



Strål
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Swedish Radiation Safety Authority

Author: SSM's Scientific Council on Electromagnetic Fields

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Recent Research on EMF and Health Risk

Eleventh report from SSM's Scientific Council on
Electromagnetic Fields, 2016

Including Thirteen years of electromagnetic field research
monitored by SSM's Scientific Council on EMF and health:
How has the evidence changed over time?

SSM perspective

Background

The Swedish Radiation Safety Authority's (SSM) Scientific Council on Electromagnetic Fields monitors current research on potential health risks with a correlation to exposure to electromagnetic fields, and provides the Authority with advice on assessing possible health risks. 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 each year on the current research and knowledge situation.

Objectives

The report has the objective of covering the previous year's research in the area of electromagnetic fields (EMF). The report gives the Swedish Radiation Safety Authority an overview and provides an important basis for risk assessment.

Results

The present annual report is the eleventh in this series and covers studies published from October 2014 up to and including September 2015. The report covers different areas of EMF (static, low frequency, intermediate, and radio frequency fields) and different types of studies such as biological, human and epidemiological studies. This report also includes an overview of how scientific evidence of different causal links between exposure and health risks have changed over the past thirteen years. The annual report also has a section covering other relevant scientific reports published recently.

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Preface

In 2002, the Swedish Radiation Protection Authority (SSI) established an international scientific council for electromagnetic fields (EMF) and health with the main task to follow and evaluate the scientific development and to give advice to the authority. The SSI was the responsible authority until July 2008.

That year, the Swedish government reorganized the radiation protection work and the task of the scientific council is since July 2008 handled by 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 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 eleven in the series and covers studies published from October 2014 up to and including September 2015.

The eleven reports cover a large variety of issues on health effects of exposure to various types of electric, magnetic and electromagnetic fields. Some of these reports were more thematic, while others covered a broad area of effects. In an introductory overview of this eleventh report the findings of scientific research are discussed with a focus on the question whether and how evidence for health effects has changed over the last thirteen years.

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Stockholm in April 2016

Leif Moberg
Chair

Thirteen years of electromagnetic field research monitored by SSM's Scientific Council¹ on EMF and health: How has the evidence changed over time?

Introduction

In the late 1990s and the beginning of the 2000s possible health risks from electromagnetic fields were beginning to create quite a lot of anxiety among the general public in Sweden as well as in some other countries. At that time the authority responsible for radiation protection in Sweden was the Swedish Radiation Protection Authority (SSI), a predecessor to the current Swedish Radiation Safety Authority (SSM).

Reports on possible effects of electromagnetic fields were often noticed in the media. The researchers were interviewed and warnings for cancer and other severe health risks were presented, often in a rather dramatic way. In the first years of the 2000s the third generation (3G) of mobile telephony was launched in Sweden. This caused a lively debate and often individuals living in the neighbourhood of the masts complained about health risks from the transmitters.

In this already rather heated situation the national Swedish Television in the beginning of 2002 showed an investigating program² about health risks from mobile telephony. The program was influenced by reports on possible health risks. Several Swedish research groups were active in the area of exposure to electromagnetic fields. Of special interest to the general public were health risks from mobile telephony. In the program, SSI was accused of not taking the health risks from the mobile telephony systems seriously. It was obvious to the Director General of SSI that something had to be done to thoroughly evaluate possible health risks from exposure to electromagnetic fields.

There was one additional reason why SSI was anxious to have a good understanding of the state of scientific knowledge regarding risks from exposure to electromagnetic fields. In 2002, a national system of Environmental Quality Objectives³ was launched in Sweden. "A Safe Radiation Environment" was one of the 15 national objectives which covered all types of environmental threats. This objective included both ionizing and non-ionizing radiation. The Government appointed SSI as the responsible authority for "A Safe Radiation Environment".

Therefore, in spring 2002, the Director General of SSI decided to form a scientific council on EMF with the task to follow and evaluate the scientific development and to give advice to the authority regarding EMF exposure and possible health risks.

In the past 13 years SSI/SSM has published 11 reports of its International Scientific Council, covering a large variety of issues on health effects of exposure to various types of electric, magnetic and electromagnetic fields. Some of these reports were more thematic: for instance the focus of the 2003 report was on epidemiological and experimental

¹ In the first annual reports the Council was referred to as the IEG, the International Expert Group. In this draft the word Council is used throughout.

² In Swedish: Uppdrag granskning

³ In Swedish: Miljömål

cancer research, the blood-brain barrier and heat shock proteins and the 2004 report focused on possible health risks from mobile telephony systems, while others covered a broad area of sources. In this overview the findings of scientific research are discussed with a focus on the question whether and how evidence for health effects has changed over the last 13 years. The text is grouped by broad categories of frequency: static fields (0 Hz), extremely low frequency (ELF) fields (>0 Hz-300 Hz) and radiofrequency (RF) fields (10 MHz-300 GHz).

Static fields

For the public, the most important source generating exposure to static magnetic fields (0 Hz) is magnetic resonance imaging (MRI). In MRI devices, a combination of very strong static magnetic fields and radiofrequency fields (RF) are used to generate an image of internal structures of the objects investigated. MRI has become a very important medical diagnostic tool. Thirteen years ago, little research on the health effects of MRI exposure was available. If one moves too fast in a strong static magnetic field, a time-varying magnetic field is induced and over the last years, epidemiologic studies have reported short-term effects of the exposure on specific symptoms (especially vertigo, phosphenes, metallic taste) among radiographers working with MRI. These observations have been confirmed by double blind, randomized human provocation studies demonstrating that movements in MRI fields can affect subjective sensations, postural control and performance. These effects occur more easily with stronger fields, which is important to recognize, taking into consideration that the strength of MRI devices is increasing. In some clinics machines operating at 7 tesla are in use – for comparison: a fridge magnet has a strength of about 0.005 tesla. The recent studies have led to recommendations that symptoms can be avoided if the speed of movement through the field is limited.

In several studies using cultured cells it has been observed that after exposures to static fields in the order of those of fridge magnets, an increased level of reactive oxidative species (ROS) could be measured. ROS causes increased oxidative stress and may result in increased damage to biological material. In whole organisms such as experimental animals exposure to static fields even thousands of times higher than that of fridge magnets has never led to any adverse health effects, so most likely any increased oxidative stress is compensated for by internal mechanisms. Epidemiologic studies on long-term exposures to static fields were mostly conducted in welders and aluminium-industry workers, where also other, potentially hazardous exposures (especially fumes) could have been at work. Such co-exposures make these studies difficult to interpret compared to exposure to static magnetic fields alone.

Extremely Low Frequency (ELF) electric and magnetic fields

Based on studies performed in the last decades of the previous century, an association has been consistently observed between the occurrences of childhood leukaemia and being long-term exposed to relatively high levels of extremely low frequency (ELF) magnetic fields (>0 Hz-300 Hz) as generated by the electric power system. Increased risks are observed with fields above 0.3-0.5 microtesla; average fields in households are usually around 0.1 microtesla, but large local variations occur. Several new epidemiological studies have been described in the SSM reports, which overall confirmed the previous studies. Nevertheless, little progress has been made to reveal the underlying biophysical mechanism for these epidemiological associations. In some studies using cultured cells an in-

creased level of oxidative stress has been observed. But elevated ROS (reactive oxygen species) levels have not led to any adverse health effects in animals, nor can these levels be linked to childhood leukaemia development. A mouse model for leukaemia has recently been developed, but this also failed to provide evidence for a causal relation between leukaemia development and exposure to ELF magnetic fields. Without support from cell and animal studies, there is still uncertainty as to whether long-term exposure to ELF magnetic fields can actually lead to childhood leukaemia.

Progress has been made for research on female breast cancer. Thirteen years ago a possible link was hypothesized but now it is fairly certain that there is no causal relation with exposure to ELF magnetic fields.

Hardly any data was available on the relation between ELF magnetic field exposure and Alzheimer's disease when SSM started this series of reports. In the meanwhile several new studies on occupational ELF magnetic field exposure and Alzheimer have been published. Several recent studies have suggested slightly increased risks with a tendency of an exposure-response pattern. Similar to the relation with childhood leukaemia, no evidence from experimental studies is available that suggests a causal relation and confounding and publication bias is a concern for occupational studies.

Also for Amyotrophic Lateral Sclerosis (ALS) epidemiologic research has mainly been conducted in the last 13 years. First studies primarily assessed risk in so-called "electrical occupations" and it was not clear whether associations may be due to ELF magnetic field exposure or electric shocks. More recently, studies have started to evaluate mutual exposure to ELF magnetic fields and electrical shocks at work. However, the studies are inconsistent and the puzzle is not yet solved. In an animal model for ALS no effects of ELF exposure were observed, so these studies did not support the epidemiological data. Progress has been made on the previously open question of a relation between exposure to ELF magnetic fields and Parkinson's disease. In this case the new available data suggest the absence of an effect. The same can be concluded concerning cardiovascular diseases.

Some evidence has been obtained for effects of ELF magnetic field exposure on the brain electrical activity, but no effects on memory or cognition have been observed. Many factors influence brain activity (e.g. level of alertness/sleepiness, caffeine intake), so the effects of ELF magnetic fields are an example of a physiological effect. It is not known that this leads to adverse health effects.

In the last 13 years little epidemiologic research on symptoms and ELF magnetic field exposure has been conducted. However, in the few experimental studies investigating acute symptoms such as headache or dizziness in human volunteers no association was seen. In general, the strength of the evidence for an association has somewhat decreased over time.

Radiofrequency (RF) electromagnetic fields

Most research in the past decade has been done into a possible relation between mobile phone use and brain tumours. Epidemiological studies have provided weak indications for an association between frequent and long-term use of a mobile phone and gliomas (malign tumours of the brain tissue) and vestibular schwannomas (also called acoustic neuromas, a benign tumour of the vestibulocochlear nerve that connects the ear to the inner

brain). The evidence is not very clear and unequivocal, however. Altogether it provides no or at most little indications for a risk for up to approximately 15 years of mobile phone use. No empirical data are available for longer use; however, cancer rates in Sweden and other countries do not show any increase that might be attributed to the massive mobile phone use that started in the beginning of this century. There are no indications from the few studies with cultured cells, that RF fields are capable of initiating a tumour. Many animal studies have been performed using a large spectrum of tumour types and long term, often lifelong, exposure. With very few exceptions, no effect of RF exposure on tumour growth and development has been found.

