavoci et al. (2013) investigated the effect of different combinations of static (DC) and alternating (EC) magnetic fields tuned on resonance conditions for potassium in a human neuroblastoma BE(2)C cell line. The results obtained in 41 cells analysed by whole cell patch clamp before, during and after exposure did not show significant differences between exposed and not exposed cells. The authors concluded that the hypothesis of “ion parametric resonance” is not confirmed, although other ion channels, also at single channel level, should be investigated.

Iorio et al. (2013) exposed C2C12 mouse myoblasts to a 50 Hz (1 mT) ELF-MF for 6, 12, 18 and 24 h to investigate skeletal myoblast migration. A transient increase was detected in cells exposed for 6 h that was lower at 12 h and disappeared for longer exposure duration. Sham-exposed samples did not show differences compared to negative controls. Expression of µ- and m-calpain (proteins involved in myoblast motility) was enhanced after 30 min exposure, but not at 2 and 6 h exposure. For 2 h exposure µ-calpain localization was changed, showing a translocation towards the membrane extension. This latter observation was confirmed by the lack of EMF-induced migration when a calpain inhibitor was added to cell cultures. Moreover, the EMF-stimulatory effect on calpains activity was also associated with changes in actin dynamics. The authors concluded that their results suggest a crucial role for the calpain system in mediating the ELF-MF stimulatory effect on myoblast migration.

2.1.3 Conclusions on ELF cell studies

The conclusions on ELF in vitro studies of the previous Council report are still valid: 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

The 2013 Council report (SSM, 2013:19) concluded on the experimental studies using ELF fields: “A number of studies indicated adverse effects of generally long term exposure to ELF magnetic fields in the millitesla range on reproduction and development in various animal species. Other studies indicated increased oxidative stress, again mostly by exposures at levels well above the current exposure limits. One study showed indications for tumour growth inhibition by a 100 mT field, but with only small numbers of animals. Replication is necessary to obtain more insight. In general, the latest animal studies do not contribute to the understanding of a mechanism that could explain the association found in epidemiological studies between long term exposure to ELF magnetic fields below 1 μT and an increased risk of childhood leukaemia. Hence, there is still a need for dedicated studies in this area using new animal models."

The studies published in the past year do not contribute much to this understanding. Most of them focus on effects on the brain and behaviour, reproduction and development, and oxidative stress. Most studies looked at the effects of ELF magnetic fields; only one considered effects of ELF electric field exposure.

2.2.1 Memory and behaviour

Cui et al. (2012) exposed mice to sham, 0.1 or 1 mT 50 Hz fields for 4 h per day during 12 weeks. After the last exposure, several behavioural tests were performed, following which the animals were sacrificed and the brains removed for assessment of parameters indicating oxidative stress (discussed below). No effect of exposure was observed on body weight and motor function, but in the animals exposed to the highest level, memory was slightly impaired.

Korpinar et al. (2012) exposed rats to 10 mT 50 Hz fields continuously for 21 days. They then used several tests to measure behaviour. No effects of the exposure were found on activity in general and on exploration activity, but stress and anxiety-related behaviour in the exposed rats were significantly enhanced.

A daily 8 h exposure to a 3 mT 60 Hz magnetic field during 25 days was given to mice by Kitaoka et al. (2013). They then performed four different behavioural tests every other day, while the exposures continued. So the last test was done after 32 days of exposure. In two of the tests, significant differences were observed between real and sham-exposed groups. The real exposed animals were slower to enter from the dark in the light, and moved less in a swim test. This might indicate anxiety and depression-like behaviour, according to the authors. The levels of corticosterone and adrenocorticotrope hormone (ACTH) in plasma were assessed after the end of the behavioural tests. The corticosterone level was higher in the exposed animals, but the levels of ACTH did not differ. This is consistent with the observed behavioural changes.

Wang et al. (2013) investigated the spatial memory in adolescent mice that had been exposed to a 2 mT 50 Hz magnetic field for 1 hour per day from day 23 to 35 after birth. No effects were observed in a test of short-term memory, but when long-term memory was tested this was shown to be slightly improved in the exposed animals compared to the sham-exposed controls. Body weight of the animals was not affected by the ELF exposure.

Another research group from China, Duan et al. (2013b) exposed mice for 4 hours per day during 28 days to a 8 mT 50 Hz field. Several animals were treated with procyanidins extracted from lotus seedpods that have an antioxidant action. Directly following the last exposure session the memory of the animals was tested, and after that they were killed and blood and tissue was collected for the determination of a number of compounds indicating oxidative stress. In contrast to the previous study, body weight in the ELF-exposed groups was lower than in the sham controls. This effect was partly counteracted by the administration of procyanidins, but only at the highest of three doses. Memory in the exposed animals was less than in the sham controls, and also this was in part counteracted by the administration of procyanidins.

Zhang et al. (2013a) exposed rats to a 100 µT 50 Hz field for 12 weeks, most likely continuous. Some groups were also treated with aluminum chloride, which simulates symptoms seen in Alzheimer's disease. At the end of the exposure period, memory was tested, and the animals were killed and the brains removed for further analysis. The growth of the animals during the exposure period was lower in the aluminum-alone and aluminum plus ELF groups. The groups treated with aluminum performed significantly worse in the memory test, but there was no effect of the ELF exposure on memory. There were also significant morphological changes consistent with Alzheimer development in the aluminum treated groups, but not in the group treated with ELF magnetic fields alone. The field exposure had no effect on the symptoms induced by the aluminum treatment.

2.2.2 Brain physiology

Balassa et al. (2013) exposed rats to ELF magnetic fields continuously for 1 week. The animals were treated either prenatally to a field of 0.5 mT, or at an age of 3 days to a field of 3 mT. After the end of the exposure, the brain was removed and excitability of different regions of the brain was measured in brain slices. In both exposed groups, the excitability in the hippocampus and neocortex was increased.

Kumar et al. (2013) investigated the effect of ELF exposure on pain induced by formalin in rats with spinal cord injury. The animals were exposed to an 18 µT field for 2 hours per day, 7 days per week for 8 weeks. At the end of the exposure period the pain response was assessed. Next, the animals were killed and the brains removed for further testing. The pain response in the rats with spinal cord injury was significantly decreased compared to sham controls; ELF exposure restored the pain response. The concentrations of several neurotransmitters in the brain were changed after spinal cord injury, but the levels were normal in the group that received additional ELF exposure.

El Gohari et al. (2013) assessed the effect of daily administration of caffeine for 15 days on brain electrical activity, and the effect of (co-)exposure to a 0.2 mT ELF field for 3 hours per day during the same period. Every five days during and for 15 days after the treatments, the EEG was recorded. Exposure to ELF alone resulted in an increase in mean power amplitude in the motor cortex and a reduction in the visual cortex, and an increase in the overall power amplitude in the brain. These effects were partly counteracted by the administration of caffeine. In the recovery period after the ELF exposure the values returned to control levels.

Celik et al. (2013) investigated the influence of exposure to ELF fields on the accumulation of manganese in various tissues of the rat. Four groups orally received different dose levels of manganese every two days for 45 weeks, and four other groups the same doses, but combined with 1.5 mT 50 Hz exposure 5 days per week for 4 hours daily during the same period of 45 days. Manganese accumulated in kidney, liver and brain, and ELF exposure increased the accumulation.

The influence of ELF magnetic field exposure on expression of the heat shock protein hsp70, a stress indicator, and DNA damage in various parts of mouse brain was studied by Villarini et al. (2013). They exposed the animals to 50 Hz fields of 0.1, 0.2,1 or 2 mT for 15 hours per day during 7 days. The animals were then sacrificed either directly or 24 hours later. No effects were found on hsp70, except for a slight increase in hsp70 mRNA in the group treated with 0.1 mT. This is most likely a spurious result. The animals treated with 1 or 2 mT showed an increased level of DNA damage directly following the last exposure, but this had disappeared 24 hours later.

Fadakar et al. (2013) studied the effect of ELF exposure on the induction of seizures in mice by injection of the drug pentylentetrazol in the brain. The animals were exposed to 0.1 mT fields for 2 hours per day. When exposure was for 1 or 3 days or 2 weeks, no difference was observed in the drug dose needed to induce seizures. Daily exposures during 1 month increased the threshold drug dose, thus providing some sort of protection.

Gutiérrez-Mercado et al. (2013) investigated the effect of exposure to a 120 Hz magnetic field of 0.66 mT, 2 hours per day for 10 days, on the vascular permeability in central areas the brain, that have a simpler blood-brain barrier than other brain areas. They observed an increase in capillary permeability and an increase in vascular area.

2.2.3 Fertility

Tenorio et al. (2013) investigated the fertility of male rats after exposure to a 60 Hz field of 1 mT. Testicular damage was inflicted by a heat shock, and then the animals were exposed to the ELF field for 15, 30 or 60 days. In control animals, spermatogenesis was fully restored after 60 days, while in the exposed animals still extensive damage was present at that time. The blood testosterone level was not affected by the exposure.

Kim et al. (2013a) exposed mice to a 100 µT 60 Hz magnetic field for 2, 4, 6 or 8 weeks continuously, or to a 2, 20 or 200 µT field for 8 weeks. Body and testicular mass were not affected by any of these exposures. There was a duration-dependent increase in apoptotic cells in the animals exposed to 100 µT for 6 and 8 weeks, and a dose-dependent increase in the groups exposed to 20 and 200 µT. The number of sperm in the epididymis was decreased in mice exposed to 100 µT for 8 weeks, and the diameter of the seminiferous tubules was reduced in those exposed to 200 µT for 8 weeks.

Duan et al. (2013a) exposed male rats to a 500 µT 50 Hz field for 4 hours per day, 7 days per week, for 4 and 8 weeks. They determined several endpoints related to testicular function and spermatogenesis, including body mass, masses of testes and epididymis, sperm count and abnormal sperm ratio in the caudal epididymis, serum testosterone level, testicular histology, frequency of 14 stages of the cycle of the seminiferous epithelium and of four stages of meiosis I, germ cell apoptosis and testicular oxidative status. No effects of exposure on any of these endpoints were observed.

Testicular function in rats after ELF exposure was also assessed by Akdag et al. (2013b). They exposed the animals to 100 and 500 µT fields for 2 hours per day, 7 days per week, for 10 months. In testis tissue, no effects of the exposures were observed on parameters indicating oxidative stress, or on sperm count and sperm morphology. However, long-term exposure to a 500 µT field increased the activity of caspase-3, an indicator of apoptosis.

Tomás et al. (2012) performed a field study into the reproduction of Great Tits (*Parus major*). During nine breeding seasons they studied a population of these birds living close to an overhead power line and compared that with a reference population at some distance from the line. Mean exposure near the line was 0.2 ± 0.03 µT, and away from the line 0.0006 ± 0.0002 µT. In exposed nests, the number of eggs was increased by 7% and the egg volume by 3%. No difference in numbers of hatched eggs and fledged young was observed. This study therefore shows a biological effect without reproductive consequences.

2.2.4 Development

Fournier et al. (2012) continuously exposed pregnant rats to a complex low-frequency field “designed to interfere with brain development”. Exposure levels were 2–50 nT, 30–50 nT, 90–580 nT and 590–1200 nT. Only in the 30–50 nT exposed group, changes in the development of the hippocampus and in learning were observed. The authors consider this to be a window effect.

Shams Lahijani and co-workers performed a series of studies on the development of chicken embryos exposed to 50 Hz magnetic fields. In the first study, they exposed fertilized eggs to 1.33, 2.66, 5.52 or 7.32 mT for 24 hours and investigated the development of the spleen after 19 days of incubation following the exposure (Lahijani et al., 2013). They observed a dose-dependent decrease in spleen size, hyperemia, damage in spleen parenchyma, a decrease in the numbers of splenic nodules, an increase in the number of polymorphonuclear cells and sinusoidal spaces of spleens, an increase in the level of alkaline phosphatase activity, and an increase in the number of apoptotic cells, deformed nuclei and swollen mitochondria in the exposed embryos. They conclude that ELF exposure resulted in changes in the spleen which could impair the function of the immune system.

Using the same experimental setup, Shams Lahijani et al. (2013) incubated the eggs for 14 days following exposure and studied the development of the heart of the embryos. They observed several changes in morphological and ultrastructural parameters. The largest changes were found, however, in the 2.66 mT group, with less or no changes in the 5.52 and 7.32 mT groups. It is hard to explain why there should be a window effect.

2.2.5 (Cyto)toxicity, oxidative stress

In a study described earlier under section 2.2.1 Memory and behaviour, Cui et al. (2012) exposed mice to sham, 0.1 or 1 mT 50 Hz fields for 4 hours per day during 12 weeks. After the last exposure the brains were removed for assessment of parameters indicating oxidative stress. In the animals exposed to the highest field strength, an increased level of malondialdehyde, a parameter indicative of oxidative stress, was measured in two areas of the brain. No changes in this group were observed for three antioxidant parameters, but these were decreased in the low-exposure group. So in both groups there was an increased level of oxidative stress.

In a study described under section 2.2.1 Memory and behaviour, Duan et al. (2013b) exposed mice for 4 hours per day during 28 days to a 8 mT 50 Hz field. Several groups were treated with procyanidins extracted from lotus seedpods that have an antioxidant action. Following the last exposure session the animals were killed and blood and tissue was collected for the determination of a number of compounds indicating oxidative stress. Oxidative stress in the ELF-only exposed animals was increased and the procyanidins reduced this effect in an exposure-dependent manner.

Akdag et al. (2013a) exposed rats to 100 or 500 µT ELF magnetic fields for 2 h per day during 10 months. They then assessed in the brain protein carbonyl (PC) and malondialdehyde (MDA) as indicators of oxidative damage, and beta-amyloid protein (BAP) as indicator for Alzheimer’s disease. The BAP level was not significantly altered after either ELF treatment, but both

PC and MDA were increased, in a dose-dependent way, indicating increased oxidative damage in the brain.

Rageh et al. (2012) exposed 10-days old rats continuously to 50 Hz, 0.5 mT magnetic fields for 30 days and measured genotoxic and cytotoxic damage in brain and bone marrow cells. Malondialdehyde and superoxide dismutase in brain were increased, indicating increased oxidative stress. The activity of glutathione was not altered. Brain cells also showed an increase in DNA damage as measured by the comet assay. In bone marrow cells, an increase in cells with micronuclei and an increased mitotic index were observed. These findings indicate a higher level of damage in the exposed animals.

Martínez-Sámano et al. (2012) exposed rats to a 2.4 mT ELF magnetic field for 2 hours. In brain tissue the activity of superoxide dismutase and catalase was reduced, while no effects were observed on glutathione, nitric oxide, total cholesterol, and triacylglycerol levels, as well as on corticosterone in plasma. ELF exposure combined with movement restraint also decreased glutathione and nitric oxide levels. These results show that acute exposure to ELF appears to be a mild stressor that leads to some adaptive responses due to the activation of systems controlling the brain oxidative balance.

Alcaraz et al. (2013) assessed micronucleus formation in mouse bone marrow cells as a result of exposure to a 200 µT 50 Hz magnetic field continuously for 7, 14, 21 or 28 days. An increased number of micronucleated cells was observed in the exposed groups, but more in the positive controls exposed to 50 cGy of X-rays. The antioxidants dimethyl sulfoxide (DMSO), 6-n-propyl-2-thiouracil (PTU), grape-procyanidins (P) and citrus flavonoids extract diminished the damage from the X-ray treatment, but had no effect on the number of micronuclei in bone marrow cells of ELF exposed animals.

Glinka et al. (2013) exposed rats for 30 minutes per day to a 10 mT 40 Hz field for 6–14 days. They then assessed the antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GPO) and glutathione S-transferase (GST), as well as the concentration of malone dialdehyde (MDA) as an indicator of lipid peroxidation rate, in the liver and blood serum. In blood, mitochondrial SOD was increased after 6 days of exposure, but not at 10 and 14 days. In the liver, it was decreased at 14 days only. No effects were observed on cytosolic SOD in both blood serum and liver. In blood serum GPO was increased at 10 and 14 days, but no effects were observed in liver. GST was increased only in liver at 6 days of exposure. MDA in liver was decreased at 14 days of exposure. According to the authors these results suggest the inhibition of phospholipid peroxidation and subsequent stabilization of cellular membranes, but the variable results make this questionable.

Akpinar et al. (2012) exposed rats to ELF electric fields of 12 or 18 kV/m for 1 hour per day during 14 days. They investigated visual evoked potential as retinal function. In brain and retinal tissue they determined thiobarbituric acid reactive substances (TBARS) as indicator of lipid peroxidation, total antioxidant status, total oxidant status and the oxidant stress index. Brain and retina TBARS, total oxidant status and the oxidant stress index were significantly increased and total antioxidant status decreased after exposure to both electric field levels. Visual evoked potentials were delayed. All effects were stronger in the 18 kV/m group compared to the 12 kV/m one.

2.2.6 Physiology

α-Amylase is used as a stress marker in humans and has been shown to reduce cell proliferation. It is therefore considered of potential importance in carcinogenesis. In a study to assess its relevance as a parameter for magnetic field effects in humans, Fedrowitz et al. (2012) determined α-amylase levels after ELF exposure in the mammary glands of two strains of rats with different stress sensitivities. Stress-sensitive Fischer 344 (F344) rats were continuously exposed for 1, 7, 14 or 28 days to a 100 µT field, and less stress-sensitive Lewis rats for 14 days. Two parts of the mammary glands were investigated: the cranial part (closest to the head) and the caudal part (closest to the tail). In the first of two experiments, α-amylase activity was enhanced in the cranial mammary glands of F344 rats after 14 and 28 days of exposure, and in Lewis rats after 14 days, while no effects were observed in the caudal glands in both strains. In the second experiment, with only 14 days exposure, no effects were noted in the cranial glands in both strains, while an increase in α-amylase was observed in the caudal glands in F344 rats only. These inconsistent results do not provide a strong argument for use of α-amylase as a parameter indicating magnetic field effects in humans.

Costa et al. (2013) determined the effect of ELF magnetic field exposure on the growth of blood vessels in the yolk sac of developing Japanese quail embryos. After 48 hours of incubation, part of the egg shell was removed, which exposed the yolk sac. The eggs were then exposed to a 60 Hz magnetic field at 0.90–1.13 mT for 3 x 1, 2, 3 or 4 hours at 8-hour intervals, or for 24 hours continuously, for 1 or 2 days. At the end of the exposure period, the extent of the vascular network was determined using two parameters derived with fractal analysis. Differences between the real and sham-exposed groups, indicating a retarded vascular growth, were only found after 1 day of exposure, for the group exposed for the 2-hour periods for both fractal parameters, and for the groups exposed for the 3-hour periods for one parameter. No differences were observed in any of the groups exposed for 2 days. The authors conclude that there is a window effect, but since they did not correct for multiple analyses the findings may be a chance result.

Prato et al. (2013) investigated the effect of very weak ELF magnetic fields on the experience of pain in mice. The animals were first shielded from environmental static and ELF magnetic fields for 1 hour per day during 5 days.

This induced a strong analgesic effect, i.e. the animals were less susceptible to pain. Exposure during the shielded period to a 44 µT static magnetic field had an only marginal influence of this effect, but exposure to a 33 nT 30 Hz field reduced the analgesic effect by 60%.

Ince et al. (2012) exposed rats to manganese and an ELF magnetic field to investigate the effect of these treatments, alone or combined, on calcium, zinc, magnesium and phosphorus in rat teeth. These elements are thought to be involved in caries. The ELF exposure was to a 50 Hz magnetic field of 1 mT for 4 hours per day for 45 days. Both ELF exposure and daily manganese treatment, as well as the combination of the two, decreased the calcium and phophorus levels in teeth, while the magnesium and zinc contents were increased. This indicates an increased risk of caries and a decreased resistance to tooth decay.

Another group from the same Turkish university (Dogru et al., 2013) used both pulsed and sinusoidal ELF magnetic fields to study whether they might have a positive influence on gingiva. Rats were exposed to 1.5 mT 50 Hz fields for 6 hours per day, 5 days per week and 28 days. Both the pulsed and sinusoidal fields increased the number of lymphocytes in the gingival epithelium, as well as the proliferation of the epithelial cells. Moreover, the level of E-cadherin, a substance that is an indicator for the barrier function of the epithelium, was increased. The authors conclude that the ELF treatments might be beneficial. This contrasts the suggestion of the risk for increased tooth decay from the previous study.

Salehi et al. (2013) investigated the effect of ELF magnetic field exposure on immune parameters in rats. They exposed the animals to a 100 µT 50 Hz field for 4 hours per day during 3 months and measured serum levels of interferon-γ and several interleukins (IL). Moreover they determined the production of these substances by whole spleens and whole blood in vitro. At the end of the exposure period, the serum IL-12 level was decreased. Also the in vitro production of IL-6 by whole spleens and whole blood was increased. The levels of interferon-γ, IL-4, and IL-6 in serum and that of interferon-γ, IL-4, and IL-12 in spleen and whole blood culture were not significantly different between the exposed and control groups. These results indicate down-regulation of type 1 T helper cells (involved in eliminating cancer cells, bacteria and viruses) and up-regulation type 17 T helper (Th17) cells (that have an inflammatory action). Aberrant regulation of Th17 cells may play a significant role in the pathogenesis of inflammatory and autoimmune disorders, but these have not been connected to ELF magnetic field exposure.

In search for a possible mechanism to explain the association observed in epidemiological studies between ELF magnetic field exposure and an increased risk of childhood leukaemia, Kabacik et al. (2013) studied gene transcription in mouse bone marrow cells following a 2-hour exposure of the animals to a 100 µT 50 Hz field. In a pilot study, several genes were found to be up-regulated, but in a larger experiment this was not reproduced. The authors state that technical limitations in the accuracy of the assays and biological variation may prevent subtle changes to be detected.

2.2.7 Therapeutic applications

Several studies investigated therapeutic applications of ELF fields (Das et al., 2012b, El-Bialy and Rageh, 2013, Manjhi et al., 2013, Park et al., 2012, Rezaei Kanavi et al., 2012). 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 studied and observed

2.2.8 Conclusions

The exposure levels used in many studies are in the millitesla range and therefore considerably higher than those to which people can be exposed in daily life and higher than the current exposure limits. This means that there is no direct relevance of these experiments for human health. Several other studies used exposure to levels equal to the 1998 ICNIRP exposure limits (i.e. 0.1 mT for the general public and 0.5 mT for workers; in 2010 these have been increased to 0.2 and 1 mT, respectively). These studies are relevant for human exposures, although such exposure levels are seldom encountered.

For memory function, both increases and decreases have been observed, as well as no effect, for exposures to field ranging from 0.1 to 8 mT and various exposure schedules. An increase in stress-related behaviour was observed with exposures of 3 and 10 mT.

Exposures to field strengths ranging from 0.1 to 1.5 mT resulted in a number of effects on brain physiology: an increase in heat shock protein expression and DNA damage, in excitability of the brain and in overall and motor cortex EEG power, but a decrease in visual cortex EEG power; an increased permeability of capillaries and an increase in vascular area; and an increase in accumulation of manganese. A more protective effect was an increase in the dose of the drug pentylentetrazol needed to induce seizures. A notable finding is the restoration of the decrease in pain response effectuated by spinal cord injury by exposures as low as 18 µT.

Exposures ranging from 0.1 to 1 mT had variable effects on testis function and spermatogenesis. No conclusions can be drawn from these studies. A field study on birds indicated some effects of exposures to 0.2 µT fields on the size of the brood, but not on the overall reproductive success.

In a study using an unspecified type of field in the range of 2–1200 nT to expose pregnant rats, an effect on the development of the hippocampus and on learning in the offspring was detected, but only for the range of 30–50 nT. The question is, whether this is a window effect, or a spurious result. In other studies, exposures of chicken embryos to 50 Hz field in the range of 1.33–7.32 mT resulted in effects on the spleen size and increased apoptosis. Also effects on the heart were observed, but only with 2.66 mT. Again, the question is, whether this is a real window effect.

A number of studies investigated oxidative stress in various tissues. Increased levels of oxidative stress were observed in brain following exposures to fields ranging from 0.1 to 2.4 mT. In blood and liver, exposure to 8 or 10 mT led to increased oxidative stress, although the results for 10 mT were not consistent. In bone marrow, DNA damage was observed following exposures to 0.2 or 0.5 mT. The only study into effects of exposure to ELF electric fields found increased oxidative stress in brain and retina with fields of 12 or 18 kV/m

The remaining studies looked a variety of physiological effects. In one study with exposure to fields as low as 33 nT a negative effect on analgesia was observed. In other studies, fields of 0.1 mT had variable effects on α-amylase levels and immune parameters, and no effect on gene transcription. A study exposing the animals to 0.90-1.13 mT fields found a reduction in growth of blood vessels after one day of exposure, but not after two. Finally, in two studies into dentistry, exposure to 1 mT resulted in changes in tooth mineral content indicating an increased risk of caries, but exposure to1.5 mT had a positive effect on the gingiva.

In general, the results of the studies are not very consistent. In some studies a function may be increased and in others decreased, while dose-responses cannot be derived. Most of the results are from single studies that need to be replicated in order to establish whether the observed effects are real or not. Also the large variety of exposure schedules used does not add to get a unified picture. Finally, none of these studies provide information that can be used in the interpretation of the association found in epidemiological studies between ELF magnetic field exposure and an increased risk of childhood leukaemia.

2.3 Human studies

The previous Council (SSM, 2013:19) report concluded that “ELF MF do not seem to have any effects on general physiology (cardiovascular responses, postural control), but effects have been reported related to cortical reactivity, EEG, and short-term memory. The relation of these individual findings to each other remains to be further studied.”

Since then four studies (one methodological, two on effects on electrophysiology and one on other physiological parameters and symptoms) have been published.

2.3.1 Reviews and methodological issues

Since mechanisms are difficult to investigate based on experimental data Modolo et al. (2013) developed biophysical models based on systems of mathematical equations as one approach to overcome some of the problems inherent in experimental data. The biophysical models simulate how the brain tissue interacts with ELF MFs and allows hypotheses testing. They come up with the hypothesis that exposure at 60 Hz MF in the mT range can modulate synaptic plasticity, a hypothesis which needs to be confirmed by further experimental studies.

2.3.2 Electrophysiology

Using an intermittent (2s on, 3s off) sine-wave magnetic field Shafiei et al. (2012) investigated whether ELF MF alters EEG power at the frequency of stimulation. EEG segments of 2s to be included in the analysis were taken from the off-periods of the MF. MF frequencies of 3, 5, 10, 17 and 45 Hz were used. For each frequency a 2 min closed eyes and a 2 min open eyes condition were recorded. A small coil (2 cm outer diameter) producing a flux density of 100 µT at 1.5 cm distance (or no field for sham) was placed onto 5 different scalp locations applying a specific frequency (T4: 3 Hz, T3: 5 Hz, F3: 10 Hz, Cz: 17 Hz and F4: 45 Hz). 19 healthy male subjects (25.6 ± 1.6 years) were studied. It is not clearly mentioned whether the study was single- or double-blind. The analysis showed that the EEG was not significantly affected in the frequency band of stimulation. Sporadic statistically significant alterations of the EEG have been observed for other frequency bands and various regions. However, there was no discussion of possible chance effects due to multiple testing (5 exposures * 5 EEG locations * 7 spectral bands).

Based on the intention to affect the EEG for a therapeutic application and on the idea of a "resonance effect" of the EEG to an ELF magnetic field Amirifalah et al. (2013), from the same group as Shafiei et al (2012), studied potential effects of weak ELF MF in 10 healthy women aged 23 to 30 years. An intermittent (9s on, 7s off) MF exposure of 180 s was applied for each of three ELF frequencies 10 Hz, 14 Hz and 18 Hz in a randomized order. Subjects had exposure and sham sessions (crossover design). MFs were delivered using two small coils at the scalp locations C3 and C4 simultaneously. In order to generate a "pulsed" MF, which was expected to be more prone to effects, a unipolar rectangular electrical signal was used to drive the coils. However, the given calculation of the "Time-Changing ELF MF Rate" seems not to be correct, since the given steep slopes would require much higher voltage pulses at the coils used. The measured magnetic flux density 1.5 cm below a coil was 200 µT. EEG for the analysis was taken from off periods of the exposure intervals and from 2 min blocks pre and post each exposure frequency (or sham). During exposure no significant difference in the absolute and relative power of EEG bands were observed. For 10 Hz MF, a decrease in beta (15-25 Hz), sensimotor (13-15 Hz) and theta (4-8 Hz) EEG was found after exposure in comparison to during exposure. A resonance effect was not observed.

2.3.3 Other endpoints

Kim et al. (2013b) investigated possible effects of a 32 min exposure to a 60 Hz 12.5 µT magnetic field on perception, eight subjective symptoms and physiological changes. The 12.5 µT magnetic field was chosen since according to the authors this was the strongest magnetic field measured directly under transmission lines in the Republic of Korea. Two groups of subjects were investigated: a) 30 adults (15 females, 27.9 ± 5.9 years) and b) 30 teenagers (16 females, 14.8 ± 1.4 years) in a double-blind randomized cross-over study. The magnetic field was applied to the head by a pair of coils (distance 50 cm) constructed for this study, background fields were controlled for. Information on heart rate, respiration rate and heart rate variability was collected for 5 min for each of four different stages: pre-exposure, after 11 and 27 min of exposure, and post exposure. Data analysis is based on comparison of changes from baseline (pre-exposure measure) by exposure. The authors did not find significant exposure effects on these physiological parameters.

2.3.4 Conclusion on ELF human studies

The recent study on physiological parameters (Kim et al., 2013b) underlines the conclusion from the previous Council report that ELF MF do not seem to have any effects on general physiology. The two recent electrophysiological studies add to the conclusion that effects on the EEG have been observed which is in line with the results of an Italian expert working group review (Di Lazzaro et al., 2013). It is, however, difficult to distinguish between statistically significant and physiologically meaningful effects. At least the latest studies indicate that stimulation with various low frequencies did not lead to any resonance effects in EEG activity.

2.4 Epidemiological studies

In the previous Council report (SSM, 2013:19) 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. Further, some studies indicated a possible association between neurodegenerative diseases (in particular Alzheimer’s diseases 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

In Iran, Mahram et al. (2013) conducted a survey where the effects of ELF-MF on pregnant women residing close to power lines were analysed. Magnetic fields were measured under power lines to define areas as exposed or unexposed, although no information was given about cut-off points to differentiate the one from the other area, number of measurement points, duration of measurements, number of lines that were assessed, voltage level of the lines and so on. Unexposed areas were defined as areas within two or three blocks of the exposed areas, in order to reduce potential for confounding by socioeconomic status. Exposed women resided all within about 25m of a power line and had an average exposure of about 0.3 µT, unexposed women about an exposure of 0.04 µT. The authors describe that they invited all pregnant women of the respective areas to participate, but did not provide information as to how these women were identified, how many were invited and what the response rate was. Mothers filled in questionnaires upon delivery of the child. The study included 380 pregnant women, of which 222 were characterized as exposed and 158 as unexposed. Information about pregnancy duration, birth weight, length, head circumference, fetal growth, gender and congenital malformations were collected through direct questions and from local health centres and the hospital where the delivery occurred. The authors found no significant differences between the exposed and unexposed groups for all endpoints, indicating no detrimental effect of magnetic field exposure on the assessed birth outcomes. However, exposure assessment and recruitment is poorly described. Potential confounders were only considered in a very crude way, which is a limitation of this study.

2.4.2 Child development

A cross-sectional study evaluated the association between ELF-MF exposure from power lines and neurobehavioural tests in primary school children (Huang et al., 2013). Spot measurements of ELF-MF levels were taken in classrooms, corridors and playgrounds of two primary schools in Guangzhou, China. 437 children, aged 9-13 years, were included in the study. Parents filled in a questionnaire regarding demographics and self-reported exposures at home, and the children performed a test battery of four neurobehavioural computerized tests (visual retention test, simple reaction time, digit symbol, pursuit aiming test). Median exposure levels were 0.03 µT (IQR 0.02-0.04) in the first and 0.2 µT (IQR 0.19-0.31) in the second school, which was placed less than 100 m from a 500kV line. Students between the two schools had a similar distribution in terms of demographics such as school age, BMI, sex, nationality, household income and other aspects, but students from the school with the lower ELF-MF exposure were more likely to be boys and were a bit older. After controlling for potential confounders, students in the exposed school were found to score lower on all of the four tests, with statistically significant differences in the visual retention as well as the pursuit aiming task. Although the investigators accounted for a range of potential confounders, residual confounding is of concern because the two schools may attract different populations of children. Also, there is no known mechanism how the ELF-MF at the low levels encountered in the exposed school, could affect neurobehaviour in the children.

2.4.3 Childhood cancer

In a case-control study performed in the Czech Republic (Jirik et al., 2012), children aged younger than 15 years and diagnosed with childhood leukaemia (predominantly acute lymphoblastic leukaemia), were included. 79 controls were identified from medical records (from children who had visited the hospital for other reasons than cancer) and matched on age, sex and area of residence (district or town) 1:1 to the cases. ELF-MF were measured and cut-offs of 0.2, 0.3 and 0.4 µT were investigated. No increased risk emerged from any of the analyses; all OR remained just below unity, with wide confidence intervals (13 cases and 14 controls were included in the highest exposure category). In a previous publication, the measurement strategy was reported to be based on spot measurements directly outside of homes and in schools, and supplemented with some repeat measurements to assess variation over days and seasons, measurements inside some of the homes, three personal measurements, and measurements in the vicinity of power lines (Jirik et al., 2011). Given that the analysis was based on spot measurements outside of homes, exposure misclassification could have contributed to the result reported here. The sample of the study is small and thus the power low to observe an increased risk. In addition, the large proportion of cases and controls in the highest exposure category is implausible. In other childhood leukemia studies, the proportion of children exposed to levels >0.4 µT is below 5%, in particular in Europe. In general, case and control recruitment is not well described and, based on the limited available information, selection bias seems likely.

Lagorio et al. (2013) evaluated feasibility of a measurement-based exposure assessment to benzene in a small case-control study performed between 2002-2004 for childhood leukaemia cases diagnosed between 2000-2001 in seven Italian provinces. For a subset of 48 cases and 77 controls, measurements of benzene as well as of 48 hour measurements of ELF-MF in the child's bedroom were available and could be analysed with regard to potential confounding of these two exposures. A positive correlation between benzene exposure and ELF-MF was detected, but cases were not more likely to have lived in residences exposed to higher levels of ELF-MF compared to controls. The small sample size precludes from firm conclusions.

Keegan et al. (2012) published a large case-control study on paternal occupational exposure assessing 33 different types of exposures at work. The authors analysed about 15 000 cases of childhood leukaemia, of cases born and diagnosed between 1962 and 2006 in Britain, matched to control children from the national birth registry. Controls were matched on sex, date of birth and birth registration sub-district. Paternal occupation was extracted from birth registration records and exposures assigned to occupations based on occupational hygienist ratings. All leukaemias were analysed separately from (acute) lymphoid leukaemia, acute myeloid leukaemia and other leukaemias. Including all cases of leukaemia, the OR for children of fathers exposed to ELF-MF was 1.08 (95%CI 0.98-1.19). Increased risks emerged only in the subgroup of “other leukaemias” with an OR of 1.64 (95%CI 1.14-2.38). Strength of the study is its sheer size and that it is based on registry data, thus making it not likely that results were affected by participation bias and/or reporting bias. It is unclear, however, why an older exposure classification based on occupational hygienists rating was applied in this study. Job exposure matrices are available that are based on measured magnetic field exposure data and it might have been more informative to use those instead.

In France, a case-control study was performed on childhood leukaemia and residential distance of the place of residence at the time point of the diagnosis to the next overhead power line. 2779 children and 30 000 controls were included into the study (Sermage-Faure et al., 2013). Power lines of different voltage levels, 63-150 kV as well as 225-400 kV (VHV – “very high voltage overhead power line”), were evaluated. Over all children and all power lines combined the OR was 1.2 (95%CI 0.8-1.9) for children living within a distance of 50 m to a power line compared to children living further away. No increased risks were observed for the subgroup of children aged 5-14 years (OR=1.0, 95%CI: 0.3-3.3 and OR=0.9, 95%CI: 0.4-2.1), for the two voltage levels, respectively. However, increased risks were found for 0-4 year-old children living within 50 m of a VHV line (OR=2.6, 95%CI: 1.0-6.9), but not when living within 50 m of the lower voltage-level lines (OR=1.1, 95%CI: 0.5-2.3). For the VHV lines, risks were increasing when the analysis was restricted to those children with very high quality of the geo-coding (i.e. the exact geo-location of the address where children were living had an uncertainty of < 20 m), with an OR of 4.1 (95%CI: 1.3-13.3). As a registry based study, the results would not be affected by participation bias or by reporting bias. Some degree of residual confounding might still play a role, given that the authors could not adjust for socioeconomic status (SES). However, the association between SES and childhood leukaemia is not very clear and it is also unclear why this should induce an effect in one of the age groups but not the other. It would have been preferable if the authors had not evaluated distance to the lines, but actual exposure to ELF-MF, but this step is still work in preparation, as the authors write.

In a reanalysis of 11 studies, Swanson et al. (2012) evaluated if the geomagnetic field could have acted as an effect modifier on previous analyses of childhood leukaemia and magnetic field exposure. The approximate geomagnetic field for the study area and the mid-year of the years of case diagnosis was determined and a meta-regression was performed. This was done in order to assess if individual study results of the association between ELF-MF exposure and childhood leukaemia differed according to levels of the geomagnetic field. Geomagnetic fields varied between 22 and 57 µT, but meta-regression provided no evidence that the observed heterogeneity between the previous studies was due to the geomagnetic field. However, all except one study came from a similar range of latitudes and therefore there was only little contrast in the geomagnetic field and hence little power to investigate the research question in the first place.