The studies of the effects of RF exposure on brain activity in humans have mostly found changes, in particular during sleep after and during exposure. The effects are, however, not entirely consistent, and in particular effects observed during waking are diverse. No indications have been obtained that these changes translate into behavioural effects or any other adverse health effect. For instance, a number of human and animal studies did not find cognitive functions to be affected by RF exposure (which was confirmed in a number of cases in replication studies).

In the last 13 years many studies addressed the occurrence of symptoms and exposure to RF fields (10 MHz-300 GHz) applying carefully controlled double blind conditions in the laboratory, using either a mobile phone or a mobile telecommunication antenna as source of RF fields. These studies have indicated that acute effects do not occur as the result of RF exposure. However, symptoms do occur or are aggravated in some subjects when they think they are being exposed. This is called the nocebo effect. Several, mostly cross-sectional, epidemiological studies have investigated associations between the presence of mobile phone base stations in the vicinity and the occurrence of symptoms. Such studies are not suitable for determining any exposure-response relationship, also because the nocebo effect can occur when people know about the presence of a mobile phone base station in the neighbourhood. In general, there is increasing evidence over the years for absence of acute risks.

Thirteen years ago several studies reported increased childhood and adult leukaemia cancer rates in the vicinity of strong broadcast transmitters. In the meanwhile, four large case-control studies did not observe an increased risk for childhood leukaemia. Also for adult cancer several other studies did not see an increased risk in the vicinity of large transmitters. So there is increasing evidence for the absence of an increased risk for cancer for persons living in the vicinity of a transmitter.

Finally, a topic that has received quite some attention during the last years is the effect of exposure of the male genitals to RF fields from a mobile phone when this is carried in a trouser pocket. Several epidemiological and human and animal experimental studies reported some effects, primarily on the semen quality, which theoretically could lead to reduced fertility. However, almost all of these studies were of low quality in terms of how the studies were designed and analysed and the results are therefore not informative regarding the presence or absence of potential risks. Furthermore, animal studies did not support those effects.

Final remarks

A lot of research has been performed in the 13 years since the SSI/SSM started to monitor the research on EMF by a Scientific Council. In general, more clarity has been obtained

on the absence of a number of adverse health effects that were suspected to be resulting from exposure to electric, magnetic or electromagnetic fields of different frequencies. Some questions have not been answered satisfactorily and thus need more research. It is of concern that the design of the studies is not always adequate because that can lead to results that are not informative. It is thus important to critically review scientific studies on a periodic basis. The Scientific Council of SSM will continue monitoring and reporting on the literature on this topic.

Tretton år av forskning om elektromagnetiska fält sammanställd av SSM:s vetenskapliga råd för EMF och hälsa: Hur har kunskapsläget ändrats över tid?

Introduktion

Under slutet av 1990-talet och början av 2000-talet började möjliga hälsorisker från exponering för elektromagnetiska fält orsaka en hel del oro bland allmänheten i Sverige liksom i ett antal andra länder. Den ansvariga myndigheten för strålskyddsfrågor i Sverige var vid den tiden Statens strålskyddsinstitut, SSI, en föregångare till Strålsäkerhetsmyndigheten, SSM. Rapporter om möjliga hälsoeffekter från exponering för elektromagnetiska fält uppmärksammades ofta i media. Forskare intervjuades och det utfärdades varningar för cancer och andra allvarliga hälsorisker, ofta i ganska dramatiska ordalag. Under de första åren av 2000-talet började den tredje generationens mobiltelefoni (3G) att lanseras i Sverige. Det orsakade en livlig debatt och ofta klagade personer boende i närheten av planerade basstationer på hälsorisker från sändarna.

I detta redan ganska infekterade läge sände Sveriges Television i början av 2002 ett program i serien Uppdrag granskning om hälsorisker från mobiltelefoni. Programmet var influerat av rapporterna om möjliga hälsorisker. Flera svenska forskningsgrupper var aktiva inom området hälsorisker från elektromagnetiska fält. Allmänheten var särskilt intresserad av eventuella risker från mobiltelefoni. I programmet anklagades SSI för att inte ta frågan om hälsorisker från mobiltelefoni på tillräckligt allvar. Det var uppenbart för SSI:s generaldirektör att något måste göras för att på ett trovärdigt sätt utvärdera möjliga hälsorisker från exponering för elektromagnetiska fält.

Det fanns ytterligare en orsak till att SSI var angeläget att ha särskilt god kunskap om kunskapsläget rörande hälsorisker från exponering för elektromagnetiska fält. Under 2002 lanserades ett nationellt program för miljömål i Sverige. Ett av de 15 miljömålen i programmet, som var avsett att täcka alla typer av miljörisker, var "Säker strålmiljö". "Säker strålmiljö" inkluderade både joniserande och icke-joniserande strålning. Regeringen gav SSI uppdraget att vara ansvarig myndighet för "Säker strålmiljö".

Under våren 2002 beslöt därför SSI:s generaldirektör att inrätta ett vetenskapligt råd för elektromagnetiska fält med uppgiften att följa den vetenskapliga utvecklingen inom forskningsområdet och ge råd till myndigheten om exponering för elektromagnetiska fält och möjliga hälsorisker.

Under de senaste 13 åren har SSI/SSM publicerat 11 rapporter från sitt internationella vetenskapliga råd. Rapporterna har täckt olika slag av möjliga hälsoeffekter från exponering av elektriska och magnetiska fält. En del av dessa rapporter har varit mer tematiska: t.ex. så fokuserades 2003 års rapport på epidemiologisk och experimentell cancerforskning, blod-hjärn-barriären samt värmechockproteiner och 2004 års rapport avhandlade enbart möjliga hälsorisker från mobiltelefonisystem. Övriga rapporter har täckt in ett brett område av exponeringskällor. I den här översikten diskuteras de vetenskapliga fynden utifrån frågan om, och i så fall hur, evidensen för hälsoeffekter har förändrats under de

senaste 13 åren. Texten har ordnats utifrån breda frekvensområden: statiska fält (0 Hz), lågfrekventa (ELF) fält (>0 Hz-300 Hz) och radiofrekventa fält (10 MHz-300GHz).

Statiska fält

Allmänheten exponeras för starka statiska magnetfält främst vid undersökningar med magnetresonanstomografi. Vid sådana undersökningar utgörs exponeringen av en kombination av mycket starka statiska magnetfält och radiofrekventa fält. Magnetresonanstomografi har blivit ett mycket viktigt medicinskt diagnosverktyg. För 13 år sedan fanns mycket få forskningsresultat publicerade om hälsoeffekter i samband med exponering från magnetresonanstomografer. Om man rör sig för snabbt i ett starkt statiskt magnetfält så induceras ett tidsvariabelt magnetfält i kroppen. Under de senaste åren har epidemiologiska studier visat på korttidseffekter av specifika symtom, särskilt yrsel, ljusförmimmelser och metallsmak i munnen, hos personal som arbetar med magnetresonanstomografi. Observationerna har bekräftats i dubbelblinda randomiserade provokationsstudier som visar att rörelser i fält från magnetresonanstomografer kan påverka subjektiva upplevelser, balans och prestanda. Effekterna uppträder oftare ju starkare fälten är, vilket är viktigt att ta hänsyn till eftersom styrkan hos de magnetresonanstomografer som används tenderar att öka. Vid en del kliniker används maskiner där fälten har en styrka på 7 tesla - som jämförelse: en kylskåpsmagnet har en styrka på ungefär 0,005 tesla. Nya studier har lett till rekommendationer om att begränsa hur snabbt man rör sig i fältet för att undvika symtom.

I ett flertal studier med odlade celler har man, efter exponering för statiska fält av ungefär samma styrka som en kylskåpsmagnet, uppmätt förhöjda nivåer av reaktiva syreföreningar (ROS). ROS medför en ökad oxidativ stress och kan orsaka ökade skador på biologiskt material. I organismer, som till exempel försöksdjur, har exponering för statiska fält upp till tusen gånger starkare än kylskåpsmagneter aldrig lett till några skadliga hälsoeffekter, så förmodligen kan ökad oxidativ stress kompenseras av interna mekanismer.

Epidemiologiska studier med långtidsexponering för statiska fält har framför allt gjorts på svetsare och arbetare inom aluminiumindustrin där också andra potentiellt farliga exponeringar (i synnerhet rök) kan ha påverkat utfallet. Sådana kombinerade exponeringar gör det svårt att utvärdera dessa studier jämfört med exponering för enbart statiska magnetfält.

Lågfrekventa (ELF) elektriska och magnetiska fält

Baserat på studier som genomförts under de sista årtiondena av 1900-talet har man genomgående sett ett samband mellan förekomst av barnleukemi och långtidsexponering för relativt höga nivåer av lågfrekventa magnetfält, framför allt fält orsakade av kraftledningar. Förhöjda risknivåer har observerats vid fält som överstiger 0,3-0,5 mikrot Tesla. Genomsnittliga fält i bostäder ligger normalt kring 0,1 mikrot Tesla, men stora lokala variationer förekommer. Flera nya epidemiologiska studier, som i stort bekräftar tidigare resultat, har redovisats i EMF-rådets rapporter. Tyvärr har få framsteg gjorts när det gäller att hitta den underliggande biofysikaliska mekanismen för dessa epidemiologiska samband. I några studier med odlade celler har ökad oxidativ stress observerats, men förhöjda nivåer av reaktiva syreföreningar (ROS) har inte lett till skadliga hälsoeffekter hos djur, inte heller kan dessa nivåer kopplas till utveckling av barnleukemi. En musmodell för leukemi har nyligen utvecklats, men inte heller med denna modell har man kunnat hitta ett orsaks-

samband mellan exponering för lågfrekventa magnetfält och utveckling av barnleukemi. Utan stöd från cell- och djurstudier så är det fortfarande osäkert om långtidsexponering för lågfrekventa magnetfält verkligen kan orsaka barnleukemi.