Data of nine earlier studies addressing exposure to magnetic fields and childhood leukaemia were used to set-up a cohort study on survival as well as event-free survival of childhood leukaemia cases with respect to ELF-MF (Schuz et al., 2012). In all of the original studies, magnetic fields had been measured in the homes of the children, with exception of two studies (performed in Denmark and in Sweden), where magnetic fields from power lines had been modelled. In the current analysis, 3073 cases were included and categorized according to their exposure into groups of <0.1, 0.1-0.2, 0.2-0.3, >0.3 µT. No exposure-response relationship was observed across these exposure categories, with hazard ratios (HR) of 1.42 (95%CI 0.99-2.05), 1.27 (95%CI 0.65-2.50) and 0.96 (95%CI 0.49-1.89) for overall survival, and 1.10 (95%CI 0.82-1.46), 1.14 (95%CI 0.69-1.89) and 0.76 (95%CI 0.44-1.33) for event-free survival, respectively. The underlying idea of the analysis was to test if magnetic fields promote growth of leukaemia cells and thus also lead to a higher recurrence of the disease. In addition, by only including cases, the study was designed to circumvent potential bias introduced in the original studies by differences in participation of cases and controls: Original studies could have been affected if controls with higher exposure did not participate, which could lead to an underestimation of exposure in controls. As acknowledged by the authors, a limitation of the study is the use of the original exposure assessment and no information on further residential history after diagnosis was available. This may have produced substantial exposure misclassification if the exposures had changed during the 3-21 years of follow-up (49 years for the sub-analysis including the data set from Sweden). Given the severity of the disease and that the investigators in the original studies performed measurements in the homes, parents must have been aware of the study hypothesis. It is therefore the question in how far parents were inclined to change place of residence after participation in the study. As a consequence it is unclear whether there is a true absence of association or whether an underlying risk was missed due to exposure misclassification.

2.4.4 Adult cancer

In a large case-control study, cancer incidence and exposure to ELF-MF from power lines was evaluated (Elliott et al., 2013). Cases as well as controls were selected from the national cancer registry, with cases and controls registered between 1974 and 2008 and of ages 15-74 who were included. 7,823 leukaemia cases, 6,781 brain/ central nervous system cases, 9153 malignant melanoma cases and 58,404 breast cancer cases were analysed. Controls were persons with a range of cancers that were described as “cancers not considered to be associated with electric and magnetic fields”, many of which were cancers of the gastrointestinal system. Cases and controls were frequency matched 1:3 (1:1 for breast cancer) on year of diagnosis and region. For the address at the time point of diagnosis, distance to power lines (primarily 275 or 400 kV lines) as well as modelled exposure to ELF-MF from power lines was evaluated. The statistical analysis was adjusted for age, sex, and area-level deprivation and rurality. No statistically significant increased risks emerged from any of the analyses, with ORs for living within 50 m of a power line of 1.11 (95%CI (0.83-1.48), 1.22 (95%CI 0.88-1.69), 0.82 (95%CI 0.61-1.11) and 1.01 (95%CI 0.85-1.21) for leukaemia, brain/ central nervous system, malignant melanoma and breast cancer, respectively. ORs for modelled magnetic field exposure were similar.
Strength of the study is that it is large, based on registry data, and that both distance as well as magnetic field exposure levels were available. The study also includes many highly exposed persons than could be previously analysed, in particular persons with exposures levels > 1 µT. It has been criticized (Schuz, 2013) that cancer patients were used as controls, although cancers that have previously been associated with the exposure to electromagnetic fields were excluded from the pool of controls. Given previous reviews (Kheifets et al., 2008) that highlighted differences in results of occupational ELF-MF exposure by subgroups of cancers (in particular the different types of leukaemia), and since the study was able to include a relatively large group of exposed cases, it would have been informative to also see results on acute or chronic/ lymphocytic or myelogenous leukaemia.

Sorahan (2012) reported cancer morbidity in a cohort of over 80,000 employees of the former Central Electricity Generating Board of England and Wales. Employees had worked for the company for at least 6 months in the time between 1973 and 1982. Cancer morbidity was evaluated for the period 1973-2008. Overall, risk estimates of the cancer incidence compared to the general population was slightly below expectation. Brain cancer and leukaemia were close to unity in this analysis, which is of interest, given that especially these cancer types have been previously associated with ELF-MF exposure. Increased risks were found in male workers for mesothelioma, non-melanoma skin cancer, and prostate cancer, and in women for the small intestine and nasal cancer. Apart from age and gender no other factors are considered in this analysis. A major concern for that type of analysis is the so called "healthy worker effect" which means that people who are employed are often healthier on average than the whole population.

A "hypothesis-generating" study was performed by Rodriguez-Garcia et al. (2012) on the population of El Bierzo, Spain. El Bierzo is described as a highly industrialised part of the country, at an altitude of about 500-600 m and enclosed by a mountain ring, with close to 150,000 inhabitants living in 39 municipalities. The authors calculated standardised incidence rates of all acute leukaemias, as well as stratified by acute lymphoblastic leukaemia (ALL) and acute myelogenous leukaemia (AML) occurring in El Bierzo between 2000 and 2005 on some exposure categories: Exposure was assessed as distance of the municipality centre points to pollutant facilities as well as to the maximal density of high-voltage power lines. The standardised incidence rate of AML was higher in municipalities closer than 10 km compared with those further away from maximal density of high-voltage power lines, and higher in those municipalities within 5 km from a thermoelectric power plant compared to those further than 5 km. The association was not observed for ALL. Given that the hypothesis of an association of (childhood) leukaemia exists for quite some while now, it remains unclear why this study was performed. In addition, increased ELF-MF exposure would be expected only in very close distance categories to the power plants/lines, but not across the distances that were evaluated here. ELF-MF diminishes very quickly with distance from the source and the categories assessed in this publication are not suitable to differentiate low from high exposed inhabitants. Finally, the authors suggest air pollution levels as alternative causes for the observed higher incidence of AML and ALL in the valley, but such exposures were not evaluated.

Li et al. (2013) published results of a large cohort study of 267,000 workers from about 500 textile factories in Shanghai, China. Women were enrolled in the study between 1989 and 1991 and were followed-up for breast cancer until July 2000, using medical reports and cross linkage to the cancer registry. 1,763 breast cancer cases were observed and a nested case-control analysis was performed, with 4,780 women matched as controls to the cases. Measurements were collected from 1,115 workers in 57 factories, and these measurements were used to develop a job-exposure-matrix (JEM). All occupations of the work history of the women were linked to the JEM and cumulative exposure was evaluated using Cox regression. No increased risks emerged from the analyses comparing higher to lower exposed women. This result is in line with a large amount of previous publications, as highlighted by Feychting in an invited commentary to the study (Feychting, 2013). The author stated in the commentary that: “With the existing knowledge about biophysical mechanisms and consistent epidemiologic evidence, we can be confident that exposure to ELF magnetic fields does not cause breast cancer. Further epidemiologic studies on ELF fields and breast cancer will have little new knowledge to add”.

The association between the exposure to ELF-MF and female breast cancer was meta-analysed by Chen et al. (2013a). 23 studies from 1991-2007 were included in the current analysis. Overall, studies showed a very small increased risk with an OR of 1.07 (95%CI 1.02-1.13) and moderate heterogeneity between studies (I^2= 39%). This result is in contrast to a relatively recent meta-analysis from (another) Chen et al. (2010) that included 15 studies published between 2000 and 2009 and reported an OR of 0.99 (95%CI 0.9-1.09).

Sun et al. (2013) presented a meta-analysis on male breast cancer. 18 studies were included, of which 7 were case-control and 11 were cohort studies. The majority of the studies addressed occupational exposure. The number of included cases ranged from 2 to 203 persons in the individual studies. Pooled across all studies, a slightly increased risk was reported with a RR of 1.32 (95%CI 1.14-1.52) and with little heterogeneity between studies (I^2=25%). Male breast cancer accounts for about 1% of all breast cancer cases. Given that it is a relatively rare disease, one could have assumed that only those studies that find at least a few exposed cases get published and that therefore the results were mainly driven by publication bias. Interestingly, there was no evidence of any funnel plot asymmetry (p-value of Begg’s test = 1.0), which speaks against such an assumption.

2.4.5 Neurodegenerative diseases

Frei et al. (2013) reported a case-control analysis where all adult persons living in Denmark diagnosed with neurodegenerative diseases between 1994 and 2010 were included. Persons diagnosed with Alzheimer’s disease, vascular dementia, other dementia, Parkinson’s disease, multiple sclerosis and motor neuron disease were defined as cases. Distance of the residential address to the closest high-voltage power line was assessed. Per case, 6 controls were matched on age and gender to the cases. Residential history of the 20 years preceding the diagnosis was evaluated with respect to the distance of the building to the next power line. In line with a previous Swiss analysis (Huss et al., 2009), distances in categories of 0-50 m, 50-200, 200-600 m were compared to living in distances beyond 600 m. However, power lines with levels of 132-400 kV were included whereas in the Swiss study only very high voltage lines (220-380 kV) were considered. Further analyses were performed by duration of living at a distance of 50 m to a power line and for Alzheimer’s disease also by age (65-75 years, >75 years). No increased risks were found for distance or duration categories for the neurodegenerative diseases with HRs for ever having lived within 50 m of a power line around unity for all investigated outcomes. An exception was reported for younger Alzheimer's cases: Risks for persons 65-75 years old and living within 50 m of a power line had a HR of 1.92 (95%CI 0.95-3.87) and this was higher when only diagnoses after 2003 were taken into account (HR 2.59, 95%CI 1.17-5.76). With only 5 Alzheimer's cases who had ever lived within 50 m of a 220 or 400 kV line the study was underpowered to address risks for persons living close to lines with very high voltage levels, which would be expected to generate higher exposure to magnetic fields. Interestingly, for these 5 persons the HRs reported in the Danish study were very close to those in the Swiss study (1.31, 95%CI 0.5-3.5 and 1.25, 95%CI 0.8-1.9, respectively). The study would have been more informative if magnetic field exposure had been modeled.

Das et al. (2012a) published a case-control study performed in the Burdwan Medical College and Hospital, India. 110 cases of amyotrophic lateral sclerosis and 240 age and sex matched controls were included in the study. Controls were acquaintances (excluding family members) and other patients attending the neurology department, without clear specification for which diseases the controls had visited the neurology department. Cases and controls were interviewed regarding exposures of the preceding 10 years. Neither cases nor controls were judged to have been exposed to high levels of electromagnetic fields, but for 8 cases (7.3%) and three (1.3%) of controls there was report of electrical trauma (electrical shock or injury). This translated into an OR of 5.8 (95%CI 1.4-34.5). It is a strength of the study that electrical trauma was verified with medical documentation. However, it is somewhat unclear how affected persons could have acquired electrical trauma without anyone being exposed to ELF-MF fields. Given the discussion around the Motor Neuron Disease Amyotrophic Lateral Sclerosis (ALS) and whether electrical trauma or exposure to magnetic fields could be the relevant exposure, a more in-depth description of the occupations would have been of interest in this context.

A meta-analysis on occupational exposure to ELF-MF and neurodegenerative diseases was performed by Vergara et al. (2013). 42 studies were included, of which 20 addressed Alzheimer's disease, 21 Motor Neuron Disease including Amyotrophic Lateral Sclerosis, 18 Parkinson's disease, 9 dementia and 5 Multiple Sclerosis. Studies published between 1983 and 2011 were included in the analysis. Small increased risks were calculated from random-effects meta-analysis on Alzheimer's disease (RR 1.27, 95%CI 1.15-1.4) as well as Motor Neuron Disease (RR 1.26, 95%CI 1.1-1.44), but not for Parkinson's disease (0.97, 95%CI 0.91-1.03), dementia (1.05, 95%CI 0.96-1.14) or Multiple Sclerosis (0.98, 95%CI 0.85-1.12). For Alzheimer's disease, increased risks were detected in those studies using estimated ELF-MF field levels, but for Motor Neuron Disease, increased risks were found in studies analysing occupational titles. Some evidence for funnel plot asymmetry was found for studies reporting on Alzheimer's disease or Motor Neuron Disease, which suggests publication bias. This meta-analysis could be described as the most comprehensive to date, and results of the meta-analysis do not deviate strongly from previous systematic reviews (Garcia et al., 2008, Hug et al., 2006, Zhou et al., 2012, Santibanez et al., 2007). Different from previous meta-analyses is that risk estimates also of specific, single occupations were included (e.g. for electricians or welders alone).

2.4.6 Cardiovascular diseases

A Dutch case-cohort study (Koeman et al., 2013) explored the association between occupational ELF exposure and mortality caused by cardiovascular diseases (CVD). The full cohort consisted of 120,852 persons in the age group 55-69 years recruited in 1986 through The Netherlands Cohort Study on diet and cancer. The participants completed a questionnaire on occupational history, dietary habits and other potential risk factors for cancer. Deaths were identified through the Dutch Bureau of Genealogy for the period 1987 to 1996, corresponding to 10 years of follow up. In total, 8,200 CVD deaths were traced, and of these, information on relevant occupational history and potential confounders was available for 6,151 cases (75%). Analyses were based on a random sample of 3,881 persons of the cohort, and all incident cases of CVD mortality. 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. The median intensity of ELF in these categories translated into approximately: background (0.11 µT), low (0.19 µT) and high (0.52 µT). Ever low or high exposure, exposure duration and cumulative exposure were considered as exposure metrics. The models were adjusted for gender, age, smoking, alcohol, education and body mass index. The hazard ratio (HR) of total CVD mortality in relation to occupational ELF showed no association for ever low or high exposure (HR 1.02 (95% CI: 0.93-1.13)) or exposure duration (RR per 10 y of exposure: 0.98 (95% CI 0.95 to 1.02) in men) or in analyses of cumulative exposure. Absence of association was confirmed in stratified analyses by sex, smoking status and alcohol intake or when addressing various subtypes of CVD. This study does not indicate an association between ELF-MF exposure and cardiovascular diseases which is in line with previous research on this topic.

2.4.7 Other outcomes

In a cross-sectional study in the car industry, stampers and welders were included; their exposure to ELF-MF as well as noise was assessed, Liu et al. (2013b). Welders were classified as "high exposed" and compared to stampers, which were classified as "low exposed". Median exposure to ELF-MF was higher across sixteen spot measurements in the welders' workplace (0.5 µT) compared to the median of six spot measurements (0.07 µT) in the stampers workplace, but noise levels did not differ. Self-reported health as well as several blood markers was assessed in 123 “unexposed” and 229 “exposed” persons. Several blood parameters differed between the two groups, but of self-reported health only hair loss was reported more often in the “exposed” group. The authors did not describe how spots were selected for the measurements or how long and when measurements were performed (e.g. during or after work shifts). While the authors described that workers did not differ with respect to gender, they also wrote that all subjects were males. Especially welders would be expected to be exposed to a whole range of substances, and not exclusively to EMF. Differences of health outcomes across the groups can therefore not be attributed to the exposure to EMF alone. Multiple testing was not accounted for and could have contributed to the findings. While additional information on potential confounders was available, analyses were not adjusted for such factors.

Chromosome aberration and micronucleus assays were investigated in Coimbatore, India (Balamuralikrishnan et al., 2012). 20 persons without previous exposure to ELF-MF (“unexposed”) were compared with 50 exposed workers: 28 persons classified as “direct exposed”, these were persons responsible for operating and maintaining the electricity transmission network (210 and 440 kV levels), and 22 persons were grouped as “indirect exposed”; these were office workers of the same departments. Measured ELF-MF around the power generation and transmission lines were reported to vary between 0.3 and 21 µT. All four selected endpoints (chromatid and chromosome aberration, total chromosomal aberration and micronucleus frequency per 1000 cells) differed significantly in the group of the “direct exposed” compared to “unexposed” persons. The differences remained in stratified analysis according to smoking status or age group.
The authors describe having performed personal measurements, but the results of these measurements are not reported in the publication. It is therefore unclear to what level of ELF-MF the workers in the different groups were exposed. While it is mentioned that the control group had no previous ELF-MF exposure, it is not listed what kind of occupations the persons in this group had. For the interpretation of the study it would have been informative to additionally learn what other kind of exposures the workers could be exposed to and if that could have affected the reported results. Finally, results differed across smoking status and age groups, and results were presented stratified across these two factors, but analyses could also have been adjusted for both factors at the same time. Other factors were not considered in the analyses, which is a strong limitation.

To investigate the effect of ELF-EMF produced by magnetostrictive cavitrons on the serum cortisol level, a convenience sample of 18 dentists and 23 dentistry students (Mortazavi et al., 2012b) were randomly assigned to an exposure group (n=21) or a control group (n=20). Blood samples were collected twice between 8:30 and 9:30, and between 11:30 and 12:30, so before and after using cavitrons, the exposure source assessed here. Before starting the work cortisol levels of exposed and unexposed participants did not differ strongly, whereas at noon the exposed workers had statistically significant lower cortisol levels. There are several factors that make the results of this study difficult to interpret: First, it is unclear how study participants were randomised into exposure groups in this observational study. Second, duration of using cavitrons was reported, but not the associated exposure levels. Other factors that might have influenced cortisol levels were not considered in the analysis (e.g. age of the participants) and it was not reported what kind of activity the exposed and non-exposed did during the study morning apart from using cavitrons. In summary, it is not clear whether the results are affected by different activity patterns between exposed and non-exposed and no firm conclusions can be drawn from this publication.

In a French study the profiles of numerous haematological and immune system parameters of 15 substation workers of 225 and 400 kV stations, workers employed for a period between 1 and 20 years were compared with 15 control subjects with similar personal characteristics and diurnal rhythm (Touitou et al., 2013). All study participants were healthy and male. During one night, blood samples of participants were taken every hour between 20:00 and 8:00 and analysed for red blood cells, haemoglobin, haematocrit, platelets, mean platelet volume, total white blood cells, lymphocytes, monocytes, eosinophils, basophils, neutrophils, Ig (Immunoglobulin) A, IgM, IgG, CD (cluster of differentiation) 3, CD4, CD8, natural killer cells, B cells, total CD28, CD8+ CD28+, activated T cells, interleukin (IL)-2, IL-6, and IL-2 receptor. Data were analysed with repeated measures ANOVA without considering covariates apart from time and exposure-time interaction. ELF-MF was measured during one week with an Emdex II. Weekly geometric mean ELF-MF exposure of the substation workers was 0.72 µT (range: 0.1-2.6 µT). For the controls weekly geometric mean exposure was 0.04 µT (range: 0.004-0.092 µT). None of the haematological and immune system parameters differed between exposed workers and controls. In another publication of the same study (Touitou et al., 2012), blood chemistry parameters were assessed. Statistically significant differences between groups were reported for glucose, sodium, chloride and phosphorus, of 10 tested parameters. It was, however, not reported if exposed had higher or lower values than unexposed. The careful outcome and exposure measurements are strengths of this study. However, the small sample size and lack of confounding adjustment is a limitation. In a review from the same authors it was concluded that animal and human studies on the effect of ELF-MF exposure on melatonin and cortisol, two markers of the circadian system, provided contradictory results (Touitou and Selmaoui, 2012). Similar conclusions were reached in a review on human and animal studies addressing pineal melatonin level disruption by Halgamuge (2013).

So called “dirty electricity” consists of high-frequency voltage transients in the 50 and 60 Hz power supply system generated by arcing, sparking and devices that interrupt currents flow. Milham and Stetzer (2013) reported the result from an intervention study performed in a public library where “dirty electricity” was reduced from over 10,000 Graham/Stetzer to below 50 G/S units by installing plug-in capacitive filters on 11th of October 2011. In 7 volunteers working in the library, urinary dopamine end phenylethylamine (PEA) was determined a few days before and after the intervention and every 2 weeks for the next 18 weeks. According to the authors, dopamine level and PEA gradually increased after the intervention (with an initial decline for dopamine). However, only averaged values are presented, but not the variation across individuals and no data analysis is provided regarding statistical inference of the differences over time. The result table shows a rather high variation for the averaged parameters. In addition, the authors describe that at baseline, of the seven participants, four had elevated levels, two had decreased and one person had normal levels. Over the duration of the project, the number of participants was reduced to six, and it is unclear if the change of the average values was influenced by the one drop-out. Finally, the assessed parameters may be influenced by many other factors including alcohol or coffee consumption or seasonality, but these factors were not considered in the study. It is also a limitation of the study that only one single baseline measurement was taken prior to the intervention. The concept of “dirty electricity” is not established in scientific research. It is not clear what the unit “Graham/Stetzer” exactly refers to and only three studies can be found in Pubmed that used this unit. For these reasons no conclusions can be drawn.

2.4.8 Conclusions on ELF epidemiological studies

New epidemiological studies on ELF MF exposure and cancer tended to confirm previous results. One large French study found some indications for an increased childhood leukaemia risk whereas small studies on this topic had too little power to be informative. Interestingly, a large pooled analysis found no evidence that survival rate of childhood leukaemia patients was affected by ELF MF exposure, but the study might have been affected by exposure misclassification. With respect to adult cancer, absence of risk was confirmed in most studies. In particular, with respect to breast cancer, evidence of absence of risk has increased with a large, well conducted cohort study of 267,000 workers. Similarly, a large Dutch general population cohort study confirmed the absence of risk for cardiovascular diseases in ELF MF exposed workers.

The main result of a Danish cohort study on ELF MF from power lines and Alzheimer’s disease did not indicate an increased risk for people living within 50 m of a high voltage power line. However, the power of the study was too small to address risk related to the highest voltage lines and one subgroup analysis pointed to an increased risk for people aged 65 to 75 years. A comprehensive meta-analysis found an increased risk for Alzheimer's disease and the Motor Neuron Disease Amyotrophic Lateral Sclerosis (ALS) mostly based on occupational studies. However, publication bias is of concern for the occupational studies and, as discussed in the previous Council report, it is unclear whether electric shocks and not magnetic fields are involved in the development of ALS. Thus, the question whether ELF MF causes Alzheimer's disease or ALS is still not resolved and might be further investigated.

3. Intermediate frequency (IF) fields

3.1 Cell studies

A paper has been published by Sakurai and co-workers dealing with the effect of frequencies related to induction heating cooktops. They exposed human-fetus-derived astroglial cell line (SVGp12) for 2, 4 and 6 h to 23 kHz magnetic fields at 2 mT to evaluate the effect of gene expression. No effect on gene expression profile was detected by comparing exposed and sham-exposed cell cultures. In contrast, heat treatment at 43°C for 2 h used as positive control significantly altered gene expression (Sakurai et al., 2013).

3.2 Animal studies

Win-Shwe et al. (2013) used male and female C57BL/6J mice (only n=3/group/sex) in a control (sham-exposed), an exposure, or a recovery (one week after exposure) group for testing the effect of an intermediate frequency magnetic field (IF-MF) (21 kHz, 3.8 mT, 1 h/d for 2 weeks) on memory function-related genes and histopatholgy of the hippocampus. For data evaluation animals from both sexes were pooled to n=6/group because no sex differences in the following parameters were seen. Twenty-four hours after final exposure, the relative mRNA expression levels of the N-methyl-D aspartate (NMDA) receptor subunits NR1, NR2A, and NR2B as well as transcription factors [calcium/calmodulin-dependent protein kinase (CaMK) -IV, cyclic AMP responsive element binding protein (CREB)-1and neurotrophins (nerve growth factor (NGF), and brain-derived neurotrophic factors (BDNF)] did not change significantly in the IF-MF-exposed mice. In addition, the histological morphology of the hippocampus remained normal in the exposed mice. In summary, IF-MF did not affect the expression levels of memory function-related genes in the hippocampus. The authors stated that the findings suggest that IF-MF exposure may not affect cognitive function in the present animal model.

3.3 Conclusions on IF

Because only one in vitro and one animal paper are available in this frequency-range, no general conclusions can be drawn.

4. Radiofrequency (RF) fields

4.1 Cell studies

The possible effects of RF exposure have been evaluated considering DNA integrity, apoptosis and protein expression in several human and animal cell cultures.

4.1.1 DNA integrity

Speit et al. (2013) repeated some of the experiments carried out in the framework of the EU-funded REFLEX project, where genotoxic effects were reported in several cell lines after RF exposures. In this study Speit and co-workers attempted to replicate the induction of micronuclei and DNA migration (alkaline comet assay) in HL-60 cells exposed for 24 h (5 min on/10 min off cycles) to 1800 MHz, CW, at a SAR of 1.3 W/kg. By using the same exposure system and the same experimental protocols as the authors of the original study, they failed to confirm its findings. They did not find any explanation for these conflicting results.

Waldmann et al. (2013) tested the genotoxicity of an 1800 MHz GSM signal on human peripheral blood lymphocytes of 20 healthy donors in a large age-range (16-65 years) by looking at different endpoints, viz. chromosomal aberrations, sister chromatid exchanges, micronuclei and strand breaks (using the alkaline comet assay). Stimulated cells from each donor were exposed for 28 h to 0.2, 2 or 10 W/kg. None of the endpoints examined showed results different from the sham-exposed control. Therefore, the results of this study, carried out by six independent laboratories, indicated no evidence of genotoxic effects induced by RF.

Vijayalaxmi et al. (2013) investigated the effect of 2 h exposure to 2450 MHz (CW and WCDMA modulation) on the induction of micronuclei in peripheral blood lymphocytes from 4 donors. After RF exposure, cells were stimulated to divide. For each donor, positive controls (1.5 Gy gamma rays) and cultures treated with melatonin were also set up. No increased (?) induction of micronuclei was detected in RF-exposed cultures compared to sham-controls. Melatonin did not induce variation in the number of micronuclei. As expected, positive controls exhibited a significant increase in micronucleus frequency that was reduced by melatonin.

Xu and co-workers exposed six different cell types to an 1800 MHz GSM signal (SAR=3 W/kg), for 1 or 24 h (5 min on/10 min off cycles). No changes in the average number of foci per cell was detected after 1 h exposure in each of the six cell types examined, while 24 h exposure resulted in a significant increase of foci formation in two cell types. However, the elevated number of foci was not associated with DNA fragmentation (using the comet assay), cell cycle arrest, cell proliferation or viability changes, although a slight but not statistically significant increase in ROS formation was detected. The authors concluded that RF is able to induce foci formation in a cell-type dependent manner, but that the induced DNA damage may be reversible or compensated by DNA repair pathways (Xu et al., 2013).

Sannino et al. (2013) exposed stimulated cultures of peripheral blood lymphocytes from four male healthy donors for 20 h to 1950 MHz radiofrequency fields at an SAR of 0.3 W/kg. For sham exposure a separate chamber was used. The temperature control experiment was not simultaneously run. At 48 h, the cells were subjected to 1.0 or 1.5 Gy X-ray irradiation (XR). After a 72 h total culture period, cells were collected to examine the incidence of micronuclei (MN). No effect was recorded in cultures exposed to RF alone with respect to sham-exposed cultures while there was a significant decrease in the number of MN in 2 out of 4 and 3 out of 4 lymphocyte cultures exposed to RF + 1.0 and 1.5 Gy XR, respectively, as compared with those subjected to XR alone. According to the authors, the observations confirm and extend previous results on RF-induced adaptive response obtained by the same research group where a protective effect of RF was also detected against DNA damage induced by Mitomycin-C , a chemical mutagen (Sannino et al., 2009, Zeni et al., 2012). Unfortunately, a detailed discussion on potential mechanisms for the adaptive response as well as on the subject responder vs. non-responder is missing. Finally, the Zeni et al. paper does not show a normal linear dose response.

Opposite results were reported by Liu et al. (2013a). They exposed mouse spermatocyte-derived GC-2 cells to 1800 MHz (GSM-talk mode) for 24 h (5 min on/10 min off cycles). An increase in the extent of DNA migration was found when a SAR of 4 W/kg was tested, as assessed by the FPG modified comet assay. It allows, by using glycosidase, to detect oxidative damage caused by reactive oxygen species at the level of DNA molecule. No effects were detected at lower SAR values (1 and 2 W/kg). Moreover, an increase of DNA adducts and of ROS production was also detected, while no DNA strand breaks were observed by the alkaline comet assay. The authors suggested that RF exposure may produce oxidative DNA damage, although it should be noted that 4 W/kg is a SAR value higher than the exposure limit suggested by the ICNIRP.

In a paper from Hintzsche and co-workers, human primary dermal fibro-blasts (HDF cells) and a keratinocyte cell line (HaCaT) were exposed to a 106 GHz field in different conditions to evaluate primary DNA damage (by the comet assay) and chromosomal damage (by the micronucleus assay).

Cell cultures were exposed from below with a collimated Gaussian beam in a modified incubator at defined environmental conditions for 2 h, 8 h, and 24 h with different power density ranging from 0.4 – 20 W/m^2, representing levels below, at, and above current safety limits. Neither DNA strand breaks nor alkali-labile sites in the comet assay, or chromosomal damage in the form of micronucleus induction were detected (Hintzsche et al., 2012).

4.1.2 Apoptosis

Jin et al. (2012) pre-exposed human promyelocytic leukemia HL-60 cells to 900 MHz RF (at an average SAR of 0.25 μW/kg) and then treated them with the chemotherapeutic drug doxorubicin. Cell cultures were also set up to test the effect of RF alone. No effects of 900 MHz RF exposure were detected. An increased cell proliferation, decreased apoptosis, increased mitochondrial membrane potential, decreased intracellular Ca^{2+} and increased Ca^{2+}-Mg^{2+}-ATPase activity were detected in RF-exposed and doxorubicin-treated cells compared to cells treated with doxorubicin alone, indicating an adaptive response to the RF exposure. This finding confirms the results obtained by the authors in previous studies carried out in vivo (Cao et al., 2011, Jiang et al., 2012).

4.1.3 Protein expression

Zhang et al. exposed human lens epithelial cells to 1800 MHz, GSM modulation, for 2 h at SARs of 2 and 4 W/kg. With RT-PCR they found 3 genes with different expressions, compared to sham controls and the results of western blot assay indicated that two proteins involved in the protein quality control (VCP and USP35) were up-regulated, while a protein involved in protein secretion (SRP68) was down-regulated (Zhang et al., 2013c).

Zhijian et al. (2013) investigated protein expression in human B lymphoblastoid cells (HMy2.CIR) exposed for 24 h (5 min on/10 min off cycles) to an 1800 MHz GSM signal at an SAR of 2 W/kg. By using the protein microarray they found a differential expression of 27 proteins, related to DNA repair, apoptosis, oncogenesis, cell cycle and proliferation. Western blot assay showed a significant down-regulation in the expression of RPA 32, together with a significant up-regulation of p73 expression, proteins involved in DNA repair and in apoptosis, respectively.

These results are in line with previous publications on protein expression following RF exposure, as reported by Leszczynski in a recent review paper, where the author stated that, due to the small number of studies and variety of study design, the information provided is very limited and no firm conclusions can be drawn on the effect of RF fields on the proteome (Leszczynski, 2013).

4.1.4 Conclusion on RF cell studies

Although some repetition studies have been carried out, most of the studies reported do not support an effect of RF EMF on DNA damage or cell death, and only minimal effects on protein expression.

4.2 Animal studies

The previous Council report (SSM, 2013:19) described animal studies on radiofrequency fields mostly addressing brain function and chemistry. It was concluded that RF-EMF may influence the brain function of animals. Studies on genotoxicity, reproduction and cancer were inconclusive regarding the results and poor study design. The current Council report deals with the same topics as previous reports firstly addressing the brain, secondly genotoxicity and physiology and fertility.

4.2.1 Brain function and behaviour

Bilgici et al. (2013) examined the oxidative stress in the brain tissue and serum of 22 restraint adult male Wistar rats after exposure to a CW 900 MHz EMF at a whole body SAR of 1.08 W/kg for 1 h/day for 3 weeks. In addition, a second group (n=22) received garlic powder (500 mg/kg/day per os) prior to EMF-exposure. A further 22 males served as controls. Malondialdehyde and advanced oxidation protein product (AOPP) increased in rat brain tissue exposed to the EMF. Garlic reduced these effects. No significant difference in the nitric oxide (NO) brain levels was seen, and paraoxonase (as a parameter for lipid oxidation) was not detected in the brain. But a significant increase in the NO levels was shown in the serum after EMF exposure, and garlic did not affect this increase. The authors concluded that the significant increase in brain lipid and protein oxidation is due to EMF exposure, whereas garlic has a protective effect against this oxidative stress.

Megha et al. (2012) evaluated the intensity of oxidative stress, cognitive impairment and inflammation in the brain of Fischer-344 rats sham-exposed or exposed to 900 MHz EMF or1800 MHz EMF at an whole-body SAR of 5.953×10^{-4} or 5.835×10^{-4} W/kg, respectively. Male (150–200 g) F-344 rats (n=6/group) received whole body exposure to RF-EMF in a TEM cell for 2 h/d, 5d/wk for 30 days. After the end of the exposure period, all animals were tested for spatial memory performance using the Elevated plus maze and Morris water maze. Finally, all animals were sacrificed and total brain protein, brain MDA, protein oxidation, GSH, IL-6 and TNF-α in the rat brain were determined. Compared to sham controls, a significant impairment in cognitive function and induction of oxidative stress in brain tissues of EMF-exposed rats were reported. Further, significant increase in level of cytokines (IL-6 and TNF-alpha) was observed following EMF exposure. The study might indicate that increased oxidative stress due to EMF exposure may contribute to cognitive impairment and inflammation in brain.

The same research group sham-exposed or exposed 6 male (150–200g) Fischer-344 rats per group to 900 MHz EMF (whole-body SAR $8.4738x10^{-5}$ W/kg) in a TEM cell for 2 h/d, 5d/wk for 30 days (Deshmukh et al., 2013a). On day 30 and 31, significant impairment in cognitive function (as evaluated by data of the Elevated plus maze and Morris water maze tests) and increase in oxidative stress, as evidenced by the increase in levels of MDA (marker for lipid peroxidation) and protein carbonyl (marker for protein oxidation) as well as unaltered GSH content in blood, were observed. According to the data presented, the described RF-EMF had a significant effect on cognitive function and was also capable of leading to oxidative stress.

In a third experiment the above group (Deshmukh et al., 2013b) exposed in the (obviously) same TEM cell exposure unit male Fischer rats to EMF for 30 days at three different frequencies: 900, 1800 and 2450 MHz again at an whole-body SAR of about $6 x 10^{-4}$ W/kg. Four groups (n=6/group) were used: Group I (Sham exposed), Group II: 900 MHz ($5.953x10^{-4}$ W/kg), Group III: 1800 MHz ($5.835x10^{-4}$ W/kg), Group IV: 2450 MHz ($6.672x10^{-4}$ W/kg). It is assumed, that groups I – III are the same as described by Megha et al. (2102). At exposure end animals were sacrificed, and the alkaline comet assay was applied to cells of brain tissue. The research group stated DNA damaging effects due to the EMF radiation in brain. They concluded “that low SAR microwave radiation exposure at these frequencies may induce DNA strand breaks in brain tissue”.

Haghani et al. (2013) tested whether maternal EMF exposure of rats would affect the cerebellum of the offspring. Ten pregnant Wistar rats were exposed to 900-MHz pulsed EMF irradiation (from a cell phone positioned at 40 cm distance from the animal’s cage and operating at constant power, resulting in an SAR of 0.5 – 0.9 W/kg) for 6 h/d during the entire gestation period. Further 10 dams were sham-exposed. Exposure was stopped “following each birth”. Ten pups per group (weaned on day 23) were tested at postnatal days 30-32. Cerebellum-related behaviour was analyzed by using motor learning and cerebellum-dependent functional tasks (Accelerated Rotarod, Hanging and Open field tests). Whole-cell patch clamp recordings were used for electrophysiological evaluations. Behavioural abnormalities in RF-EMF-exposed rats were not observed. Whole-cell patch clamp recordings revealed neuronal excitability of Purkinje cells in the RF-EMF rats. After-hyperpolarization amplitude, spike frequency, half width and first spike latency were altered. Summarizing, prenatal EMF exposure resulted in altered electrophysiological properties of Purkinje neurons, but the exposure did not alter cerebellum-dependent functional tasks.

4.2.2 Genotoxicity

For a classical test of micronucleus (MN) induction in peripheral blood (PB) and bone marrow (BM), Jiang et al. (2013) pre-exposed adult (25 g) male ICR mice to RF-EMF, 900 MHz at an SAR of 0.548 W/kg for 4h/day for 7 days (‘adaptation dose’) and then subjected the mice to an acute whole body dose of 3 Gy γ-radiation (GR) from a ^{60}Co source (‘challenge dose’). The experimental set-up consisted of 6 groups with 10 males each: 1) Unexposed controls, 2) 3 Gy GR, 3) RF, 4) RF+GR, 5) Sham, 6) Sham+ GR. MN data of RF+GR were compared with GR alone. In both, PB and BM, the MN indices were similar in unexposed controls and those exposed to RF alone, while a significantly increased MN frequency was observed in mice exposed to GR alone. RF + GR exposure resulted in a significant decrease in MN indices compared to RF alone. I.e., pre-exposure of mice to non-ionizing RF might be capable of 'protecting' the immature erythrocytes from genotoxic effects of subsequent γ-radiation.