Framsteg har gjorts när det gäller forskning om bröstcancer hos kvinnor. För 13 år sedan fanns hypoteser om ett möjligt samband, men nu bedöms det som tämligen säkert att det inte finns något orsakssamband mellan exponering för lågfrekventa magnetfält och bröstcancer.

När SSI/SSM startade sin rapportserie fanns det knappast några data tillgängliga om samband mellan exponering för lågfrekventa magnetfält och Alzheimers sjukdom. Sedan dess har ett flertal studier av yrkesexponering för lågfrekventa magnetfält och Alzheimers sjukdom publicerats. Flera nyare studier antyder en liten riskökning med en tendens till ett samband mellan exponering och respons. I likhet med sambandet för barnleukemi finns inget stöd från experimentella studier som skulle tyda på ett orsakssamband. Dessutom är arbetsmiljöstudier ofta behäftade med svagheter som förväxlingsfaktorer (confounding factors) och snedfördelning vid publicering (publication bias).

Också för ALS (amyotrofisk lateral skleros) har epidemiologiska studier genomförts främst under de senaste 13 åren. De tidigaste studierna uppskattade främst riskerna i s.k. elektrikeryrken och det var oklart om de samband som rapporterats kunde bero på exponering för lågfrekventa magnetfält eller elektriska stötar. Nyare studier har börjat utvärdera en kombination av exponering för lågfrekventa magnetfält och elektriska stötar i arbetslivet. Resultaten av studierna är dock inte samstämmiga och frågan är ännu inte löst. I en djurmodell för ALS såg man inga effekter av exponering för lågfrekventa magnetfält, så dessa studier ger inget stöd till resultaten från de epidemiologiska undersökningarna.

Framsteg har gjorts i den tidigare öppna frågan om ett möjligt samband mellan exponering för lågfrekventa magnetfält och Parkinsons sjukdom. Resultat från nyare studier tyder inte på att det finns något samband. Samma slutsats kan dras för hjärt-kärlsjukdomar. Det förefaller som att exponering för lågfrekventa magnetfält kan påverka hjärnans elektriska aktivitet, men man har inte sett några effekter på minne eller kognition (t.ex. kunskap, tänkande, information). Många faktorer påverkar hjärnans aktivitet (t.ex. grad av vakenhet/sömnighet, intag av kaffe), så effekterna av de elektromagnetiska fälten är exempel på fysiologiska effekter och vad man vet leder detta inte till några skadliga hälsoeffekter.

Under de senaste 13 åren har epidemiologisk forskning om symtom från exponering för lågfrekventa magnetfält varit mycket begränsad. I de få experimentella studier som undersökt akuta symtom som huvudvärk och yrsel hos frivilliga försökspersoner har dock inga effekter av exponeringen kunnat ses. Sammanfattningsvis har sannolikheten för ett samband minskat något med tiden.

Radiofrekventa fält

Forskningen har under den senaste tioårsperioden väsentligen handlat om ett möjligt samband mellan användning av mobiltelefoner och hjärntumörer. Epidemiologiska studier har gett svaga indikationer på ett samband mellan flitigt och långvarigt användande av mobiltelefon och ökad risk för gliom (elakartade tumörer i hjärnans stödjevävnad) och hörselnervstumör (en godartad tumör på den nerv som förbinder örat med de inre delarna

av hjärnan). Evidensen är emellertid inte särskilt klar eller entydig. Sammantaget finns det inga eller få indikationer på någon risk för upp till ungefär 15 års användning av mobiltelefon. Empiriska data saknas för längre användningstider, dock visar cancerstatistik från Sverige och andra länder inte någon ökad incidens som skulle kunna hänföras till den kraftiga ökning av mobilanvändning som kom i början av 2000-talet. Från de få studier som gjorts på odlade celler finns inga indikationer på att radiofrekventa fält skulle kunna initiera en tumör. Många djurstudier har gjorts för ett stort antal tumörtyper och lång, ofta livslång, exponering. Med mycket få undantag har man inte funnit någon påverkan på tumörbildning eller tumörutveckling.

De studier som gjorts om påverkan av radiofrekventa fält på hjärnans aktivitet har oftast funnit förändringar, särskilt under sömn, under eller efter pågående exponering. Förändringarna är dock inte helt samstämmiga, och särskilt förändringar som observerats när försökspersonerna är vakna varierar. Det finns inget som tyder på att dessa förändringar skulle kunna övergå i beteendeförändringar eller några andra skadliga hälsoeffekter. Ett antal studier på människor och djurstudier kunde inte finna någon påverkan av radiofrekventa fält på kognitiva funktioner. Detta har även bekräftats i ett antal upprepningsstudier.

Under de senaste 13 åren har många studier ägnats åt exponering för radiofrekventa fält och förekomsten av olika symtom. Detta har skett genom användning av noggrant kontrollerade dubbelblinda förhållanden i laboratoriet och med användning av antingen en mobiltelefon eller en telekommunikationsantenn som radiofrekvent källa. Dessa studier har indikerat att akuta effekter inte uppkommer som ett resultat av exponering för radiofrekventa fält. Dock uppkommer symtom, eller förvärras symtom, hos sofliga personer när de tror att de är exponerade. Detta brukar kallas för en placeboeffekt. Ett flertal epidemiologiska studier, oftast tvärsnittsstudier, har undersökt samband mellan förekomsten av symtom och närhet till basstationer för mobiltelefoni. Den typen av studier är inte lämpliga för att bestämma ett samband mellan exponering och respons, också för att en placeboeffekt kan inträffa när personer vet att det finns en basstation för mobiltelefoni i grannskapet. Med åren har evidensen ökat för att den typen av exponering inte medför någon förhöjd risk för akuta effekter.

För 13 år sedan rapporterade flera studier om ett ökat antal fall av leukemi, både för barn och vuxna, i närheten av starka TV- och radiosändare. Sedan dess har fyra stora fallkontrollstudier inte kunnat finna någon förhöjd risk för barnleukemi. Ett flertal andra studier som gjorts har inte heller kunnat se någon förhöjd cancerrisk för vuxna i närheten av starka sändare. Det är allt mer som talar för att det inte finns någon förhöjd cancerrisk för personer som lever i närheten av en sändare.

Slutligen, ett område som har rönt en hel del uppmärksamhet under senare år är påverkan på de manliga genitalierna från exponering för radiofrekventa fält från en mobiltelefon som bärs i en byxficka. Flera, såväl epidemiologiska som djurstudier och experimentella studier på människor har rapporterat om en del effekter, framför allt på spermiekvalitet, vilket teoretiskt skulle kunna leda till minskade möjligheter att få barn. Nästan alla dessa studier är emellertid av så låg kvalitet när det gäller design och resultatanalys att de inte bidrar med någon information rörande potentiella risker. Inte heller djurstudier stöder de rapporterade effekterna.

Slutkommentar

Mycket forskning har genomförts under de 13 år som gått sedan SSI/SSM började rapportera om kunskapsläget inom EMF-området genom sitt vetenskapliga råd. I allmänhet har mer klarhet vunnits, framför allt om frånvaron av ett antal skadliga hälsoeffekter som misstänktes vara orsakade av exponering för elektromagnetiska fält av olika frekvenser. Några frågor har ännu inte fått tillfredsställande svar och kräver därför ytterligare forskningsinsatser. Det är oroande att utformningen av gjorda studier inte alltid är lämplig eftersom detta kan leda till meningslösa resultat. Det är därför viktigt att regelbundet kritiskt granska vetenskapliga studier. Strålsäkerhetsmyndighetens vetenskapliga råd för EMF kommer att fortsätta att granska, och rapportera om, litteraturen inom detta område.

Executive Summary, 2016 Report

Static fields

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

Cell studies

Most of the new *in vitro* studies suggest that static magnetic fields, given alone, do not induce variation of a number of biological endpoints, including DNA damage, apoptosis and proliferation. In contrast, results from combined exposures suggest that static magnetic fields are able to modify (by increasing or decreasing) the effect induced by well-known chemical or physical agents.

Animal studies

Only one rat study was identified describing hematological and muscle biochemical parameters. The authors' conclusion towards an adaptive response to a hypoxia status following static magnetic field exposure is questionable. An independent replication is recommended.

Human studies

One of the two new studies indicates that there seem to be gender differences in the way static magnetic fields affect dizziness. The other study, which suffers from some methodological reporting weaknesses, indicate that exposure to static magnetic fields may transiently affect cortical excitability and brain activity.

Epidemiology

Epidemiological studies on static fields are restricted to exposure from MRI, which is a mixture of radiofrequency fields, motion-induced time-varying magnetic fields and strong static magnetic fields. The new epidemiological studies confirm previous study results where an association between MRI work and acute symptoms was observed. No effects on behaviour were seen in small children that underwent a single MRI examination as foetus.

Extremely low frequency (ELF) fields

The exposure of the general public to ELF fields (>0 Hz-300 Hz) 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 latest studies did not consistently observe an association. However, these did not use new approaches and the same limitations as in previous research apply. Thus, the conclusion from previous Council reports still holds: associations have been observed, but a causal relationship has not been established.

Cell studies

The ELF *in vitro* studies evaluated several biological endpoints, including proliferation, differentiation and DNA damage. The results are not univocal, with increase, decrease or no difference compared to sham controls. One study, reporting DNA damage, deserves attention and should be replicated by independent investigators to be confirmed.

Animal studies

Similar to the previous report, most studies used one exposure level only and normally less than 1 mT at 50 Hz. Again brain function and behaviour-addressing neurodegeneration was a topic. Also hypothesis- and mechanism-driven studies were rare. Two studies indicated that exposure to ELF magnetic fields in the 1 mT range may interfere with the activity of brain cells, thereby generating behavioural and cognitive disturbances. But inconsistent results regarding regulation of the different neurotransmitters gave no clear picture. Therefore, potentially underlying mechanisms and consequences remain unknown. Single papers addressing general health gave no basic news. Unfortunately and due to the lack of an appropriate animal model, none of the studies addressed childhood leukaemia, which is still of epidemiological relevance.