4.2.3 Physiology

Jin et al. (2013) exposed 3 groups of 80 (40 male and 40 female) SD rats to RF-EMF signals for 45 min/d, 5 d/wk, for up to 8 weeks. Group 1 was sham-exposed, group 2 was exposed to a 849 MHz CDMA signal at 4 W/kg SAR, and group 3 was simultaneously exposed to the 849 MHz CDMA signal (SAR=2 W/kg) and to a 1.95 GHz WCDMA signal (SAR=2 W/kg) resulting in a total SAR of 4 W/kg. At 4 and 8 weeks after exposure start, 40 rats (20 of each sex) of each experimental group were autopsied and the parameters of the endocrine system including melatonin, thyroid stimulating hormone (TSH), stress and sex hormone were evaluated. Overall, exposure of rats for 8 weeks to either CDMA RF alone or to simultaneous CDMA and WCDMA RF did not affect serum levels of melatonin, TSH, triiodothyronine (T3) and thyroxin (T4), adrenocorticotropic hormone (ACTH) and sex hormones (testosterone and estrogen).

Bodera et al. (2013) investigated the effects of RF-EMF and opioid (tramadol) exposure in healthy rats and in rats with persistent inflammation induced by Complete Freund's Adjuvant (CFA) given 24 h before RF-EMF exposure and tramadol application. Rats were injected with 0.1 ml CFA or paraffin oil (vehicle) into their left hind paw, and 24 hours later far-field exposed (20 V/m, 0.05 A/m) to an antenna emitting a GSM 1800 MHz signal. Restraint (?) rats (in “plexiglass enclosures”) were sham- exposed or exposed once for 15 min. Immediately before RF-EMF exposure, rats received intraperitoneally 20 mg/kg tramadol or *water* as vehicle (1 ml/kg). Eighty male, 220–250g weighing Wistar rats were divided in 8 groups (n=10/group). Groups 1 - 4 consisted of healthy rats, 10 receiving tramadol only, 10 sham-exposed (control), 10 tramadol + RF-EMF, and 10 RF-EMF. Similarly the CFA pretreated inflammation groups 5 - 8 were 10 CFA / tramadol-rats, 10 CFA controls, 10 CFA / tramadol + RF-EMF, and 10 CFA / RF-EMF exposed rats, respectively. After a single 15 min RF-EMF exposure a significant reduction in total antioxidant capacity (ORAC) was reported both in healthy animals and those with paw inflammation. In addition, a synergistic mode of action between RF-EMF and administered tramadol in rats treated with CFA was demonstrated. A plausible explanation for the synergism could not be given and needs further evaluation.

4.2.4 Effects on reproduction and juvenile animals

Ozorak et al. (2013) determined the effects of both Wi-Fi (2.45 GHz)- and mobile phone (900 and 1800 MHz)-induced electromagnetic radiation on oxidative stress and trace element levels in the kidney and testis of growing rats from pregnancy to 6 weeks of age. Thirty-two 12-weeks old maternal Wistar rats and their 96 male offspring were equally divided into four groups (n=8 mothers, and n=24 offspring per group). The 2.45 GHz, 900 MHz, and 1800 MHz groups were whole-body exposed (217 Hz pulses, at a SAR of about 0.1 W/kg) for 60 min/day during pregnancy and growth, controls were “cage-stressed”. After 4, 5, and 6 weeks, kidney and testis samples were taken (n=8/group/time point). Data regarding lipid peroxidation, oxidative stress and trace elements in kidney and testis were determined. The researchers concluded that Wi-Fi and mobile phone RF-EMF caused “oxidative damage by increasing the extent of lipid peroxidation and the iron level, while decreasing total antioxidant status, copper, and GSH values”. Furthermore they stated that the tested RF-EMF may result in “precocious puberty and oxidative kidney and testis injury in growing rats”.

Tas et al. (2013) used14 Wistar rats, 4 to 5 months old, in two groups (sham and exposure group, n=7/group) for investigating testes and semen quality after one year of RF-EMF exposure. Rats of the RF-EMF group were exposed to a 900 MHz GSM signal. “Point” (presumably meaning local peak), 1 g and 10 g SAR levels of testis and prostate were found at 0.0623 W/kg, 0.0445 W/kg and 0.0373 W/kg, respectively. In a carousel system restrained rats were exposed as well as sham-exposed 3h/d, 7 d/wk for one year. At the end of the study, (right) epididymal sperm count, sperm motility and abnormal sperm rate, organs weights of left testis and epididymis, prostate and seminal vesicle and right testis histopathology were evaluated. No differences were observed in sperm count and progressive motility. Compared to sham control, morphologically normal spermatozoa rates were higher in the exposure group ($p<0.05$). Histopathology of the right testicle and epididymis, of prostate and seminal vesicle was within normal limits including similar diameters of seminiferous tubules. However, the tunica albuginea was thinner in the exposure than in the sham-exposure group.

4.2.5 Studies with little or missing exposure and other data

The following studies are separately reported because of poor dosimetry or other missing data. Therefore the described or claimed results are not evaluable.

Aboul Ezz et al. (2013) sham-exposed and exposed adult male Wistar rats to EMF (1800 MHz, modulated at 217 Hz, SAR= 0.843 W/kg), and sacrificed them after 1, 2 and 4 months of 1 hour daily RF-EMF exposure as well as after 4 months RF-EMF exposure plus 1 month recovery period. Significant changes in monoamines (dopamine, norepinephrine and serotonin) in four selected areas of adult rat brain were reported. Unfortunately, the control data and number of animals per group are missing. Nevertheless, the authors concluded that RF-EMF exposure in adult rats “may cause disturbances in monoamine neurotransmitters and this may underlie many of the adverse effects reported after EMR including memory, learning, and stress”. Overall, the experiment is inadequately reported. Therefore, the study cannot be evaluated.

Celikozlu et al. (2012) exposed single housed male and female Wistar rats “during prenatal and postnatal periods until they were 80 days old.” Commercial cell phones (GSM-900 standby mode for a whole day, talking mode for 30 min/d) were placed inside the wall of the animal cages. No further information on age, number of rats per group, exposure level(s) etc. was given. The authors stated that the cell phones increased blood glucose and serum protein level, decreased body weight (gain) and affected blood cholesterol concentrations. Numbers of pyramidal neurons were decreased and numbers of ischemic neurons were increased in the brain cortex. However, this study lacks adequate exposure control and dosimetry and is generally poorly described. It can therefore not be evaluated.

El-Bediwi et al. (2013) exposed two groups of 20 Wistar rats each to CW 900 MHz EMF (1h/d, 7d/wk) for 3 and 6 months respectively. A third group (n=10) served as control. A mobile phone produced the 900 MHz test signal and was placed in the centre of the cage(s). No data on power density or SAR calculation are given. Blood of the aorta was analysed for some haematological and biophysical parameters. Compared to controls, an exposure duration-dependent decrease of red blood cells, white blood cells, and platelets was reported. Blood viscosity and plasma viscosity values increased whereas "osmotic fragility" decreased after RF-EMF exposure. Due to missing basic information, e.g. missing data of exposure level(s), this study cannot be evaluated.

Khirazova et al. (2012) exposed 10-12 week old rats to a 905 MHz GSM signal once for 2 h at a SAR of 1.67 W/kg using a test cell phone. No data on dosimetry were presented. Acute (5 min after exposure) or delayed effects (24 h after exposure) on behavioural activity were evaluated in an open field test comparing the two (acute or delayed) test groups to the respective sham controls (n=10/group/sex). In RF-EMF exposed rats acute and delayed changes in locomotor, orientation, and exploratory activities as well as in anxiety levels were seen in both sexes. Glucocorticoid plasma levels and the blood levels of "antioxidant defense system" ADS (defined by the authors as 'non-peptide thiols, SOD-like and catalase activities in blood hemolysate, hemoglobin in blood, SOD-like activity of blood plasma, plasma levels of ceruloplasmin, lipid hydroperoxides, total protein and thiobarbituric acid-reactive substances') increased. Gender differences were observed and their inconclusiveness discussed.

On another poorly described study, Köktürk et al. (2013) put mobile phones inside the walls of the cages and exposed male and female Wistar rats to GSM-900 signals during the entire pre- and postnatal periods (until postnatal day 80, group EMF1). In the EMF2 group, the rats were similarly exposed to EMF pre- and postnatally; in addition, they were orally treated with *Lycopersicon esculentum* (tomato) extract (~2 g/kg). For neurodegeneration caspase-3-labeled Purkinje neurons and granule cells were evaluated. In the cerebellum, the EMF1 group showed a significant increase in the number of caspase-3-labeled Purkinje neurons and granule cells compared to controls. In comparison with EMF1, the EMF2 group exhibited significantly fewer caspase-3-labeled Purkinje neurons and granule cells. Dark neuron degeneration (of Purkinje neurons) was seen in EMF1 group. In EMF2, the presence of dark Purkinje neurons was reduced compared to EMF1 group. The authors summarize: "The results indicated that apoptosis and neurodegeneration in rats exposed to EMF during pre- and postnatal periods may be reduced with *Lycopersicon esculentum* extract therapy."

Meo and Al Rubeaan (2013) used 5 groups consisting each of 8 male, 2 months old (150–160 g) Wistar rats and exposed them over different durations (0 [control]; < 15 min, 15–30 min, 31–45 min, 46–60 min) per day over a period of 3 months to commercial handsets of mobile phones operating at 1800 MHz. The cell phones were placed in the centre of the cages (housing 8 rats each) with the answering mode switched on during the daily exposures. At the end of the 3 months exposure period the rats were kept fasting overnight for 12 hours and sacrificed at 10-10.30 a.m. Fasting blood serum glucose and insulin was determined. The Homeostatic Model (HOMA-B) was applied for the assessment of β-cell function and (HOMA-IR) for resistance to insulin. Those rats exposed the 1800 MHz signal for longer than 15 min a day for a total period of 3 months had significantly higher fasting blood glucose levels whereas serum insulin showed an increase starting with the period 31-45 min compared to controls. Insulin resistance was significantly increased in the groups that were exposed for 15–30 and 46–60 min/day compared to the control rats. The presented data may indicate an association between "long-term exposure to activated mobile phones and increase in fasting blood glucose and serum insulin" in rats. But the study lacks an adequate description of the exposure, therefore it cannot be evaluated.

In the behavioural study of Narayanan et al., 2013, groups of 12 male 6-8 weeks old Wistar rats were cage-control housed, sham-exposed (switch off mode) or received a whole body exposure to RF-EMF (900 MHz) from a beneath the cage positioned active GSM mobile phone with a peak power density of 146.60 μW/cm² for 1 h/d and 28 days(Narayanan et al., 2013).

No data on dosimetry within the cage were given. On day 29, an ele-vated plus maze (EPM) test revealed that the percentage of entries into the open arm, percentage of time spent and distance travelled on the open arm were reduced in the RF-EMF exposed rats, as well as the rearing frequency and grooming frequency. Defecation boli count was higher in the RF-EMF group. Total distance travelled, total arm entries, percentage of closed arm entries and parallelism index did not show differences between the RF-EMF exposed rats compared to the two control groups (sham and cage control). The authors conclude that mobile phone radiation could affect the emotion-ality of rats without affecting the general locomotion.

Tumkaya et al. (2013) aimed to investigate the effects of mobile phone exposure on the testes of rats during pubertal development. 12 male 45 days old Sprague Dawley rats were used. The RF-EMF group (n = 6) was whole body-exposed to a mobile phone (800 MHz - 915 MHz carrier frequency, 217 Hz modulation frequency, max. peak power 2 W) at an SAR of 0.48

W/kg for 1 h a day (7–8 p.m., i.e. active night time for rats) over 45 days. However, the exposure was from a mobile phone inside the cage that was kept in talking mode. It is not clear how a mean SAR of 0.48 W/kg can be derived if no temporal and spatial variations of exposure are taken into account. Presumably the SAR was calculated using the maximum output of the phone. The control group (n = 6) remained unexposed. After 45 days (?), blood samples were taken and testes were processed with routine paraffin histology, sectioned and stained with H&E, caspase 3, and Ki-67. Testicular weights and morphometric sizes were similar in both groups. In the RF-EMF group only, slight vacuolization "during specific changes of the spermatogenesis", slight dilatation of interstitial capillaries and a mild edema were reported. No (significant) differences in both Ki-67 and caspase-3 "immunopositivity" were seen between the two groups. In addition, the electrolyte concentration of Ca^{++}, CL^{-}, K^{+}, Mg^{++}, Na^{+} in the blood was similar between control and exposed group. Unfortunately, data on histological scoring were not presented (though announced in *Materials and Methods)* and the histological pictures seem to be arbitrarily chosen (different magnification between fig. 2 and 3, different details of the photos in fig. 2). The sentence "phones were used … for 45 days and continued during postnatal period." is misleading. The study does not describe any postnatal exposure.

Even if exposure to RF-EMF may slightly alter some reproductive parameters in rats, the relevance of the reported changes for humans is questionable - especially when taking into account study size, study quality and degree of changes.

4.2.6 Conclusion

The majority of the recent RF animal studies still lack a clear working hypothesis and adequate study design. Often the exposure systems and dosimetry are poorly described. If any international recommendations for description of laboratory animal experiments are taken into consideration they are only partly followed.

Overall, the animal studies provide weak indications of possible effects on oxidative stress and brain function including behaviour and emotionality. The reported effects on genotoxicity, hormones, glucose, male fertility and reproduction are mostly originating from single studies and need well-designed replication.

4.3 Human studies

The previous Council report (SSM, 2013: 19) concluded that "it now seems to be a well-established fact that there is no demonstrable effect by RF EMF on cognitive functions. This may of course be due to the non-existence of the effects or the coarseness of the measures to reveal more subtle effects. The brain imaging studies are the most suitable method for studying the EMF effects on the human central nervous system. Based on the imaging studies during the past 10 years, an interesting question arises. Studies with very short-term exposures have not shown any effects in adults , e.g. (Kwon et al., 2012c), or in children (Lindholm et al., 2011), whereas studies with longer exposures (at least 30 min) have demonstrated local decrement of glucose metabolism (Kwon et al., 2011) or haemoglobin concentration (Spichtig et al., 2012) in the adult brain. Therefore, we may conclude that the exposure duration, as well as cumulative exposure, should be more carefully studied, even though even also long exposures do not have any effect on cognitive functions (Sauter et al., 2011)". [2]

Since then ten human experimental studies have been published addressing various outcome parameters. However none of them was related to either glucose metabolism or haemoglobin concentration.

4.3.1 Electrophysiology

In a randomized sham-controlled parallel group design pilot study Vecchio et al. (2012) investigated the effect of a 45 min exposure to a GSM signal (902.4 MHz, modulation frequencies: 8.33 and 217 Hz) on inter-hemispheric functional coupling of closed-eyes waking EEG in 10 epileptic patients. The data were compared to data from 15 age-matched controls from previous reference studies. In comparison to controls, patients showed a statistically significant higher inter-hemispheric coherence of alpha rhythms (about 8-12 Hz) in the frontal and temporal region under GSM exposure as compared to sham. The study thus confirmed that the inter-hemispheric synchronization is even more evident in epileptic patients than in young and elderly healthy subjects (Vecchio et al., 2010, Vecchio et al., 2007). The functional coupling of homologous cortical areas could indicate a higher risk for seizures which, however, were not observed in the patients of the pilot study sample.

Loughran et al. (2013) investigated a possible effect of a 30 min GSM exposure (900 MHz) on the resting waking EEG in 22 adolescents (12 males and 10 females, 10–13 years) in a randomized double-blind coun-ter-balanced cross-over design with three exposures levels: sham, "low" (peak spatial SAR 0.35 W/kg) and "high" (peak spatial SAR 1.4 W/kg). Two subjects had to be excluded due to high frequency noise in the signal. The results showed that for none of the four considered localisations (C3, C4, O1 and O2) an exposure effect could be observed immediately after exposure nor 30 or 60 min after the exposure. The authors conclude that the "results suggest that contrary to popular belief, adolescents are not more sensitive to mobile phone emissions" (Loughran et al. 2013, p. 1303). With

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[2] The Kwon et al. 2012 paper in this citation is the paper listed as Kwon et al. 2012a in the reference list

20 subjects standardized effect sizes of 0.66 can be detected as statistically significant with a two-sided error probability of 5% and a power of 0.8 in the post-hoc paired t-tests. Since the EEG shows maturation dependent changes and since the biological variation in adolescents usually is much larger than the variation in chronological age, it might be that the sample was too small to detect relevant exposure dependent differences.

4.3.2 Sleep and EEG

Lustenberger et al. (2013) used an experimental RF signal (carrier frequency 900 MHz with a special intermittent pulse modulation scheme adhering to the timing of sleep EEG patterns – spindles and slow oscillations) with all-night exposure to explore possible mechanisms by which RF exposure could affect cortical excitability during sleep and to investigate whether RF EMF exposure could affect sleep-dependent performance improvement. The sample consisted of 16 young male subjects (18-21 years) who were exposed in a randomized double-blind sham controlled cross-over design. Under exposure a reduced total sleep time ($p = 0.04$) and consequently a reduced sleep efficiency ($p = 0.04$) were observed. The reduced total sleep time corresponded to an increase in wake after sleep onset ($p = 0.03$), NREM sleep and REM sleep were not affected. Analyses of the power spectra of the sleep EEG revealed a statistically significant increase in NREM power for frequencies up to 10 Hz under exposure towards the end of the night. The slow wave activity (0.75-4.5 Hz) during the 4^{th} NREM sleep episode was significantly higher as compared to sham ($p < 0.05$). The EEG in the spindle frequency range (12-15 Hz) was not affected. In the 4^{th} NREM episode (but not in the episodes 1 to 3) a RF EMF burst-related increased response in the slow wave activity range was observed

To investigate sleep-dependent performance Lustenberger et al. (2013) used a finger sequence tapping task. They observed a reduced performance improvement – as indicated by a reduced variance of the reaction time ($p = 0.03$) – under real exposure as compared to the sham condition.

In a randomized double-blind cross-over design with three exposure conditions Schmid et al. (2012) studied 1) whether the modulation of a RF EMF signal (900 MHz carrier frequency) with frequencies above 20 Hz is necessary to affect the sleep EEG and 2) whether the same effects can be seen with a magnetic field pulsed with the same frequency components as the RF field. The sample comprised 25 healthy young men (20-26 years) and the conditions were a 2-Hz pulse modulated RF signal and a 2-Hz pulsed magnetic field besides sham exposure. Subjects were exposed for 30 min prior to sleep. Under exposure with the 2-Hz pulse modulated RF signal a reduced amount of REM sleep in the second sleep cycle as compared to sham was observed ($p < 0.03$). This was the only affected sleep variable. No effects on the macrostructure of sleep were observed under MF exposure. For RF exposure a significant increase in EEG power was observed in the spindle frequency range (13.75-15.25 Hz) with regard to NREM sleep as well as to NREM stage 2 sleep for the whole night and sleep cycles 1, 3 and 4. For RF exposure increases were also observed in the alpha frequency range (7.75-12.25) during REM sleep. These effects were not seen with MF exposure. EEG power in the delta and the theta frequency range of NREM sleep were affected by both RF and MF exposure. The study concluded that pulse modulated RF as well as pulsed MF can have effects on brain physiology.