Human studies

Two new studies have been published and both indicate that ELF magnetic fields may modulate cortical brain activity; results concerning related performance data were heterogeneous.

Epidemiology

New studies on ELF magnetic field exposure and childhood leukaemia were small and do not alter the current interpretation on this subject. In adult cancer studies, no indication for a risk increase was seen in a large cohort study investigating use of electric blankets in relation to thyroid cancer and also not in a large study on occupational ELF magnetic field exposure and acute myeloid leukaemia. For ALS, a large population-based Swedish study suggested that electric shocks, but not ELF magnetic field exposure, may be a risk factor for the working population less than 65 years of age. This is in contrast to studies that appeared last year that suggested it may be the other way around. This question therefore remains as yet unresolved.

For non-vascular dementia, a Dutch study provided some indications for an association with ELF magnetic field exposure. Only few observational studies addressing ELF magnetic field exposure and symptoms have been published during the last decade and correspondingly, study results are scarce. A large cross-sectional survey found some associations with self-reported exposure to electrical devices. The limitation for the interpretation of this finding is that both outcome and exposure are reported by the same person.

Intermediate frequency fields

The intermediate frequency region of the EMF spectrum is defined as being between the low frequency and the radiofrequency ranges (300 Hz-10 MHz). Despite increasing use of intermediate frequency magnetic field-emitting sources such as induction cooking and anti-theft devices, scientific evaluation of potential health risks is scarce. For some of these sources, exposure assessment, especially of induced internal electric fields, remains challenging. 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 different kinds of surveillance systems. Studies on possible effects associated with chronic exposure at low levels are particularly relevant for confirming adequacy of current exposure limits.

Radiofrequency fields

The general public is exposed to radiofrequency fields (10 MHz-300 GHz) from different sources, such as radio and TV transmitters, cordless and mobile phones and their supporting base stations and wireless local area networks. Among parts of the public there is concern about possible health effects associated with exposure to radiofrequency fields. Particularly, in some countries, concern about the use of Wi-Fi in schools has grown in recent years.

Cell studies

The new *in vitro* studies confirm the previous Council conclusions: several endpoints have been investigated and in most cases no effect of the exposure was detected. Nevertheless, in some investigations, effects on parameters related to apoptosis have been reported, although transient.

Animal studies

The latest animal studies on the effects of exposure to radiofrequency fields again show some indications for an increase in oxidative stress, even with exposure to SAR values as low as 25 mW/kg, so below the current exposure limits, but the findings are not consistent. Increased oxidative stress might lead to health effects, for instance by increasing DNA damage, which may lead to a higher risk of cancer. One study found effects, including increased DNA damage, in brain tissue, after exposure to SAR values as low as 0.58 mW/kg. This is an extremely low exposure level and in order to verify these findings, the study should be replicated. The replication of a study that found an increased risk of cancer led to similar results, but these were inconsistent in that they did not show an in-

creased risk with increasing exposure levels. Moreover, the animal model used is very specific and most likely not predictive of effects in humans.

Human studies

Consistent with previous studies the only sleep study published found an effect of the NREM-EEG power of the sleep-EEG. However, deviating from previous findings, the spindle frequency range was not affected. The effects were observed for the slow activity (delta and theta frequency ranges). In this study with 128 electrodes no significant cluster of electrodes could be observed when controlled for multiple testing. Furthermore, effects could not be replicated within subjects. The waking-EEG studies showed a decreased alpha activity in the resting state EEG-activity recorded with eyes closed and no effects on slow cortical potentials and related performance parameters. Except for vigilance in one study, cognitive performance was not affected and conflicting results have been observed in a working memory task. Effects on mood, well-being, somatic complaints, subjective sleep quality and physiological parameters, which were addressed in single studies, have not been observed.

Epidemiology

A new large Norwegian study did not indicate that mobile phone use of the mother during pregnancy is a risk for adverse effects regarding reproductive health. However, to answer the question whether radiofrequency EMF exposure of the foetus is related to adverse pregnancy outcomes, more sophisticated exposure assessment methods are needed. Regarding mobile phone use and brain tumour risk, little new data was published and several papers deal with reanalyses of already published data. As a consequence, little has changed in the rating of the evidence. Studies on symptoms confirmed previous findings pointing to an absence of association with exposure from fixed-site transmitters, although non-differential exposure misclassification remains a challenge for these studies. With respect to self-reported mobile phone use, associations with symptoms have been reported in studies of children and adolescents. However, associations were not restricted to call duration but also to other aspects of mobile phone use such as using them for entertainment. This indicates that other factors than radiofrequency exposure such as sleep deprivation due to nightly mobile phone use, blue light from the smart phone screens or lack of recreation due to overuse might be relevant in that context. There are an increasing number of low quality studies which are uninformative for health risk assessment.

General comment

As in previous years, a number of studies had to be excluded from the analysis. Most of them provided no or incomplete dosimetric information, or failed to include sham-exposed controls. Without dosimetric information, any effects cannot be related to an exposure level and without a sham-exposed group it is not possible to attribute any effects to the actual EMF exposure. Studies lacking this information are a waste of money and effort and should not have passed the peer-review system.

Sammanfattning på svenska, 2016 års rapport

Statiska fält

Exponering för statiska fält (0 Hz) som är mycket starkare än det naturligt förekommande geomagnetiska fältet kan förekomma 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 för medicinsk diagnostik. Studier på frivilliga försökspersoner har visat att rörelser i starka statiska fält kan inducera elektriska fält i kroppen och orsaka yrsel och illamående. Tröskelvärdena för dessa effekter tycks dock variera avsevärt mellan olika individer. Personal som arbetar med magnetresonanstomografi kan påverkas av dessa övergående symtom.

Cellstudier

De flesta av de nya *in vitro*-studierna pekar mot att exponering för enbart statiska magnetfält inte orsakar biologiska effekter som t.ex. DNA-skador, apoptos eller proliferation. Resultat från exponeringar av statiska magnetfält i kombination med välkända kemiska och fysikaliska agens indikerar däremot att statiska magnetfält kan förändra (genom ökning eller minskning) effekten av dessa.

Djurstudier

Bara en studie för statiska fält har identifierats. I den studerades hematologiska och muskelbiokemiska parametrar på råttor. Författarnas slutsats om en förmodad adaptiv respons till ett tillstånd av syrebrist efter exponering för ett statistiskt magnetfält är tveksam. En oberoende upprepning av studien rekommenderas.

Studier på människa

En av två nya studier tyder på att det kan finnas könsskillnader i hur exponering för statiska magnetfält orsakar yrsel. Den andra studien, som lider av svagheter i rapporteringen av försöksmetoden, antyder att exponering för statiska magnetfält skulle kunna ge en övergående påverkan på hjärnbarkens retbarhet och på hjärnaktiviteten.

Epidemiologi

Epidemiologiska studier av statiska fält är begränsade till användning av magnetresonanstomografi, där exponeringen består av en blandning av radiofrekventa fält, rörelseinducerade tidsvariabla magnetfält och starka statiska magnetfält. De nya epidemiologiska studierna bekräftar tidigare resultat där ett samband mellan arbete med magnetresonanstomografi och akuta symtom observerats. Inga effekter rörande beteendepåverkan kunde ses hos små barn som genomgått en enstaka undersökning med magnetresonanstomografi under fosterstadiet.

Lågfrekventa fält

Allmänheten exponeras för lågfrekventa (ELF) fält (>0-300 Hz) i första hand från kraftledningarna med frekvenserna 50 och 60 Hz och från elektriska installationer och elektriska apparater i byggnader. När det gäller sambandet mellan exponering för lågfrekventa magnetfält och utvecklingen av barnleukemi visar de senaste studierna inte samstämmigt på samband. Inga nya undersökningsmetoder har dock använts i dessa nya studier som därför har samma begränsningar som tidigare forskning. Därför gäller fortfarande slutsatsen från Rådets tidigare rapporter: samband har observerats men något orsakssamband har inte kunnat fastställas.

Cellstudier

Flera olika biologiska effekter har undersökts i *in vitro*-studier av exponering från lågfrekventa fält, inklusive cellproliferation, celldifferentiering och DNA-skador. Resultaten är inte entydiga, med ökning, minskning eller ingen skillnad jämfört med oexponerade kontroller. En studie, som rapporterar skador på DNA, förtjänar uppmärksamhet och bör upprepas av oberoende forskare för att kunna bekräftas.

Djurstudier

Liksom i Rådets föregående rapport har de flesta nya studier använt endast en exponeringsnivå, vanligen lägre än 1 mT vid 50 Hz. Återigen har ett av ämnesområdena varit hjärnans funktion och beteendepåverkan av neurodegenerering. Hypotes- och mekanismdrivna studier är sällsynta. Två studier indikerade att exponering för lågfrekventa magnetfält av storleksordningen 1 mT kan påverka aktiviteten hos hjärnans celler, och därigenom orsaka beteendemässiga och kognitiva störningar. Men motsägande resultat vad gäller regleringen av de olika signalsubstanserna ger ingen klar bild. De möjliga underliggande mekanismerna och deras konsekvenser förblir därför okända. Enskilda rapporter rörande allmän hälsa ändrar inte kunskapsläget. Olyckligtvis, främst beroende på avsaknad av en lämplig djurmodell, har inte någon av studierna rört barnleukemi, som fortfarande är av epidemiologiskt intresse.

Studier på människa

Två nya studier har publicerats och båda antyder att lågfrekventa magnetfält kan påverka hjärnbarkens aktivitet. Resultaten avseende relaterade prestanda var inte entydiga.

Epidemiologi

De nyttillkomna studierna om ett eventuellt samband mellan exponering för lågfrekventa magnetfält och barnleukemi var små och ändrar inte det gällande kunskapsläget. En stor kohortstudie som undersökte användning av elektriska filter och ett möjligt samband med sköldkörtelcancer hos vuxna gav inga indikationer om ökad risk. Ingen ökad risk för akut myeloisk leukemi kunde heller ses i en stor studie av yrkesrelaterad exponering för lågfrekventa magnetfält. I en stor svensk befolkningsbaserad studie om ALS rapporteras att elektriska stötar, men däremot inte exponering för lågfrekventa magnetfält, kan vara en riskfaktor för den yrkesarbetande befolkningen under 65 år. Detta motsäger studier som kom förra året som tvärtom indikerade att exponering för lågfrekventa magnetfält, men

inte elstötar, kunde utgöra en ökad risk för ALS. Den här frågan är därför fortfarande olöst.

En holländsk studie gav vissa indikationer på ett samband mellan exponering för lågfrekventa magnetfält och icke-vaskulär demens. Bara ett fåtal observationsstudier rörande exponering för lågfrekventa magnetfält och samband med olika typer av besvär har publicerats under det senaste årtiondet och följaktligen är resultaten knapphändiga. En omfattande tvärsnittsstudie fann vissa samband mellan symtom och egenrapporterad exponering för elektriska apparater. En svårighet med att utvärdera den studien är att både utfallet och exponeringen har rapporterats av samma person.

Intermediära (IF) fält

Det intermediära frekvensområdet (300 Hz-10 MHz) av EMF-spektrat ligger definitionsmässigt mellan det lågfrekventa och det radiofrekventa områdena. Trots en ökande användning av apparater som medför exponering för intermediära fält, som induktionsspisar och larmbågar i butiker, så har möjliga hälsorisker utvärderats endast i mycket liten utsträckning. Exponeringsbestämningen, särskilt för interna elektriska fält, är fortfarande en utmaning för den här typen av apparater. Mycket få experimentella studier rörande hälsoeffekter från exponering för intermediära fält finns tillgängliga, och inga slutsatser kan dras för närvarande. Ytterligare studier skulle vara värdefulla eftersom människor exponeras för dessa fält i ökande grad, till exempel från olika typer av elektroniska övervakningssystem. Studier av möjliga effekter av kronisk exponering för låga nivåer är särskilt betydelsefulla för att bekräfta tillförlitligheten i gällande rikt- och gränsvärden.

Radiofrekventa fält

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

Cellstudier

De nya *in vitro*-studierna bekräftar slutsatserna i Rådets tidigare rapporter: flera olika effekter av exponeringen har undersökts men i de flesta fall har man inte kunnat se någon påverkan. I några studier har man emellertid rapporterat effekter som hänger samman med apoptos, dock var dessa effekter övergående.

Djurstudier

De senaste djurstudierna av effekter från exponering för radiofrekventa fält antyder, liksom en del tidigare studier, en ökad oxidativ stress. Detta gäller även vid exponering för så låga SAR-värden som 25 mW/kg, alltså under gällande exponeringsgränser. Fynden är dock motstridiga. Ökad oxidativ stress kan leda till skadliga hälsoeffekter, t.ex. genom ökande DNA-skador, vilket i sin tur kan medföra en ökad risk för cancer. En studie rapporterar effekter, inklusive DNA-skador, i hjärnvävnad efter exponering för SAR-värden

så låga som 0,58 mW/kg. Detta är en extremt låg exponeringsnivå och för att dessa fynd ska kunna bekräftas bör studien upprepas. Upprepningen av en annan studie som fann en ökad cancerrisk visade liknande resultat, men var inkonsekvent i den meningen att den inte visade någon ökad risk med ökande exponeringsnivåer. Dessutom är den djurmodell som användes vid försöket mycket speciell och är förmodligen inte lämplig för att förut säga effekter på människor.

Studier på människa

Den enda nya sömnstudien som publicerats visar, i likhet med tidigare studier, påverkan på sömn-EEG under NREM-fasen. Till skillnad mot tidigare studier var emellertid spindelfrekvensområdet inte påverkat. Effekterna observerades för den långsamma aktiviteten (frekvensområdena delta och theta). I denna studie med 128 elektroder kunde inte något signifikant elektrodcluster observeras vid statistisk kontroll. Dessutom kunde effekterna inte upprepas för de enskilda försökspersonerna. Studierna om vaken-EEG visade en minskad alfa-aktivitet mätt under vilostadiet med slutna ögon och inga effekter på den långsamma kortikala potentialen och därmed sammanhängande parametrar. Förutom uppmärksamhet i en enskilda studie har man inte sett någon påverkan av den kognitiva förmågan och motstridiga resultat har observerats i en uppgift gällande arbetsminne. Någon påverkan på humör, välbefinnande, somatiska besvär, upplevd sömnkvalitet eller fysiologiska parametrar, vilket undersöktes i enskilda studier, har inte observerats.

Epidemiologi

En ny stor norsk studie visade inte några indikationer på att moderns användning av mobiltelefon under graviditeten skulle utgöra någon risk för fosterskador. För att kunna besvara frågan om exponering för radiofrekventa fält kan ha något samband med fosterskador krävs emellertid en förbättrad exponeringsuppskattning för fostret. Vad gäller användning av mobiltelefon och risk för hjärntumör har få nya data publicerats och åtskilliga artiklar redovisar nya analyser av tidigare publicerade data. Följaktligen har inte mycket ändrats i bevisvärderingen. Studier avseende symtom bekräftar tidigare forskningsresultat som indikerar en frånvaro av samband med exponering från fast monterade sändare även om felklassificering av exponering fortfarande utgör en utmaning för denna typ av studier. Samband mellan symtom och egenrapporterad användning av mobiltelefon har rapporterats i studier av barn och ungdomar. Sambanden var dock inte begränsade till samtalslängd utan också till andra typer av mobilanvändning som att använda telefonen för underhållning. Detta indikerar att andra faktorer än exponering för radiofrekventa fält, som t.ex. brist på sömn orsakad av nattlig mobilanvändning, blått ljus från telefonernas skärmar eller brist på vila beroende på överanvändning kan vara relevanta i sammanhanget. Det finns ett ökande antal studier av låg kvalitet som inte ger någon ny kunskap användbar för uppskattning av hälsorisker.

Allmän kommentar

Liksom i föregående års rapporter, har ett antal studier inte kunnat utvärderas. De flesta på grund av att de gett ingen eller otillräcklig information om dosimetri vid försöken, eller att oexponerade kontroller saknas. Utan information om dosimetri kan eventuella effekter inte relateras till en viss exponeringsnivå och utan oexponerade kontroller är det inte möjligt att hänföra några effekter till den aktuella exponeringen. Studier som saknar

den här typen av information innebär ett slöseri med pengar och arbete och borde aldrig ha passerat tidskrifternas faktagranskning.

Preamble

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

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

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.⁴

⁴ 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).

It should be noted that the result of this process is not an assessment that a specific study is unequivocally negative or positive or whether it is accepted or rejected. Rather, the assessment will result in a weight that is given to the findings of a study. The evaluation of the individual studies within a sector of research is followed by the assessment of the overall strength of evidence from that sector with respect to a given outcome. This implies integrating the results from all relevant individual studies into a total assessment taking into account the observed magnitude of the effect and the quality of the studies. In the final overall evaluation phase, the available evidence is integrated over the various sectors of research. This involves combining the existing relevant evidence on a particular endpoint from studies in humans, from animal models, from *in vitro studies*, and from other relevant areas. In this final integrative stage of evaluation the plausibility of the observed or hypothetical mechanism(s) of action and the evidence for that mechanism(s) have to be considered. The overall result of the integrative phase of evaluation, combining the degree of evidence from across epidemiology, human and animal experimental studies, *in vitro* and other data depends on how much weight is given on each line of evidence from different categories. Human epidemiology is, by definition, an essential and primordial source of evidence since it deals with real-life exposures under realistic conditions in the species of interest. The epidemiological data are, therefore, given the greatest weight in the overall evaluation stage. However, epidemiological data has to be supported by experimental studies to establish a causal link between exposure and health.

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

1. Static fields

1.1. Cell studies

Five papers are described in this section, all dealing with the effect of static magnetic fields (SMF) alone and in combination with chemical or physical agents, as reported in Table 1.1. Moreover, eight more studies have been recognized but are not presented due to the lack of unexposed (sham) controls.

Tumour necrosis factor α (TNF α)-related apoptosis-inducing ligand (TRAIL) is a cytokine, and exerts cytotoxic effects on malignant cells without affecting normal cells. However, cancer cells develop a resistance to TRAIL. To evaluate the possibility that SMF promotes TRAIL-induced apoptosis, Lin et al. (2014) exposed human breast cancer cell lines (MDA-MB-468 and T47D) and human mammary epithelial (healthy) cells to 3 mT SMF for 6, 12 or 24 h. In three independent experiments, they found a significant reduction in viability of cancer cells treated for 12 or 24 h with TRAIL and SMF ($p < 0.05$). The effect was exposure- and time-dependent. SMF alone was ineffective and no effects were detected on healthy cells. Since it is known that TRAIL-induced cell death is mainly apoptotic, Annexin V/propidium iodide staining was applied to evaluate apoptotic cells, confirming the apoptotic involvement in the observed effect. Moreover, since apoptosis was completely blocked when cells were pre-incubated with a caspase inhibitor (z-VAD-fmk), the authors suggested that the apoptotic process is caspase-dependent.

To explore the mechanisms by which SMF sensitizes TRAIL-induced apoptosis, the expression of several apoptosis-related proteins was examined. The results showed that SMF and treatment with TRAIL induced a downregulation of surviving, an anti-apoptotic protein. Moreover, it was also demonstrated that SMF causes a significant arrest of cells in the G2/M phase, whereas TRAIL alone has no such effect. Treatments with SMF plus TRAIL further increases the number of cells in the G2/M phase, as compared to either SMF alone, or TRAIL alone, treatment. These data suggest that G2/M arrest could be a possible mechanism for the synergistic effects of SMF and TRAIL on cell apoptosis.