4.3.3 Cognition

Schmid et al. (2012) also looked at exposure effects on cognition. Three different tasks were performed during the 30 min exposure prior to sleep: a simple reaction time task (SRT), a choice reaction time task (CRT) and an N-back task. A significant exposure effect was observed for reaction speed in the 3-back task and the SRT. Post hoc analyses revealed an increased reaction time in the SRT only for the MF condition. Accuracy was largely unaffected by exposure.

Loughran et al. (2013) in their study on RF EMF effects (sham, 0.35 W/kg and 1.4 W/kg) in adolescents found no significant exposure effects on speed and accuracy in a simple and complex reaction time task and in a 1- and 2-back working memory task.

Mortazavi et al. (2012a) tested the effect of a 10 min exposure to a mobile phone on reaction time in a simple reaction time task. The test was performed prior to and following exposure. Subjects were not aware of the order of exposure, which was applied at the same day with a 30 min time interval between the consecutive exposures, assigned at random. It seems to have been a single blind study. The sample comprised 160 subjects (38 females, age: 18-31 years). It is not mentioned whether time of day was controlled in the experiment. Without controlling for pre-test reaction times authors found a significantly lower reaction time after real exposure as compared to sham. Under both conditions reaction times in males were significantly shorter than in females. The authors also collected data on the history of mobile phone use and found no significant differences in reaction times between groups of low, moderate and frequent users.

4.3.4 Other endpoints

Schmid et al. (2012) also looked at the heart rate, which did not show an exposure-related (sham, 2-Hz pulse modulated RF exposure and 2-Hz pulsed MF exposure) variation in neither NREM nor REM sleep.

In a study with a double-blind cross-over design Kwon et al. (2012a) investigated effects of a 32 min daytime WCDMA and sham exposure on heart rate, respiration rate and LFP/HFP (the ratio between low- and high frequency power in the power spectrum of the heart rate variability) in 20 healthy participants (9 females, 29.4 ± 5.2 years) and 17 participants with self-reported electromagnetic hypersensitivity (9 females, 30.1 ± 7.6 years). The physiological parameters were collected for 5 min each at four points in time: pre-exposure, after 11 and 27 min of exposure and post-exposure. No exposure-related differences in these physiological variables were observed.

Vecsei et al. (2013) investigated potential effects of a UMTS exposure on pain threshold perception in response to thermal stimuli applied to the finger surface in 22 healthy young subjects (10 females, 20-29 years). They used a double-blind, placebo-controlled crossover design and a positive control with topical capsaicin to validate the protocol (capsaicin lowers the thermal pain threshold - TPT). EMF exposure was delivered to the head for 30 min by a patch antenna. While the TPT was not affected by the UMTS-like EMF exposure, results indicate a slightly stronger desensitization effect across repeated trials under exposure for the contralateral side. The biological relevance of this observation, which needs to be confirmed by other studies, however, is not clear.

Mandala et al. (2013) studied effects of a 5 min exposure from either a commercial mobile phone (GSM 900) or a bluetooth headset operating in an ongoing call in the proximity of the cochlear nerve in an intraoperative setting. 12 patients with definitive unilateral Ménière's disease underwent the EMF experiment after craniotomy prior to vestibular neurectomy. In a parallel group design the patients were randomized to receive either mobile phone exposure or bluetooth headset exposure (6 patients each). Cochlear compound nerve action potentials (CNAPs) were recorded for 17 min under stimulation by alternating clicks. The first 2 minutes served as a control condition (standby mode) followed by 5 min EMF exposure. A decrease of CNAP amplitudes and an increase in latency during and after GSM exposure were found. These changes started 2 minutes after the beginning and lasted for a period of around 5 min after exposure. There was no effect of the Bluetooth exposure.

4.3.5 General conclusions on human studies

Two of the three RF studies on cognition underline the conclusion from the previous opinion that there is no demonstrable effect on cognitive functions; the other indicates a better performance under exposure. In the reporting period effects of RF on waking EEG were investigated in two studies with regard to young subjects (adolescents) and patients (epileptic), while no effect was observed in the adolescent group, patients showed an effect in the alpha frequency band. These results underline 1) that age related variations in EMF effects on the central nervous system should be considered (so far there are no studies in elderly subjects), and 2) that effects may be different in patients with CNS-related pathologies. Two sleep studies with different

ELF-pulsed RF and MF exposure underlined that effects on the sleep EEG are neither restricted to the spindle frequency range, nor to NREM sleep. Both studies also found isolated effects on the macrostructure of sleep. Here it seems that the probability of finding effects increases with the duration of exposure. No exposure-related effects in physiological parameters have been observed. Effects on RF exposure on temperature regulation and pain desensitization have been observed in single studies, and need confirmation.

4.4 Epidemiological studies

Most epidemiological studies on RF-EMF in the previous Council report dealt with intracranial tumours. 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, With respect to other outcomes, the number of studies per outcome was relatively small, and consistency of findings between various studies could not be addressed in the last report. It was pointed out that intriguing studies on child development and mobile phone use have appeared. However, the available data did not allow differentiating between effects from RF-EMF exposure and effects from mobile phone use per se (e.g. social interaction, cognitive training).

During the last year, several small surveys were published. Relatively frequently, these are occupational surveys where one group of workers is classified as exposed and another group as non-exposed. Subsequently, several health outcomes are compared between the two groups. Unfortunately, it is often limited what can be concluded from such studies. The cross-sectional design of these surveys hampers a causal interpretation of the results and makes them vulnerable to selection bias. Thus, thorough information on the participant selection procedure is required to evaluate the value of the study. Further, exposed and unexposed groups may differ in many other aspects and an appropriate data analysis has to consider confounding factors such as age, sex, or lifestyle factors that could be related to the exposure and outcomes.

4.4.1 Pregnancy outcomes

A survey reported on 500 mothers who attended the outpatient clinic at the pediatrics department at the faculty of Medicine of Gaziantep University, Turkey, with their children (Col-Araz, 2013). Maternal use of mobile phones during pregnancy was assessed by means of questionnaires. 68% of mothers reported to have used mobile phones during pregnancy. Children were on average 2.5 years old at the time point of the survey in 2009. Birth weight was not associated with mobile phone use. Pregnancy duration was found to be about a week shorter in women using mobile phones and this difference was statistically significant. The association with mobile phone use and duration of pregnancy remained also in a logistic regression model adjusted for other factors that were related with pregnancy duration. Problematic with this study is that exposure information was assessed after the outcome, so that reporting bias might account for the reported relationship. In addition, it is unclear to what kind of exposure levels the reported effects pertain to, as it might well be that mothers used mobile phones rarely. Finally, the use of mobile phones as such might be a proxy for other factors, which could be related to the assessed outcomes (and not the electromagnetic field exposure).

4.4.2 Child development

On the background of a previous study which found an association between maternal cell phone use during pregnancy and reported child behaviour problems, as reported by mothers (Divan et al., 2012), Guxens et al. (2013a) performed a similar study to explore whether they could reproduce this finding. The study by Guxens et al. was embedded in the Amsterdam Born Children and their Development study, which is a population-based prospective birth cohort study that examines the relationship of maternal lifestyle and psychosocial determinants during pregnancy to multiple aspects of development and health of the child. The study included 8,266 pregnant women who were recruited in relation to a control examination by an obstetric care provider in Amsterdam during 2003 and 2004. When the children were 7 years old, a questionnaire on the cell- and cordless phone use during pregnancy was sent to the mothers. The authors categorized the use of both types of phones into four categories: no use, < 1 call/day, 1-4 calls/day and ≥ 5 calls/day. The use of phones was also estimated according to use of hands-free. When the children were 5 years old, their behaviour was reported from primary schoolteachers as well as mothers using the Strengths and Difficult Questionnaire (SDQ), the same scale that had been applied in the Divan et al. study. This questionnaire consisted of scaled responses on several behaviour problems. After excluding the subjects with missing information on relevant covariates, 2,618 children (31.7% of eligible) were included in the study by Guxens et al. The proportion of children classified as having overall behaviour problems was 9.6% for teachers' and 3.3% for mothers' reports, respectively. Because the proportion of non-users was very small, two analysis approaches were conducted: one with non-users as the comparison group and one with low users as comparison group. All analyses were adjusted for maternal education, age, country of birth, parity, pre-pregnancy body mass index, smoking during pregnancy, second-hand smoke at home during pregnancy, alcohol consumption during pregnancy, pregnancy-related anxiety subscales, anxiety and depression during pregnancy and history of psychopathology. For the highest exposure group, odds ratios of all analyses were close to unity or even decreased. An exception was the association between teachers' report and mobile phone use, which tended to be increased, although not statistically significant (OR=2.04, 95% CI: 0.86-4.80) when using non-users as reference group. However, estimates of this analysis are unstable because only 7 cases were included in the reference group. In addition, no exposure-response pattern was observed. No increased risks across mobile or cordless phone use were observed for mother's reports of behaviour problems, which is in contrast to the study by Divan et al. Overall, the study does not indicate an association between maternal mobile phone use during pregnancy and behavioural problems in their offspring. The study considered a substantial number of potentially relevant covariates in their analyses. Outcome and exposure was not estimated at the same time, which is an advantage since it may minimize recall bias. However, retrospective exposure assessment is a limitation as well as crude exposure estimates lacking the duration of use and the low numbers in the reference categories when using non-users as reference.

In a letter to the editor, Sudan et al. (2013b) pointed out that the study by Guxens et al. had a small sample size and number of exposed cases, which resulted in unstable, inconsistent and uninformative effect estimates. To compare the results from the study by Guxens et al, Sudan et al. reanalysed the data from the study by Divan et al using similar exposure definitions and reference groups. In contrast to the study by Guxens et al, the results showed a positive significant association between prenatal cell phone use and behaviour problems in children with an overall adjusted OR of 1.33 (95% CI 1.22-1.46). There was also a clear significant exposure-response by frequency of use.

In a reply, Guxens et al. (2013b) acknowledged that their study obtained less precise risk estimates, but did not agree that their study was uninformative. They pointed out the consistent non-association between maternal cell phone use and cordless phone use on behavioural problems in children, with the fact that exposure from both devices pointed in the direction of no-association.

In Korea, data from the Children's Health and Environment Research study was used to investigate the association between mobile phone use and Attention Deficit Hyperactivity Disorder (ADHD) (Byun et al., 2013). From 7,059 children, 2,281 participated in the baseline investigation in 2008 and 1,757 in the follow-up in 2010. Average age of the children was about 9 years in 2008. Parents or guardians filled in a questionnaire including the Korean version of the ADHD rating scale and questions about mobile phone use, as well as socio-demographic factors. Blood lead levels were measured in 2008 and 2010. Data of both surveys were analysed using generalized estimating equation (GEE) models adjusted for age, gender, number of siblings, area, household income, maternal smoking during pregnancy, child's history of neuropsychiatric illness, parental history of neuropsychiatric illness, and parental marital status as time-independent covariates and blood lead levels as time-varying covariates. ADHD was not related to mobile phone ownership, age at first ownership, number of sent text messages, cumulative time spent for voice calls or use of internet on the mobile phone. An association was found for number of outgoing calls per day (p for trend: 0.03) and for average time spent for playing games on mobile phones per day (p for trend: <0.0001). In a stratified analysis according to blood lead levels, associations tended to be stronger for children with high levels (≥2.35 µg/dl lead, n=600) than for children with lower blood lead levels. Interestingly, the strongest association was found for playing games, which is not related to EMF exposure. This indicates that use of communication technique per se, but not the EMF exposure, may be related to ADHD. Unfortunately, data in this study were analysed in a cross-sectional manner. Thus, no statements can be made whether high mobile phone use occurred before parents' reporting of ADHD or the other way around. A further limitation of the study is that all exposure data was self-reported.

4.4.3 Cancer

To consider implications in relation to brain tumour risk, Redmayne (2013)used a cross-sectional design to explore how and to what extent New Zealand adolescents used mobile- and cordless phones. 373 pupils with a mean age of 12.3 years from sixteen schools in the Wellington region of New Zealand completed a questionnaire regarding their use of mobile- and cordless phones. The main exposure metrics included estimated time spent with an active cell phone close to the body, estimated time and number of calls on either phone type, extent of text- messages and functions used. In addition, the participants measured the distance between their body and phone when sending text-messages. Adolescents reported that cordless phones were the most popular choice for longer-duration phone calls and that they used mobile phones mainly for texting, internet, music and camera applications. In parallel, a review of brain tumour risk, mainly based on Interphone and the Hardell group, was performed. The author then related the exposure assessment (to the amount of cordless and mobile phone use) from this study to the results from the two reviews and concluded that adolescents might be at increased risk of brain tumours by their mid-teens. The relation between the reviews and the outcome of this study is of very limited value, and such an increase of brain cancer cases is not supported by incidence trend studies.

An English cohort study (Benson et al., 2013b) explored the relation between prospectively recorded information on use of mobile phones and the incidence of intracranial central nervous system (CNS) tumours and of other cancers among women. The cohort consisted of women recruited through the Million Women Study during the period 1996-2001 who were asked to complete a postal questionnaire about socio-demographic, medical- and lifestyle factors. 866,525 women (65%) answered the questionnaire. 74,815 women were excluded for various reasons. 791,710 women with a mean age of 59.5 years with an average of 7 years follow-up were included in analyses. Ques-

tions on mobile phone use were asked once to each participant between 1999 and 2005, regarding how often they use a mobile phone, with three options to respond: never, less than once a day and every day. In addition, the participants were asked to provide total years of use. The cohort members were linked to the National Health Service Register to obtain information on tumour incidence, stroke and ischaemic heart disease. In their analysis, the authors accounted for age, socioeconomic status, geographical region of residence, height, body mass index, smoking, alcohol intake, duration of strenuous exercise, and use of menopausal hormone therapy. The relative risk (RR) for ever versus never use of a mobile phone for all intracranial CNS tumours was 1.01 (95% CI: 0.90-1.14). Similar RRs were observed for the higher exposure categories of daily use vs never, and >10+ years of use vs never use. No increased risks were reported for glioma, meningioma and all other intracranial CNS tumours. Somewhat elevated risks emerged for pituitary tumours (1.52 (95%CI 0.99-2.33 for ever vs never use), but no exposure-response relationship was observed: higher risks were reported for shorter duration and less than daily mobile phone use. For vestibular schwannoma (acoustic neuroma), the RR for 5-9 years of mobile phone use was 1.80 (95% CI: 1.08-3.03) and for >10 years of use was 2.46 (95% CI: 1.07-5.64), with a significant positive trend across exposure categories (P=0.03). However, national data of vestibular schwannoma incidence did not show any increase in either men or women at the ages 20-79 years in England during the period 1998-2008. One of the potential explanations for this discrepancy between the cohort analysis compared to the incidence analysis is diagnosis bias, because vestibular schwannoma affects hearing: Cases using mobile phones may be more likely to be diagnosed with vestibular schwannoma because they realize a hearing problem when using mobile phones.
The strengths of this well conducted study is the consideration of confounders and the prospective exposure assessment, i.e. information from the participants was collected before the measured outcome, and can thus not be affected by knowledge of disease status, which is a limitation of case-control studies. A major limitation of this study is the fact that the information regarding exposure was collected in a broad way only and only exposure at the beginning of the follow-up time was considered. Potential changes in exposure over time have not been taken into account in the analyses. In addition, the number of exposed cases was relatively small (38 cases used a mobile phone 5 to 9 years and only 8 cases >10 years).

In a letter, Benson et al (2013a) reported updated results for vestibular schwannoma by adding two additional years to the follow-up (2010 and 2011). As a result the relative risk for >10 years of use was not increased anymore (RR=1.17, 95%: 0.60–2.27) compared to never user) based on 14 vs. 43 cancer cases and there was also no significant trend in risk with duration of use (P=0.3). This may indicate that the previous finding was a chance finding, which would explain the discrepancy between the study results and the time trends analyses.

A new case-control analysis of the Hardell group (2013b) addressed the association between wireless phone use and malignant brain tumour in Swedish cases diagnosed between 2007 and 2009. From a total of 683 eligible living cases, 593 (87%) were included in the study. For each malignant and benign case (see below, (Carlberg et al., 2013)) a population control was selected, matched on gender and age (participation rate: 85%). Interviews on exposure were conducted by phone. The interview was constructed in a way that the interviewer should not be able to reveal whether a case or control interview was conducted. Analyses were adjusted for age, gender, year of diagnosis and socio-economic index (SEI). Persons who reported having used a mobile phone for more than one year had an increased risk of 1.6 (95% CI: 0.99-2.7) and for more than 25 years a risk of 2.9 (1.4-5.8). If cordless phone use was considered as well, the odds ratio for wireless phone use were somewhat higher (1.7 (1.04-2.8) for >1 year and 3.0 (1.5-6.0) for >25 years). For total mobile phone use, ipsilateral glioma risk was higher than contralateral (1.7 vs. 1.4). For wireless phones, risk was more increased in the highest exposed brain regions (temporal, temporofrontal , temporoparietal, temporooccipital) where it reached 2.5 (1.05-5.9) for >1 year of use and 5.1 (1.8-15.0) for >25 years of use. In order to account for potential bias when using population controls, Hardell et al. (2013b) also conducted a sensitivity analyses with the meningioma cases as control; again with similar findings (OR=1.8 (1.1-3.1) for >1 year of use and 3.1 (1.3-7.0) for >25 years of use. The authors concluded that these findings support the role of RF-EMFs in the initiation and promotion stages of carcinogenesis.

Overall, all the results are very consistent in terms of expected exposure-response patterns if there were a causal association. Also the participation rate is very high, not reached anymore by other population-based epidemiological studies of this kind in Europe. In practice, blinding was unlikely to have been as successful as described in the study. There is no other obvious weakness in the study. However, several incidence time-trend analyses have demonstrated that a risk in the order of 1.6 for short term mobile phone use must be observable in incidence time-trends, which is not the case in several studies from various countries, see the previous Council report (SSM, 2013:19). Thus, there is an obvious discrepancy between these results, which is not yet resolved.

In Taiwan, Hsu et al. (2013) analysed the incidence rate and mortality of malignant brain tumours to evaluate changes in trend during the period 2000-2009, a period of intensive uptake of mobile phones in the Taiwanese population. There were no obvious trends during the period in the incidence (2.99/100,000 in 2000 and 2.38/100,000 in 2007) or in the number of deaths (1.7/100,000 in 2000 and 2009) caused by malignant brain tumours, indicating no correlation between use of mobile phones and malignant brain tumours.