Viability of U937 cells after exposure to alternating (AC; 12–50 Hz, and magnetic field strength 6.5 mT rms) and/or static (DC) magnetic fields (MF; from 2 to 6 mT) was assessed by Wocik-Piotrowicz et al. (2014). The exposures were 2.5 h long, given for 1, 2 or 3 days in presence and in absence of puromycin (PMC), a cell death inducer which acts through disturbance of protein synthesis. The results of at least six independent experiments showed absence of changes in viability of U937 cells when exposed to DC, AC or both. In cultures treated with PMC alone, about a threefold decrease in the percentage of viable cells was detected, as expected. The exposure to DC or AC MF in presence of PMC did not change the effect of PMC alone, while the combination of DC and AC MF induced a further decrease in cell proliferation, which was non-linear with respect to the frequencies tested. The maximum effect was achieved under DC MF of 6 mT, AC MF of 6.5 mT at 35 Hz. Although the authors describe the employed statistics, the p values are not reported.

Yakir-Blumkin et al. (2015) examined the effect of SMFs on neuronal survival in primary cortical and hippocampal rat neurons, a suitable experimental system for modelling the neurodegenerative state *in vitro*. Cell cultures were exposed for 1 to 7 days to SMF (5, 2.5, 1.3, 0.8, 0.4 mT), alone and in combination with the apoptosis inducer etoposide,

given at day 6. The results showed no effect of SMF exposure alone, compared to the sham-exposed samples. In co-exposed cultures a protection against etoposide-induced apoptosis in an exposure- and time-dependent manner was attained, with a stronger effect at 5 mT ($p < 0.001$). Similar results were obtained when glial cells were exposed at 5 mT.

The authors also examined the duration of the anti-apoptotic effect induced by 5 mT SMFs by maintaining, following 7 days of exposure, the SMF off for 1.5, 2.5, 3.5, 6 or 24 h. They demonstrated that a gradual decrease in the extent of protection occurred. The effect remained significant after 6 h off-SMF while by 24 h off-SMF only a slight reduction was seen.

Cultures exposed to 5 mT SMFs were also examined for the expression of several pro-apoptotic markers and the extent of mitochondrial membrane potential depolarization. A marked decrease in the expression of cleaved poly ADP ribose polymerase-1, cleaved caspase-3, active caspase-9 ($p < 0.05$), and a decrease in etoposide-induced mitochondrial membrane potential collapse was recorded ($p < 0.001$). In addition, using the L-type voltage-gated Ca^{2+} channel inhibitor nifedipine, selective to Ca^{2+} influx, they found that the anti-apoptotic effect of SMFs was mediated by Ca^{2+} influx through these channels. These findings show the potentially beneficial effect of weak SMF exposure on the central nervous system.

Zhang et al. (2014) evaluated the effect of combined exposures to a SMF and the chemotherapeutic agent cisplatin (DDP) in human leukaemia K562 cells. To this purpose, cell cultures were exposed to an 8.8 mT SMF for 4, 8 or 12 h, with or without DDP and the killing efficiency of DDP was evaluated by measuring the metabolic activity of cell cultures. The results indicated no differences between either sham-exposed samples and samples exposed to SMF alone or between sham-exposed samples and cultures treated with DDP at the selected concentration. Combined treatments inhibited the metabolic activity of K562 cells, therefore enhancing DDP-induced cytotoxicity.

The authors, by measuring extracellular DDP content, demonstrated that the SMF-induced increase in DDP cytotoxicity was related to a significant increase in DDP concentration inside the cell. Moreover, by measuring the expression of the P-gp protein (a multidrug-resistant protein) a significant decrease in its expression was detected in cultures co-exposed with respect to cultures treated with DDP alone ($p < 0.05$). They concluded that exposure to an 8.8 mT SMF enhanced the killing potency of DDP on K562 cells by increasing the quantity of DDP and the decreased expression of P-gp may be one of the reasons.

In one study, the combined effect of SMF and physical agents was investigated. Teodori et al. (2014) evaluated the induction of DNA damage in primary human glioblastoma cells exposed to 80 mT SMFs, both alone and in combination with X-ray (5 Gy). In particular, cells were exposed to SMFs alone, X-ray alone, X-ray and SMFs applied both before and after X-ray. DNA damage was analysed by Single Cell Gel Electrophoresis assay (comet assay) and the tail DNA and tail length were used as indicators of DNA fragmentation. The SMF exposure alone was 6, 12 or 24 h long and resulted in a significant increase in both parameters after 24 h exposure ($p < 0.01$). No differences were detected in cultures exposed for shorter times, as compared to sham controls. Treatments with X-ray induced a significant increase in DNA fragmentation, as expected. When SMF was applied for 6 h after X-ray or for 6 h before and 6 h after X-ray, a significant reduc-

tion of X-ray-induced DNA damage was recorded ($p < 0.001$). Similar results were obtained when treatments with SMF after X-ray were 20 h long.

The authors also investigated the effect of SMF exposure, with and without X-ray, on mitochondrial membrane potential, since mitochondria are assumed to be responsible for Reactive Oxygen Species (ROS) production. The membrane potential, known to be affected by IR, was assessed using the JC-1 mitochondrial probe. Cells were exposed to X-ray and examined after 3, 6 and 20 h of recovery, in presence or absence of SMF. The results showed that after 3 and 6 h of recovery the X-ray -induced loss of mitochondrial membrane potential was averted by exposure to SMFs ($p < 0.001$), whereas at 20 h no statistically significant difference was observed between the treatments. The authors concluded that their data suggest that SMFs modulate DNA damage and/or damage repair, possibly through a mechanism that affects mitochondria.

1.1.1. Summary and conclusions on cell studies

Most of the new *in vitro* studies suggest that SMF, given alone, does not induce variation of several biological endpoints, including DNA damage, apoptosis and proliferation. In contrast, results from combined exposures suggest that the SMF is able to modify (by increasing or decreasing) the effect induced by well-known chemical or physical agents. Unfortunately, a large number of studies have not been considered due to the lack of sham-exposed controls.

The studies are summarized in the following table:

Table 1.1 *In vitro* studies on Static Magnetic Fields

Cell type	Endpoint	Exposure conditions SMF	Effect	References
Human breast cancer cell lines (MDA-MB-468; T47D) Human healthy mammary epithelial cells	Viability	3 mT 6, 12, 24 h Co-exposure with TRAIL	No effect of SMF alone; Co-exposures: No effect in healthy cells. Dose- and time-dependent effect on viability of cancer cells via apoptosis and cell cycle arrest	Lin et al. (2014)
Human lung lymphoblasts (U937)	Viability	SMF DC 2-6 mT; 12-50 Hz AC – 6.5 mT rms DC + AC 2.5 h for 1, 2 or 3 days Co-exposure with PMC	No effect of exposure alone. Co-exposures: Enhanced PMD-induced cell death only with CD + AC	Wójcik-Piotrowicz et al. (2014)
Primary cortical and hippocampal rat neurons	apoptosis	5, 2.5, 1.3, 0.8, 0.4 mT 1 up to 7 days Co-exposure with etoposide	No effect of exposure alone. Co-exposures: protection against etoposide-induced apoptosis in a dose- and time-dependent	Yakir-Blumkin et al. (2015)
Human leukemia K562 cells	Viability	8.8 mT 4, 8, 12 h Co-exposure with DDP	No effect of exposure alone. Co-exposures: Enhanced DDP-induced cytotoxicity	Zhang et al. (2014)
Human glioblastoma cells	DNA damage, MMP	80 mT 6, 12, 24 h Co-exposure with x-rays	Increased DNA fragmentation at 24 h exposure. No effect on MMP Co-exposures: Reduction of DNA damage and loss of MMP induced by x-ray	Teodori et al. (2014)

Abbreviations: DDP – cisplatin; MMP - mitochondrial membrane potential; PMC – puromycin; ROS - Reactive Oxygen Species; TRAIL - Tumor necrosis factor-related apoptosis inducing ligand

Excluded studies

The following studies have not been considered due to the lack of sham-exposed controls: Vergallo et al. (2014), Mareziak et al. (2014), Li et al. (2014a), Jouni et al. (2014), Amin et al. (2014), Zafari et al. (2015), Kim et al. (2015a) and Reddig et al. (2015).

1.2. Animal studies

Elferchichi et al. (2015) studied hematological and muscle biochemical parameters in rats following a daily 1 h-exposure to 128 mT SMF for 15 days. Six male 7-week old Wistar rats were either SMF- or sham-exposed. After decapitation blood samples were taken and the two muscles M. soleus and M. extensor digitorum longus (EDL) removed, and frozen until Western blotting for determination of glucose transporter4 (Glut4) and monocarboxylate transporters MCT1 and MCT4. SMF-exposure resulted in a significant decrease in red blood cell count, hemoglobin, hematocrit and plasma iron values. Transferrin and plasma lactate were increased. MCT4 and Glut4 contents were elevated in the glycolytic muscle EDL only. According to the authors, the SMF-induced pseudoanemia status “seems to affect tissue oxygen delivery...and to favor the extrusion of lactate from the cell to the blood compartment.” The authors viewed the study results as an adaptive response to a hypoxia status following SMF exposure. This conclusion should be questioned in terms of study size, strong SMF exposure and lack of information on results of other studies towards a similar interpretation. An independent repetition would strengthen the hypothesis of an adaptive response.

1.3. Human studies

Since the last Council report two human provocation studies with SMF were published. Both were related to MRI scanner exposure.

Heinrich et al. (2014) investigated the effect of sex, age, field strength of SMF of MRI scanners, stress hormone levels and the somatoform disorder score (SOMS) on the sensation of dizziness in 41 healthy subjects (21 males and 20 females, mean age 26.3 years; SD = 3.7 years). The paper presents an additional analysis of data that was published by Heinrich et al. (2013). All subjects were exposed to different MRI scanners (1.5, 3.0 and 7 T) and to a mock scanner with no magnetic fields. Investigations were separated by one-week time intervals. Information on the duration of exposure is only given by Heinrich et al. (2013). Each test session consisted of two “runs”. In the first run subjects were exposed for 50 min while they were in a static condition, i.e. lying still in the MRI scanner. This was followed by a 20 min break and then a second 50 min run followed in which the table on which the subjects were lying was moved back and forth (dynamic state). The present paper focuses on dizziness as outcome since this was present under all field conditions. A logistic regression with field strength, sex, age, score of somatoform disorders, cortisol, epinephrine and norepinephrine showed that field strength ($p < 0.0001$) and sex ($p = 0.0011$) were significant predictors of dizziness, with females being more strongly affected than males. The reason for the gender differences is not known. The authors speculate that sex hormones or the menstrual cycle play a role or that males

do not admit that they feel dizzy. The authors furthermore state that women could have explicitly and/or implicitly learned to behave more sensitive.

Nojima et al. (2015) performed two experiments to investigate whether SMF can transiently alter the human intracortical inhibitory system. In the first experiment 20 healthy subjects (18 males and 2 females) were exposed to a compact magnet (surface magnetic flux density about 0.5 T, the distance to the scalp was 20 mm) for 20 min. Effects on the intracortical inhibitory system were measured by transcranial magnetic stimulation (TMS) 0, 10 and 30 min after exposure. Results were compared to pre-exposure measurements. Outcome variables were the amplitude of the motor evoked potential (MEP), the resting motor threshold (rMT), the short-latency intracortical inhibition (SICI) and facilitation (ICF) and the silent period (SP). In the second experiment 10 other subjects (7 males and 3 females) were exposed for 20 min to a homogeneous magnetic field at the centre of a 3.0 T MRI scanner. In both interventions a transient suppression of the corticospinal pathway was observed, i.e. effects were seen immediately after the end of exposure but not 10 and 30 min later. Furthermore a transient enhancement of the short-latency intracortical inhibition (SICI) was seen immediately after the compact magnetic stimulation. However, it is not reported how movements are controlled since even slight movements may affect the results.

1.3.1. Summary and conclusions on human studies

Overall one of the new studies indicates that there seem to be gender differences in the way SMF affect dizziness. The other study, which suffers from some methodological reporting weaknesses, indicates that SMF exposure may transiently affect cortical excitability and brain activity.

1.4. Epidemiological studies

The last Council report discussed the fact that MRI workers were affected by transient symptoms. There was some indication that time-varying magnetic fields were most problematic, e.g. the fields induced when moving through a static field with a strong spatial gradient. Literature on long-term effects was absent. Over the period of this report, three new studies have been published.

To investigate possible transient symptoms among MRI workers in England, Wales and Scotland a survey was conducted by de Vocht et al. (2015). MRI departments of National Health Service (NHS) sites were asked to participate and if they agreed, staff was invited to fill in a baseline questionnaire including information on personal characteristics, occupational history, medical history, stress and symptoms. They were then asked to carry a dosimeter for a shift and to monitor their tasks in addition to any occurring symptoms. 104 persons routinely working with MRI were included in the study, 70% were women and their average age was 40 years. 71% were radiographers, 17% nurses/assistants, 8% clinicians and the rest were e.g. fellows. Only 3 T and 1.5 T MRIs were present in these MRI departments. Measured shift-average static fields were about 30 mT and time-varying magnetic fields about 54 mT/s. MRI-related symptoms were reported in 4% of shifts and 53% of workers reported to have ever experienced a symptom that they attributed to the MRI. Compared to clinicians, radiographers had an OR of 8.05 (95% CI 1.96–54.84) to report symptoms and nurses or assistants an OR of 2.48 (95% CI 0.44–18.71). These symptoms were not associated with average or peak exposure to static or

time-varying magnetic fields, but with duration of shift work and duration of working with an MRI. Per additional hour of a shift, the odds of reporting MRI-related symptoms increased with 1.34 (95% CI 1.10–1.67), and per additional week-hour working with an MRI increased the risk with an OR of 1.06 (95% CI 1.03–1.10). Although relatively small, this is a well-performed study with measured information regarding actual exposure as well as reported symptoms. Surprisingly, in contrast to previous publications, no association was observed with actual exposure. The authors explain that possibly the low contrast between exposure groups (workers exposed to 1.5 T or to 1.5 T/3 T MRIs) may have caused the absence of an exposure-response relationship. If there were any threshold effects, then possibly the peak-exposure analysis would not show this kind of effects if the thresholds were not achieved. Finally, the response rate was not reported and it is unclear if persons experiencing MRI-related symptoms were more likely to participate in the study.

For a cohort of workers of an imaging device manufacturing facility in the Netherlands, Bongers et al. (2015) investigated whether the occurrence of accidents was associated with MRI-related SMF exposure. Workers were eligible if they had worked in the facility for at least one year between 1984 and 2010. Through an online questionnaire occurrence of injuries due to accidents in the past 12 months and the first (near) traffic accident while commuting to and from work was inquired. The questionnaire was answered by 1528 individuals (response rate 30%) out of 5173 workers, who were eligible for the study. Occupational exposure was obtained by linking the job title derived from pay-roll records to a previously developed job exposure matrix. Recent exposure (i.e., exposure in the 12-month period of the calendar year of interest) and cumulative career exposure was calculated in Tesla-minutes (T-min). Data were analysed with logistic regression and discrete-time survival analyses adjusted for age, sex and recent excessive alcohol use. High recent SMF exposure ($\geq 1,796 - < 11,053$ T-min) was associated with an increased risk of accidents leading to injuries (OR=4.16; 95% CI 1.14 – 15.25) or an accident treated by a physician (OR=5.78; 95 % CI 1.57 – 21.32). Corresponding OR for high career exposures ($\geq 24,597 - < 179,911$ T-min) were somewhat lower (2.20, 95 % CI 0.89 – 5.48 and 2.79, 95% CI 1.11 – 7.04, respectively). Recent and career exposure was also related to the risk of (near) accidents during the commute to work (hazard ratios of 2.49 and 2.45, respectively), but not from work.

The observed associations indicate that long term exposure to static fields from MRI may increase the risk for accidents. A hypothetical explanation could be an effect of MRI exposure on sleep quality and a subsequently increased accident risk in the morning, but sleep quality was not evaluated. The absence of an association for accidents while commuting from work to home speaks against acute effects from daytime exposure. The strengths of the study are a systematic exposure assessment based on objectively recorded job titles and a job exposure matrix, which makes bias unlikely, although non-differential exposure misclassification has likely occurred. A concern is the low participation rate. Since the accidents occurred before the work exposure, it cannot be excluded that static field exposure is related to other factors, which are predictive for an increased accident risk. This unexpected observation needs confirmation before firm conclusions can be drawn.

Bouyssi-Kobar et al. (2015) performed a survey in 72 healthy pregnant women who underwent foetal MRI. Included women were healthy volunteers who served as a control group in another study. Multiple pregnancies, chromosomal abnormalities, congenital infection, gestational diabetes treated with insulin and any maternal contraindications for

MRI were excluded from the study. MRI scans were performed in a 1.5 T MRI during the second (n=18) or third trimester (n=54) of the pregnancy, and additionally after birth (brain MRI examination). Scans lasted on average 35 minutes (range 20–51). At the average children's age of 24.5 months (range 14 to 38 months) functional outcomes were assessed by means of a telephone interview, assessing the Vineland Adaptive Behaviour Scale II (VABS), that measures communication, daily living skills, socialisation and motor skills. VABS scores were compared to general population scores. Mean scores were within the normal range for all functional domains. No statistically significant differences were detected when children with 2nd vs a 3rd-trimester scanning were compared.

This study does not provide evidence of any strong adverse effects on development of children who were prenatally scanned with a 1.5 T scanner, but the study did not have statistical power to address potential small effects. Because healthy individuals were included into the study, the authors conclude that a meaningful comparison to general population levels could be performed. It is somewhat unclear, however, in how far self-selection processes into being a volunteer for the study could have influenced the results. A weakness of the study is the relatively small size: no power calculation was presented to evaluate what degree of functional outcome impairment could have been detected in the first place, and how that compared e.g. to known environmental toxins. Finally, MRI static field strength has been slowly increasing over the last decades to include also 3 T and 7 T scanners. Since the study was restricted to 1.5 T scanners, uncertainties remain for the other scanners.

1.4.1. Conclusions on epidemiological studies

Epidemiological studies on static fields are restricted to exposure from MRI, which is a mixture of radiofrequency EMF, motion-induced time-varying magnetic fields and strong static MF. The new epidemiological studies confirm previous study results where an association between MRI work and acute symptoms was observed. A new study suggests that traffic accidents of MRI workers should be studied in more detail. No effects on behaviour were seen in small children that underwent a single MRI examination as foetus.

2. Extremely low frequency (ELF) fields

2.1. Cell studies

Eight papers are described in this section. Six of them deal with the effect of ELF exposure alone, while two papers also evaluate the effect of combined exposures with chemical or physical agents (Table 2.1). Four more studies have been recognized but are not presented due to the lack of sham-exposed controls.

Fan et al. (2015) investigated the effects of ELF-EMF exposure (50 Hz, 1 mT) on the proliferation and cytokine production of rat primary mesenchymal stem cells (MSC). The effects of mesenchymal stem cell conditioned medium (MSC-CM) on the proliferation and migration of macrophages (RAW264.7) were also investigated. MSC cultures were exposed 4 h/day for 3 consecutive days. Cell viability, measured up to seven days after exposure, increased from 3 to 7 days compared to sham controls ($p < 0.05$). Such an increase was also confirmed by an increase in DNA synthesis. In addition, at three days after exposure, flow cytometric analysis revealed a higher proportion of cells in S phase compared to sham controls ($p < 0.01$). This result was corroborated by an increase in RNA expression of several cytokines (M-CSF, SCF, TPO, LIF, IL-11 and IL-7; $p < 0.05$). The authors also reported that RAW264.7 grown in presence of a culture medium of exposed MSC (conditioned medium) exhibited an increased cell proliferation and an enhanced migration ($p < 0.05$).