In Israel, Barchana et al. (2012) evaluated the incidence of low- and high-grade gliomas in relation to the increased use of mobile phones. For the incidence of brain tumours, data was obtained from the Israeli National Cancer Registry from the period 1980-2009. The incidence rates were divided in six 5-years intervals, 1980-84, 1985-89, 1990-94, 1995-99, 2000-04 and 2005-09. For all low and high-grade glioma combined, the incidence increased in men until 2004 and then decreased again. In women incidences remained stable after 1990. In stratified analysis according to grade, high grade tumours in men also increased until 2004 and then decreased, whereas low-grade tumours decreased over the whole period. The latter pattern was also observed in women whereas high grade tumours increased gradually during the whole period. Regarding laterality of gliomas, a shift towards the left brain hemisphere was noted from 1995 and onward, although the high proportion of missing information renders this analysis rather uncertain. According to a survey in Israel regarding laterality of mobile phones, 70% of the population reported to use the mobile phone mainly on the right side of the head. In summary, the observed pattern does not suggest a causal association between mobile phone use and glioma. As a potential risk of brain tumours is likely to be in the region with greatest energy absorption, is it unlikely that exposure on the right side of the head should cause increased incidence of tumours in the left hemisphere of the brain. In addition, the coding rules for low and high grade tumours may have changed over time. If mobile phone use would indeed introduce a shift from low grade tumours to high grade tumours, one would expect to see this shift only after introduction of mobile phone use and within a reasonable latency time. Given that the shift was observed from the first observation period onwards (after 1984), well before the broad introduction of mobile phones in the population, it is unlikely to be associated with the use of mobile phones.

De Vocht et al. (2013) combined malignant brain tumour incidence data from IARC‘s (International Agency for Research on Cancer) database, GLOBOCAN, with several potential risk factors collected from HDI (United Nations Development Report for Human Development Index) and World Bank list of developments indicators and conducted a regression analysis to explore risk factors for brain tumours on an ecological level. The only exogenous risk factor consistently associated with higher brain tumour incidence for the period 1995 to 2008 was the proportion of mobile phone subscriptions. Although many developmental indices were considered by the authors, it seems likely that the proportion of mobile phone subscribers per country can act as a surrogate for case diagnosis and registration completeness, i.e. the faster the uptake of mobile phone use in a country the better the cancer detection and registration. Ecological studies of this kind might be suitable to generate hypotheses, but should be interpreted with caution because they are likely to be affected by confounding and ecological fallacy.

On the background of IARC`s evaluation of a possible carcinogenic effect of RF-EMF from mobile phones, Hardell et al. (2013a) reviewed the association between use of mobile- and cordless phones and brain tumours. This review is mainly based on studies from the Hardell group and the Interphone study and includes results of glioma and vestibular schwannoma (acoustic neuromas). In a meta-analysis of glioma, the authors reported statistically significant increased risks, OR 1.74 (95% CI 1.07-2.83) for cumulative use, ≥1640 hours. For vestibular schwannoma a significant elevated risk estimate was found for cumulative ipsilateral use of ≥1640 hours (OR 2.55, 95% CI 1.50-4.40) but not for other exposure measures. No significant increased risk was found for meningioma. This study repeats what is already known, i.e. that Interphone and the Hardell studies found increased risk for highest categories of mobile phone use. However, it cannot clarify if, and to what extent, the observed associations may be biased, e.g. due to recall bias.

Carlberg and Hardell (2012) conducted a study which intended to look at the association between glioma, wireless phones, heredity and ionising radiation. The analyses of glioma and wireless phones are similar to analyses from earlier papers by Hardell at al. (2006b, 2011) . The studies from 2006 and 2011 are mentioned in previous Council reports (SSI, 2007:4, SSM, 2013:19) and will not be further considered in this report.

Carlberg et al. (2013) conducted a case-control study to explore the association between use of mobile- and cordless phones (summarised as ”wireless phones”) and meningioma. The study included 709 (87%) cases and 1,368 (85%) controls aged 18-75 years who were diagnosed with meningioma during the period 2007-2009 in Sweden. Use of wireless phones was assessed by a self-administered questionnaire. The analyses included six latency time periods, >1-5, >5-10, >10-15, >15-20, >20-25, and >25 years of mobile phone use, laterality and cumulative use in quartiles. Adjustment was made for gender, age, year of diagnosis and socio-economic index. The overall odds ratio (OR) for wireless phone use was 1.0 (95% CI 0.7-1.5). Cumulative use of was related to a risk increase of 1.006 per 100 hours (95% CI 1.003 – 1.009). However, risk was not related to year of latency, laterality, tumour size or tumour location. The authors concluded that this study provides no conclusive evidence of an association between use of mobile and cordless phones and meningioma. This study is based on a retrospective exposure assessment and took only a limited set of potential confounding variables into account.

Hardell et al. (2013c) conducted a pooled study exploring the association between vestibular schwannoma (acoustic neuroma) and mobile and cordless phone use. The material is mainly based on an earlier study (Hardell et al., 2006a). The main results in both studies are quite similar, and the last publication does not add essentially new information.

Mornet et al. (2013) performed a systematic review of the association between use of mobile- and cordless phones and vestibular schwannoma. The review included evaluation of the available cohort studies, registry studies, case-control studies and meta-analyses. The authors do not conclude presence or absence of risk, but emphasize methodological limitations and suggest prospective studies.

In Sweden, Shu et al. (2012) analysed the incidence trends of malignant parotid and salivary gland tumours in Sweden and malignant salivary gland tumours in the Nordic countries during the period 1970 to 2009. Patients 20 years or older with salivary gland malignancies were identified from the Swedish Cancer Registry and the NORDCAN database. In 1970 the age-adjusted incidence rate of parotid gland tumours in Sweden were 0.9/100,000 person-years for men and 0.7/100,000 person-years for women. In 2009 the incidence for men and women were 0.8/100 000 person-years and 0.7/100,000 person-years respectively. The same pattern was seen for all salivary gland tumours. Although for the whole Nordic population the age-adjusted incidence rates were a little higher compared to the Swedish incidence, there was no evidence of an increase of salivary gland tumours over time with an annual percent change in incidence of -0.1% (95% CI -0.4 to -0.2) for men and -0.2% (95% CI -0.5 to -0.1) for women during the period 1979 to 2009. The Nordic countries were among the first to widely adopt usage of mobile phones in the population. It is likely that the incidence of salivary gland tumours, and especially parotid tumours, would have increased if usage of mobile phones were a noticeable risk factor for such tumours.

A recent analysis on the Danish mobile subscriber cohort focussed on the association between mobile phone use and risk of malignant melanoma and non-melanoma skin cancers as basal cell carcinoma (BCC) and Squamous cell carcinoma (SCC)(Poulsen et al., 2013), since the skin is the most exposed part of the human body when using a mobile phone. 723,421 mobile phone subscriptions in Denmark during the period 1982-1995 were obtained from Danish network operators. After excluding 200,507 non-personal subscriptions and conducting a linkage to another existing cohort with socioeconomic indicators, CANULI, a total of 355,701 persons accrued a total of 3.7 million person-years to the exposed cohort. Follow-up period for the analysis started at the age of 30 years or 1990, whichever occurred last, and ended on the date of first cancer diagnosis, death, emigration or 31st of December 2007, whichever came first. Data analysis considered age, calendar year, educational level and income.

The overall IRR for BCC at all sites for both genders combined was 0.95 (95% CI 0.92-0.98), for SCC 1.02 (95% CI 0.94-1.12) and 0.94 (95% CI

0.87-1.01), for malignant melanoma. In order to focus on the highest exposed areas of the body, separate analyses were conducted by tumours occurring at the head and neck compared to tumours at the torso and legs. For BCC there was no evidence that tumours of subscribers occurred more often in the neck region ($IRR_{head+neck}/IRR_{torso+legs}$=0.88 (95% CI: 0.74-1.05) for women and 1.07 (95% CI: 0.98-1.17) for men). These ratios were somewhat higher, although not statistically significant for long term users (≥13 years 1.40 (95%CI 0.69-2.83) for women and 1.20 (0.97, 1.48) for men). For SCC and melanoma, no indications of increased risks were observed.

The authors conclude that this study provided little evidence of an increased skin cancer risk among mobile phone users. The strength of this study include the prospective and objective exposure assessment and in its nationwide coverage. As discussed in the previous Council report (SSM, 2013:19)**,** the crude exposure proxy is useful for evaluation of risk related to long term mobile phone use but not adequate for risk related to cumulative time of use. In this analysis, exposure to UV radiation was not taken into account, such as use of solariums, outdoor work or lying at a beach. The analysis on tumour location can to some extent overcome this limitation. Nevertheless, outdoor work can be related to higher UV radiation of the head and earlier uptake of mobile phone use and thus bias this analysis approach as well. However, this would introduce an upward bias and is unlikely to explain the observed absence of association.

On the background of concern about an apparently high number of cancers in the vicinity of a mobile phone base station in Sandwell, West Midlands, UK, Stewart et al. (2012) conducted a study to examine whether the base station could be responsible for the cancers. Planning permission for the base station was granted in 1997, data on cancer incidence and mortality were collected for the time periods 1993-95 and 1999-2004. The data for the ward was compared with West Midlands as a whole. For all cancers (excluding non-melanoma skin cancers) and gender combined, elevated SIR was found for the period 1999-2001 (SIR 1.15, 95% CI 1.00-1.33), and 2001-2003 (SMR 1.27, 95% CI 1.06-1.51) but not for all other periods after the base station was in operation. When analysing for several specific cancer sites, no differences in SMR or SIR was found. The cases were a variety of different cancers that occur relatively frequently, and where some were more likely caused by lifestyle factors or family history. Thus, the collection of cancers does not fulfil the criteria for cancer clusters. The authors did not conclude that the base station was responsible for the cancers. They claim that it is unlikely that information around a single base station can either demonstrate or exclude causality. The problem with post-hoc cluster investigation is that even if they confirm a suspicion, one cannot exclude that the clusters occurred by chance and that around other base stations no such cluster would be visible.

4.4.4 Cardiovascular disease

In the above mentioned prospective English cohort study (Benson et al., 2013b) also stroke and ischaemic heart disease hospitalisation was explored in relation to mobile phone use. However, no indication for such an association was found.

In Poland, Bortkiewicz et al. (2012) conducted a study to investigate the association between exposure for EMF from radio- and TV-broadcasting and heart rate variability (HRV). 71 exposed persons aged 28-66 years with a work period ranging from 3-35 year (grouped into high (n=12) and medium (n=59) exposed) and 41 unexposed controls aged 33-64 years participated. The exposure to EMF was estimated per participant, explored metrics were maximum and average exposure, as well as cumulative exposure. In addition to blood pressure and HRV measurements, the subjects performed an interview assessing information of cardiological factors and family history, dietary habits and leisure time activities. The authors write that confounders were considered in the analysis but the methods are not described in detail. Exposed persons reported more often cardiovascular symptoms (51%) than controls (29%) and elevated blood pressure was more often measured (34 vs. 19%). The exposed group had significantly lower heart rate variability and also the frequency spectrum of the heart rate analysis was related to exposure. The authors conclude that the autonomous nervous system is affected by RF-EMF exposure. Reduced heart rate variability is a risk factor for acute coronary heart diseases. However, lack of methodological details including selection of study participants, confounding adjustment and outcome measurements leaves many open questions.

In China, Chen et al. (2013b) investigated whether long-term exposure to high intensity radiofrequency fields at 27.2 MHz among women working in a shoe factory were associated with changes of the electrocardiograms (ECG). The study included 322 workers, 224 exposed and 98 unexposed who cut and sew shoe materials, as a control group. Information regarding age, work shift, occupational status, smoking and drinking status etc. was collected through face-to-face interviews. The ECG were recorded and analysed by experienced doctors. The workers were divided into three groups according to the exposure duration; one control group, one group exposed < 2 years and one group exposed ≥ 2 years. Adjustments were made for age and drinking status. Mean exposure and SD was 64.0 ± 25.2 V/m, maximum 106.1 and the minimum was 36.0. The results demonstrated that 18.4% in the control group had abnormal ECG, compared to 25.4 in the exposed group. This difference was not significant (P>0.05). The results were neither significant when analysing the group with highest exposure, several types of ECG and duration of exposure. Little information on the study methods is provided and how the ECG has been recorded and analysed. Moreover, analyses did not take into account potentially relevant confounding factors apart from age and alcohol consumption.

4.4.5 Other outcomes

A survey of salivary flow rate and volume of parotid glands among 142 mobile phone users was published by Bhargawa et al. (2012). A convenience sample of 50 men and 50 women with self-reported mobile phone use of >2hours/day (heavy users) were compared to 20 men and 22 women with <2 hours mobile phone use /day. Within the groups, salivary flow rate was compared according to the preferred side of the head of mobile phone use. If a participant had more salivary flow on the preferred side of the head of mobile phone use, then they were additionally invited to ultrasonography to assess volume of the parotid gland. Participants had been mobile phone users for an average of 5 years prior to the survey. The authors state that average daily mobile phone usage was 7 calls per day with an average duration of calls of 3 hours/day for two third of the participants. In the heavy-users group, salivary flow was 28% higher on the preferred side of the head used for calling; this difference was statistically significant. Within the low-users mobile phone group, the difference was much less pronounced, but also slightly higher on the side preferably used for calling (8% higher flow). The pre-selection of participants with increased salivary flow rate on the preferred side of the head for mobile phone use for the volume assessment of the volume of the parotid gland is unfortunate, as it makes this assessment inconclusive. The reported duration of calling is rather remarkable in a group of persons that were nearly exclusively using prepaid phones. Previous validation studies have reported average duration of phone calls around 1-3 minutes, and a recent report stated that self-reported mobile phone usage was strongly overestimated compared with measured duration (Vanden Abeele et al., 2013). It is also unclear if outcome assessors (the investigators measuring salivary flow) were blinded with regard to mobile phone use including laterality, which might have influenced results.

In Denmark, one more study based on the Danish national birth cohort (DNBC), has been published, this time with a focus on cell phone exposure and hearing loss in children (Sudan et al., 2013a)**.** During the period 1996 to 2002, 91,661 pregnant women were enrolled in the study and information was collected on lifestyle and environmental exposures. When the children were 7 years old, mothers were invited to complete new questionnaires regarding life style, health problems and several exposures. Mothers were asked whether their 7 year-old children used a mobile phone. The response options were “no, never”, “yes, but less than one hour per week” and “yes, more than one hour per week”. So, in contrast to the previous analysis in the DNBC, only the child’s mobile phone use was analysed here. The main outcome of interest was mothers’ reporting of the child’s hearing loss. 91,256 mothers were invited to participate in the age-7 interview. 59,975 (66%)

persons completed the questionnaire. The analyses were based on information from 52,680 children, and the reason for the exclusions from the initial number is unclear. For the analyses of hearing loss, mobile phone use was dichotomized. Data were analysed with different approaches (logistic regression, marginal structural models (MSM) with inverse-probability weighting, and doubly robust estimation) and information of potential confounders was taken into account in the analyses (pregnancy-related factors (mobile phone use of the mother, alcohol use, smoking, fever), socioeconomic status, breast feeding, ear infection by age 18 months, sex, gestational age, and reduced hearing at 18 months). All three types of statistical methods gave similar results, with a tendency of an increased risk (RR=1.21-1.23) of hearing loss among children who had used a mobile phone, with borderline statistical significance. The authors state that their findings could have been affected by various biases and are not sufficient to conclude that cell phone exposures have an effect on hearing. A limitation of the study is the retrospective exposure assessment, the simultaneous assessment of exposure and outcome in the same questionnaire, which might have introduced some reporting bias, and the very broad exposure category that may include a large variation of mobile phone use. In addition, mothers' reports of hearing loss of their children are probably inaccurate. Given the large sample size a replication of the study could be valuable in order to come closer to a reliable conclusion regarding use of mobile phones and hearing loss. However, such an effort would be much more worthwhile if a mechanism would be known how mobile phone usage could possibly induce hearing loss.

Soderqvist et al. (2012) analysed blood markers of samples taken in a previous study (Söderqvist et al. 2009b), from a Swedish cross-sectional study on mobile and cordless phone use. In the current publication, associations with beta-trace protein were evaluated, but no associations were observed. For a full discussion of the study, see (SSM, 2010:44).

4.4.6 Overall conclusions on epidemiology

Most epidemiological studies in relation to mobile phone use addressed tumours in the head region. The Hardell group reported an increased risk for glioma but not for meningioma based on a new study including cases that were diagnosed between 2007 and 2009. The glioma results showed a clear exposure-response association in terms of duration and amount of exposure. However, the results are in contradiction with recent and previous time-trend studies, which do not indicate an increase of glioma cases in the last decade, which one would expect to observe if risk is increasing by 60% after one year of mobile phone use. In a recent study no increases of salivary gland tumours were observed in Sweden between 1979 and 2009. The skin of the head and the neck is the highest exposed part of the body from mobile phone use but the Danish cohort study did not find an increased risk for melanoma or other types of skin cancer in relation to mobile phone use. Many of the studies on non-cancer outcomes have considerable limitations and thus no firm conclusions can be drawn from these studies.

5. Self-reported electromagnetic hypersensitivity (EHS) and symptoms

In the scientific literature nowadays two different terms are used for persons who attribute their health problems to EMF exposure: idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) and electromagnetic hypersensitivity (EHS). In this chapter the two terms are used as synonyms according to the use of the terminology in the original papers.

However, there is a lack of validated criteria for defining and assessing EHS which has also been noted in a recent review article (Baliatsas et al., 2012). In this review it was concluded that the common criterion applied to all studies is that EHS is a self-diagnosis without established and measurable diagnosis criteria; however, previous studies have applied different criteria in terms of exposure sources (e.g. only mobile phones, all type of EMF sources etc.), which may explain a part of the huge differences in reported prevalences observed between studies. For this reason it is difficult to compare results between countries and development of EHS over time. Baliatsas et al. (2012) state that further work is required to produce consensus criteria not only for research purposes but also for use in clinical practice.

In the previous Council report it was concluded that new epidemiological studies on symptoms using an improved design rather indicate the absence of a risk from RF EMF exposure on health-related quality of life. Nevertheless, uncertainty concerns mainly high exposure levels from wireless phone use and longer follow-up times than one year.

5.1 Surveys

In order to evaluate an environmental hypersensitivity symptom inventory, Nordin et al. (2013) conducted a questionnaire survey on environmental hypersensitivity symptoms between March and April 2010 in Västerbotten (Sweden). The questionnaire, which included questions on 34 symptoms, on socio-demographic factors and on physician-based diagnoses, were sent to a random population sample aged between 18 and 79 years. After a maximum of two reminders 3,406 individuals sent back a questionnaire (response rate 45% for women and 35% for men). In terms of environmental hypersensitivities, 3.1% reported physician-diagnosed multiple chemical sensitivity, 1.4% nonspecific building-related symptoms, 0.4% idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) and 2.8% sound sensitivity. The authors did not analyse the symptom pattern with respect to the reported type of hypersensitivity. They concluded that their questionnaire was useful for the assessment of symptom prevalences in various types of environmental hypersensitivities. The IEI-EMF prevalence in this study was lower than reported in a previous Swedish study conducted in 1997, where self-reported prevalence of electromagnetic hypersensitivity (EHS) was 1.5% (Hillert et al., 2002). However, because the new study assessed physician-diagnosed IEI-EMF, whereas the older study referred to self-reported EHS, the numbers cannot be directly compared. As a consequence it is not clear whether EHS prevalence has indeed decreased in Sweden over the last decade. A limitation of the study is the relative low response rate. It is expected that concerned people are overrepresented among the responders and thus, the observed prevalences are rather over- than underestimations.

A questionnaire survey on symptoms and exposure to EMF sources was performed in 350 people aged nine years and older and living in Turkey in spring 2011 (Kucer and Pamukcu, 2013). Apparently all questionnaires were sent back. Data were analysed using chi-square tests and a number of symptoms were found more often in persons who used mobile phone or computers more than 16 minutes per day compared to those who used these devices less. The cross-sectional design, potential for reporting bias, lack of information about study population recruitment, an implausible participation rate of 100% as well as the lack of adjustment for confounding factors in the analysis mean that little can be concluded from the study results.

In Finland a questionnaire survey was conducted among 395 self-diagnosed EHS persons (Hagstrom et al., 2013)**.** From the 206 respondents (52.1%), the most common reported symptoms were related to the nervous system and included stress (60.3%), sleeping disorders (59.3%), fatigue (57.2%), concentration problems (56.7%), memory problems (54.6%) and anxiety (52.6%). When asked about the triggering sources, most commonly listed were: personal computers (50.8%), mobile phones (47.0%), light sources (21.1%), television sets (14.6%) and mobile phone base stations (7.0%). 119 respondents stated that they reduced or avoided EMF as a consequence of their symptoms. According to their own experience, the most effective treatments were dietary changes (69.4%), nutritional supplements (67.8%), increased physical exercise (61.6%) and physical treatments of the body. The official treatment recommendations of psychotherapy (2.6%) and medication (4.2%) were not judged to be helpful. The authors concluded that the official treatment protocols should take better into account the EHS-person's own perspectives.

In a Dutch survey, differences in health perception between people who registered themselves as sensitive to EMF at a non-governmental organisation (NGO) and people within the general population reporting sensitivity or non-sensitivity to EMF were investigated (van Dongen et al., 2013). The general population sample consisted of 1,009 participants (response rate 60%) of a Dutch online consumer panel. Of these, 7% reported to be sensitive to EMF. The NGO sample consisted of 116 individuals who had reported health problems with EMF in the previous 5 years. The NGO sample reported the largest amount of symptoms and the non-sensitive population sample the smallest amount of symptoms. Attribution of symptoms to EMF was also most pronounced in the NGO group and least in the non-sensitive population group. In terms of personal characteristics, the sensitive population sample was more similar to the non-sensitive population sample than the NGO sample. The authors reported that attribution of symptoms to EMF was one of the predictors of the intensity of physical symptoms. However, because of the cross-sectional design, it cannot be resolved which occurred first, the strong attribution or the severity of the symptoms. The authors speculated whether changing the perceived association between EMF and health problems in individuals with IEI-EMF might contribute to a better health experience.

Several studies indicated that there is an interaction between risk perception and EHS (Hassoy et al., 2013, Kowall et al., 2012, Tseng et al., 2013). In terms of risk management, Wiedemann et al. (2013) did not find evidence that precautionary information creates concerns and anxiety in the population as previously hypothesized. This multicentre experimental study was conducted in nine countries (Australia, Brazil, Germany, India, Japan, the Netherlands, South Africa, the United Kingdom, and the United States) with at least 400 participants per country. This study demonstrates that precautionary measures aiming to reduce concerns in the population will not work. However, governments may have other reasons for implementing precautionary limits.

In a Dutch study the roles and viewpoints of scientific experts in advising on environmental risk has been evaluated based on the Q methodology with 26 EMF experts and 21 experts in air pollution (particulate matter) (Spruijt et al., 2013). For EMF they found three roles: the autonomous scientist, the pragmatist and the action oriented expert. For particulate matter experts they identified the engaged expert, the instrumental expert and the deliberator. The authors concluded that the particular expert roles depend on the specific environmental risk.

In a British content analysis of newspaper reports, poor reporting of IEI-EMF was identified as a possible reason for people to misattribute their symptoms to EMF exposure (Eldridge-Thomas and Rubin, 2013). The study included 60 articles relating to IEI-EMF published in British newspapers between 1 January 2006 and 31 December 2011. Of these, 71.7% presented a mainly electromagnetic cause; whereas only 21.7% presented mainly a non-electromagnetic cause (6.7% did not discuss a cause). About 50% of the articles discussed treatment options, which included mostly exposure-reduction related actions (40%) or complementary and alternative therapies (20%). Articles with a scientific source were more likely to discuss a non-electromagnetic cause for the symptoms.

5.2 Extremely Low Frequency (ELF) fields

5.2.1 Human laboratory studies

In a study already described in more detail under the heading ELF, 4 2.3.3 Other endpoints, Kim et al. (2013b) also investigated effects of 60 Hz 12.5 µT magnetic fields on subjective symptoms. Information on throbbing, itch-ing, warmth, fatigue, headache, dizziness, nausea, and palpitation were ver-bally collected at the end of a 15 min pre-exposure interval, two times during exposure (sham or real) and 10 min after the end of exposure. Information on belief of exposure was collected nine times (pre-exposure, five times during exposure and three times post exposure). The authors, who adjusted significance levels for multiple testing, did neither for adults nor for teenagers find any significant exposure effect on the subjective symptoms. They furthermore found that neither group of participants could correctly perceive the magnetic field.

5.2.2 Epidemiological studies

In order to investigate the effect of ELF-EMF exposure on sleep quality, the sleep pattern of shift workers in high voltage substations were compared with shift workers of cement, tire or copper industry (Barsam et al., 2012). From a total of 67 substation workers, 41 worked in 132 kV substations (mean magnetic field exposure: 0.23 µT), 20 in 230 kV substations (0.75 µT) and the rest in 400 kV substations (0.75 µT). Sleep quality of study participants was assessed with the Pittsburgh Sleep Quality Index questionnaire (PSQI) on three consecutive days and data were analysed using repeated measure ANOVA without considering covariates. Age and BMI were similar between exposed and not exposed persons whereas educational level differed statistically significant. Most of the study participants reported poor sleep quality but differences between exposed (90.5%) and non-exposed (85.3%) were not statistically significant. The total sleep score was also not associated with ELF-MF exposure. According to the abstract, the mean time needed to fall asleep was longer for exposed workers (35.7 min.) than for non-exposed workers (28.9 min) (p-value=0.002), but these results are not presented in the paper. On the one hand, shift workers may be an interesting group for studying EMF effect on sleep because their sleep may be more susceptible to external nuisances. On the other hand, the large heterogeneity needs careful consideration of covariates and thus observed differences between exposed and non-exposed could be caused by other factors. Covariates were not considered in the analysis, the recruitment process was not clearly described and the PSQI is not an appropriate questionnaire tool to study daily changes of sleep patterns. All in all, these factors make the study uninformative regarding the association between workplace exposures to ELF-MF and sleep quality.

5.3 Intermediate Frequency (IF) fields

Hagstrom et al. (2012) evaluated the effect of a shielding cabinet for video display units (VDU) in five individuals, who previously experienced symptoms from computer work. Laptops or computer screens could be placed inside of the shielding cabinet and was reported to reduce the emissions in front of the cabinet by up to 20 dB according to measurements in the 10 to 1000 MHz range. Two out of the 5 study participants applied the shielding cabinet for 1 and 7 years, respectively and became completely free of symptoms. Two other participants who applied the shielding cabinet for two and three months experienced a partial symptom reduction whereas the 5th participant who applied the shielding for 1 week reported a slight reduction of nausea. The authors conclude that reducing the electromagnetic irradiation of the computer can reduce symptoms of electromagnetic hypersensitivity and permit affected persons to work without problems. However, besides the very small sample size, a considerable limitation for the interpretation of the study is the fact that the study was not conducted in a blinded way, meaning that participants were fully aware of the intervention. As a consequence, it cannot be excluded that placebo effects accounted for the observed improvements. It is also not clear how the five participants have been selected for the study.

5.4. Radiofrequency (RF) fields

5.4.1 Human laboratory studies

Schmid et al. (2012) who investigated possible effects of a 2 Hz pulse modulated RF signal and a 2 Hz pulsed magnetic field on the sleep EEG (see 4.3.2 Sleep and EEG under the heading Radiofrequency fields in chapter 4) did not observe any exposure-related variation in mood, well-being or subjective sleep quality. The corresponding questionnaires were completed after 30 min exposure in the evening (prior to bedtime) and upon awakening in the morning.

Kwon et al. (2012a, 2012b) investigated the possible effects of EMF RF exposure on symptoms and whether participants were able to detect exposure. The study comprised two groups: 20 healthy participants (9 females, 29.4 ± 5.2 years) and 17 participants with self-reported electromagnetic hypersensitivity (9 females, 30.1 ± 7.6 years). Subjects were exposed for 32 min in a double-blind cross-over design to either WCDMA or sham). No effects of exposure on symptoms (throbbing, itching, warmth, fatigue, headache, dizziness, nausea, and palpitation) in either group were observed, nor were subjects in either group able to detect the exposure.

5.4.2 Epidemiological studies

A cross-sectional study on 15 non-specific symptoms of ill health was conducted with 250 randomly selected inhabitants living near a mobile phone base station in Isfahan, Iran (Shahbazi-Gahrouei et al., 2013). Various symptoms were correlated with self-estimated distance to the closest mobile phone base station according to chi-square tests without consideration of covariates. It is well known that self-reported distance to next mobile phone base station is not a suitable exposure measure for epidemiological studies (Baliatsas et al., 2011, Frei et al., 2010). The lack of suitable exposure assessment and inadequate confounding adjustment makes thus this study uninformative.

In the previous Council report a prospective cohort study of young adults (20-24 years) on mobile phone use and mental health outcomes was discussed (Thomee et al., 2011). 2,701 women and 1,455 men participated in the longitudinal analysis, corresponding to 58% of the participants at baseline. In those who participated in the follow-up after one year, a high amount of mobile phone use at baseline was associated with sleep disturbances in men, and with symptoms of depression in men and women. In the meanwhile another analysis was published, investigating current stress, sleep disturbances, reduced performance and symptoms of depression in relation to computer use, email/chatting, computer gaming, computer use without taking breaks (Thomee et al., 2012). The authors report associations between sleep disturbances in all exposure categories except gaming in men. In women, all outcomes were related to computer use without taking breaks. Because computer use does usually not increase EMF exposure, the new analyses suggest that rather extended use of communication technology than EMF emissions are associated with impaired mental health in young adolescents. A limitation of the study is the low participation rate and considerable drop-out rate. Exposure assessment was based on self-reports and only a limited number of possibly relevant confounders have been considered in the analysis.

Elwood (2012) reviewed a report investigating health effects in US embassy personnel in Moscow: During the period 1953-1976 beams of microwaves were allegedly aimed at the US embassy building in Moscow. Lilienfeld (1978) and colleagues were engaged to investigate possible health effects (especially cancer) from this exposure, which resulted in a report. The frequency of the exposure was between 2.5 to 4.0 GHz, and maximum exposure values were given as up to 5 μW/cm² (5 mW/m²) 9 hours per day, with some higher values the last year of exposure. Compared to US mortality, the standardized mortality ratio (SMR) was below unity for the Moscow employees, as were heart disease and all cancers, but brain cancers were more common, although based on only 5 cases. The exposure levels were low and there was no information regarding personal exposure and the sample size of the study was very small. It is unclear if the study was performed as a post-hoc cluster analysis. In summary, the study is not informative regarding potential health effects from RF-EF.

5.5 Overall conclusions on symptoms and EHS

Since the last Council report only a few studies on symptoms and/or EHS have been published. Most studies were surveys which did not aim to investigate a causal association between EHS and EMF exposure but rather aimed at describing the distribution of EHS in the population. Experimental studies did not find indications for acute effects from ELF or RF-EMF exposure. Epidemiological studies addressing the association between EMF exposure and symptoms had severe limitations and thus the state of knowledge has not noticeably changed since the last report. However, recent findings on the interaction between risk perception and EHS may be helpful for risk management.

6. Recent expert reports

This Chapter briefly summarises some expert reports published since the last Council report. The summaries are directly edited from the executive summaries of these reports. The Council do not evaluate or comment any of the reports.

6.1 IARC Monograph on Non-ionizing radiation, part 2: radiofrequency electromagnetic fields, volume 102 (International Agency for Research on Cancer, 2013)

Overall conclusion

The IARC Monograph on radiofrequency fields was published in May 2013. Using the IARC nomenclature, a panel of experts convened in June 2011 evaluated the overall body of evidence and concluded that Radiofrequency electromagnetic fields are possibly carcinogenic to humans (Group 2B). This classification was based on data from human studies and animal studies. The experts considered that there is limited evidence both in humans and in experimental animals for the carcinogenicity of radiofrequency radiation.

While the human epidemiological evidence was mixed, positive associations observed between exposure to radiofrequency radiation from wireless phones and glioma, and acoustic neuroma came from reports of the INTERPHONE study, a very large international, multicentre case–control study and from a separate large case–control study from Sweden on gliomas and meningiomas of the brain and acoustic neuromas. The association between glioma and acoustic neuroma and mobile-phone use; was observed specifically in people with highest cumulative use of mobile phones, in people who had used mobile phones on the same side of the head as that on which their tumour developed, and in people whose tumour was in the temporal lobe of the brain (the area of the brain that is most exposed to RF radiation when a wireless phone is used at the ear). The comparative weakness of the associations in the INTERPHONE study and inconsistencies between its results and those of the Swedish study led to the evaluation of limited evidence for glioma and acoustic neuroma, as decided by the majority of the members of the Working Group.

The Monograph noted a minority opinion that current evidence in humans was inadequate, therefore permitting no conclusion about a causal association. This minority saw inconsistency between the two case–control studies and a lack of exposure–response relationship in the INTERPHONE study. The minority also pointed to the fact that no increase in rates of glioma or acoustic neuroma was seen in a nationwide Danish cohort study, and that up to now, reported time trends in incidence rates of glioma have not shown a trend parallel to time trends in mobile-phone use.

6.2 Mobile phones and cancer. Part 1: Epidemiology of tumours in the head (Health Council of the Netherlands, 2013)

Health Council of the Netherlands, publication no. 2013/11, ISBN: 978-90-5549-960-1

Overall conclusion

The present systematic analysis shows that, despite large research efforts, there is still no clarity regarding a possible association between mobile phone use and an increased risk of tumours in the brain and other regions of the head. There are some weak and inconsistent indications for an association between prolonged and intensive use of a mobile phone and an increased incidence of
gliomas. These might be explained by various types of bias and by chance, but it can also not be excluded that there is a causal relation. For the other types of tumours, including meningiomas and acoustic neuromas, indications for an increased risk are much weaker, or completely absent. Based on the available epidemiological evidence described in this report and taking into account the quality of the different studies and their strengths and weaknesses, the final conclusion from this systematic analysis is then: there is no clear and consistent evidence for an increased risk for tumours in the brain and other regions in the head in association with up to approximately 13 years use of a mobile telephone, but such risk can also not be excluded. It is not possible to pronounce upon longer term use.

6.3 OPINION of the French Agency for Food, Environmental and Occupational Health & Safety concerning the update of the “Radiofrequency electromagnetic fields and health” expert appraisal

(ANSES Opinion Request No. 2011-SA-0150)

Conclusions of the collective expert appraisal (shortened)

Analysis of the results of the expert appraisal and consideration of the data in the previous appraisal (AFSSET, 2009), gives rise to the following conclusions. Many studies in the fields of biology and epidemiology have been published since the 2009 report. Among the biology studies, many well-conducted investigations show no effects. Some studies have found biological effects in pathways that have not been well evaluated to date, and the results need to be validated (mitochondrial DNA, co-carcinogenicity, modulated signals, etc.). Until now, most of the effects appear to be transient or involve basic biological variation, demonstrating the ability of biological systems to repair or restore homeostasis. It is therefore impossible to conclude that the observed biological effects have effects on health.

Concerning the study of non-carcinogenic effects, studies on the central nervous system (CNS) are dealt with separately from the others. Regarding studies of CNS effects, in the tested experimental conditions on cellular or animal models or in clinical studies, the level of evidence is inadequate to conclude that exposure to RF fields has an effect in humans on (i) cognitive function, (ii) sleep in the short-term following acute exposure, (iii) circadian, (iv) auditory function in the short-term following acute exposure, (v) neurodegenerative disorders (amyotrophic sclerosis and Alzheimer's disease, in particular) and on (vi) other neurological diseases e.g. multiple sclerosis and epilepsy. (For (iii) and (vi) on the basis of a limited number of studies).

Concerning other non-carcinogenic effects other than CNS effects, the level of evidence is inadequate to conclude that exposure to RF fields has an effect in humans on (i) male fertility, (ii) height, weight and viability of descendants, (iii) teratogenesis and *in utero* development, (iv) the immune system, (v) the endocrine system, (vi) the cardio-vascular system, particularly haematological parameters, vasodilation, heart rate and blood pressure, (vii) well-being (in the general population), (viii) overall health (all-cause mortality, on the basis of two studies), (ix) the visual system. Only one article of sufficient quality aimed to evaluate a possible effect of RF fields on female fertility. (For (ii), (v), (vi) and (ix) on the basis of a limited number of studies, for (ix) all analysed in the 2009 AFSSET report).

Concerning the potential carcinogenic effects of radiofrequencies, the evidence level is inadequate to conclude that exposure has an effect in humans on development of (i) gliomas in the general population, (ii) meningiomas, (iii) salivary gland tumours, (iv) pituitary tumours (adenomas) (on the basis of two studies analysed in the 2009 AFSSET report), (v) leukaemia (on the basis of a limited number of studies), (vi) cutaneous (on the basis of a limited number of studies) and ocular melanomas, (vii) and on cancer incidence and mortality (all types).

Analysis of articles published since 2009 leads to the following comments. The level of evidence is limited to conclude on the risk of glioma associated with RF fields for intensive users of mobile phones, i.e. those with more than 1640 hours of cumulative exposure. An increased risk of glioma with the following characteristics cannot be ruled out (i) slightly higher increase in risk (less than 20% increase in incidence of gliomas), (ii) limited to small subgroups of users (e.g. highly intensive users), (iii) associated only with one or more rare types of glial tumours, (iv) for induction periods greater than 15 years (no data are available for longer periods).

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2014:16

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 270 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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