Huang et al. (2014) investigated whether ELF-EMFs cause similar effects in different epidermal keratinocytes under the same exposure conditions and experimental design. To this purpose, they exposed human epidermal keratinocytes, either primary (NHEK) and immortalized (HaCaT cells) to a 60 Hz EMF, 1.5 mT, from 1 up to 7 days. NHEK did not show variation in cell proliferation relative to sham controls for any exposure duration. On the contrary, a statistically significant decrease was detected in HaCaT cells after 6 and 7 days of exposures ($p < 0.05$), with an arrest of cells in G1 phase of the cell cycle and an overexpression of several cell cycle-related genes. The authors suggest that the contradictory effects induced by ELF-EMF reported in the literature might also be due to differences in the cell type sensitivity.

Ma et al. (2014) investigated proliferation and differentiation of embryonic neural primary stem cells (eNSCs) following exposure to 50 Hz ELF-EMF at various magnetic field strengths and exposure times. In particular, exposures were carried out at 0.5 mT, 1 mT and 2 mT for 3 days, or with a magnetic field strength of 2 mT for 1 day, 2 days and 3 days, with an intermittent cycle of 5 min on/10 min off under double blind conditions. No significant changes were detected in cell proliferation, evaluated by cell viability, DNA synthesis, cell cycle distribution and transcript levels of cell cycle related genes (P53, P21 and GADD45). Absence of effect was also recorded in the percentages of neurons and astrocytes differentiated from eNSCs, although the transcript levels of some early genes related to neuronal differentiation were significantly altered. The authors stated that their results suggest that 50 Hz ELF-EMF exposure may affect early gene expression of neuronal differentiation, without alteration in the percentage of neurons.

Cell proliferation was also investigated in human adipose derived stem cells (hADSCs) by Razavi et al. (2014). Cells were exposed to a sinusoidal 50 Hz ELF-EMF field with strengths of 0.5 and 1 mT for 20 and 40 min/day for 7 days. Cell cultures were divided in

four groups with the different EMF exposures. Group 1: 1 mT for 40 min/day, group 2: 1 mT for 20 min/day, group 3: 0.5 mT for 40 min/day and group 4: 0.5 mT for 20 min/day. The results obtained in at least 3 independent experiments indicated that survival and cell proliferation of hADSCs in all groups was significantly higher than that in sham groups ($p < 0.05$) except for cultures exposed at 1 mT for 40 min/day, indicating that the exposure not only is not cytotoxic, but also increases the cell number.

In a study carried out by Luo et al. (2014), the effects of ELF-EMF exposure on the neuronal membrane ion channels, especially calcium channels, and on the intracellular calcium dynamics were investigated. Postnatal 0-day-old Sprague–Dawley rats were sacrificed by decapitation and the entorhinal cortex (EC) was used to assess primary cell cultures. Samples were subjected to 24 h ELF-EMF exposure (50 Hz, 1 mT or 3 mT) in which sham or ELF-EMF intermittent exposure was applied (5 min on/10 min off cycles). By employing whole-cell patch clamp recordings and calcium imaging, it was found that ELF-EMF exposure specifically influenced the intracellular calcium dynamics, but not the membrane calcium channel activities. The authors suggested that their results suggest a novel interaction mechanism between ELF-EMF and the EC, which might partially explain the ELF-EMF-induced changes in cellular functions.

Duan et al. (2015) investigated the induction of DNA damage in mouse male germ (GC-2) cells after 24 h exposure to 50 Hz at 1, 2 and 3 mT magnetic field intensity and compared the results with those obtained for cultures exposed to 1800 MHz RF-EMF (see section 4.1). To this purpose, the alkaline comet assay, the gamma H2AX foci formation and the formamidopyrimidine DNA glycosylase (FPG)-modified comet assay were applied. The alkaline comet assay detects both single- and double-strands breaks, the gamma-H2AX assay primarily detects double-strands breaks, while the (FPG)-modified comet assay is suitable for oxidative DNA base damage evaluation. By applying the alkaline comet assay, an exposure-dependent increase in DNA damage was detected, that became statistically significant at 3 mT ($p < 0.05$). These findings were confirmed by evaluating gamma H2AX foci formation. No effects were recorded when the (FPG)-modified comet assay was applied, suggesting that the DNA damage induced by ELF exposure is not via oxidative damage. Since different results were obtained in cultures exposed to RF, the authors hypothesized a different pattern of DNA damage between ELF- and RF-EMF.

In two papers the effect of co-exposures was studied:

Cho et al. (2014) evaluated the cytotoxic and genotoxic effects of ELF-EMF exposure in cultured human lymphocytes, in presence and absence of Gadolinium (Gd), a contrast agent for magnetic resonance imaging (MRI). Human blood was drawn several times from the same donor and lymphocyte cultures were continuously exposed throughout the culture period to 60 Hz ELF-EMF of 0.8 mT (from 12 up to 72 h, according to the biological assay applied), in presence or in absence of different Gd concentrations, ranging from 0.2 to 1.2 mM. Cytotoxicity was evaluated by measuring cell viability, apoptosis and reactive oxygen species (ROS) formation. Genotoxicity was investigated by applying the micronucleus (MN) test and the alkaline comet assay. For each endpoint, at least three independent experiments were set up. A reduction in cell viability was detected in Gd-treated cells; it was enhanced by 24 h ELF exposure, at all the Gd concentrations tested and by 48 h at 0.8 mM Gd concentration ($p < 0.05$). Data on apoptosis and ROS gave similar results: the Gd-induced increase in apoptotic cells and ROS production was potentiated by ELF-EMF exposure ($p < 0.05$). Gd treatment induced DNA damage, as expected. Cultures exposed to ELF-EMF and treated with Gd showed an increased number of MN

for all the Gd concentrations tested, that was statistically significant at exposures of 0.8 and 1.2 mM ($p < 0.05$). These findings were confirmed by the comet assay: the damage induced by Gd treatments was enhanced by the ELF-EMF exposure, for all the Gd concentrations tested ($p < 0.05$). EMF exposure alone did not exert any effect on the parameters investigated, except for a slight but statistically significant increase in Olive tail moment ($p < 0.05$; comet assay).

The effect of ELF-EMF exposure on the induction of DNA damage in healthy cell lines was investigated by Jin et al. (2014). Mouse embryonic fibroblasts (NIH3T3), human lung fibroblasts (WI-38), human lung epithelial cells (L-132), and human mammary gland epithelial cells (MCF10A) were exposed to 60 Hz (1 mT) for 4 or 16 h under strictly controlled conditions of temperature. Moreover, to evaluate possible cooperative effects with well-known physical and chemical mutagens, treatments with ionizing radiation (IR) or hydrogen peroxide (H_2O_2) were also carried out before or after the EMF exposure. In addition, to mimic the condition of oncogenic activation, cell lines were forced to overexpress the oncogene c-Myc. The comet assay, employed to quantify DNA damage, revealed that the ELF-EMF exposure alone did not induce differences in exposed cultures compared to sham-exposed ones. Similar results were obtained in exposed cultures transfected with c-Myc. Moreover, no synergistic effects (additive or antagonistic) on DNA damage induced by IR or (H_2O_2) were detected. In this study it is not clear if the sham controls were actually sham.

2.1.1. Summary and conclusions for cell studies

The ELF *in vitro* studies evaluated several biological endpoints, including proliferation, differentiation and DNA damage. The results are not univocal, with increase, decrease or no difference compared to sham controls. The study by Duan and co-workers (2015) reporting DNA damage following 24 h exposure to 50 Hz, 3 mT, deserves attention and should be replicated by independent investigators to be confirmed. Moreover, as for static fields, several studies lack sham-controls and have been excluded because they are thus not interpretable.

The studies are summarized in the following table:

Table 2.1 *In vitro* studies on ELF-EMF

Cell type	Endpoint	Exposure conditions ELF-EMF	Effect	References
Rat primary mesenchymal stem cells (MSC) and macrophagocytes (RAW264.7)	Viability, proliferation and migration	50 Hz, 1 mT 4 h/day for 3 days	Increased proliferation in MSC cells; Increased proliferation and enhanced migration in RAW264.7 cells grown in conditioned medium	Fan et al. (2015)
Human epidermal keratinocytes, primary (NHEK) and immortalized (HaCaT cells)	Proliferation	60 Hz, 1.5 mT from 1 up to 7 days	No effect in NHEK cells. Decreased proliferation in HaCat cells	Huang et al. (2014)
Embryonic neural primary stem cells (eNSCs)	proliferation	50 Hz 0.5, 1 and 2 mT for 3 days; 2 mT for 1, 2 and 3 days	No effect in the percentages of eNSCs and astrocytes differentiated from eNSCs.	Ma et al. (2014)
Human adipose derived stem cells (hADSCs)	proliferation	50 Hz 0.5 and 1 mT for 20 and 40 min/day for 7 days.	Increased cell proliferation except for 40 min/day exposure at 1 mT.	Ravazi et al. (2014)
Primary rat neuronal cells	membrane ion channels; intracellular calcium dynamics	50 Hz 1 or 3 mT 24 h (5 min on/10 min off cycles)	No effect on membrane Ca ²⁺ channels; altered intracellular Ca ²⁺ dynamics	Luo et al. (2014)
Mouse male germ (GC-2) cells	DNA damage	50 Hz 1, 2 and 3 mT 24 h	Dose-dependent increase in DNA damage, not via oxidative damage	Duan et al. (2015)

Human peripheral blood lymphocytes	Apoptosis, ROS, genotoxicity	60 Hz 0.8-mT from 12 up to 72 h Co-exposure: Gd	No effect of ELF-EMF exposure alone, except for DNA fragmentation Enhanced Gd-induced cell death, apoptosis, ROS and genotoxicity	Cho et al. (2014)
Mouse embryonic fibroblasts (NIH3T3), human lung fibroblasts (WI-38), human lung epithelial cells (L-132), human mammary gland epithelial cells (MCF10A)	DNA damage	60 Hz, 1 mT 4 or 16 h Co-exposure: Ionizing radiation; H ₂ O ₂	No effect of exposure and co-exposure	Jin et al. (2014)

Abbreviations: DDP – cisplatin; Gd - Gadolinium MMP - mitochondrial membrane potential; H₂O₂ – Hydrogen peroxide; PMC – puromycin; ROS – Reactive Oxygen Species; TRAIL - Tumor necrosis factor-related apoptosis inducing ligand.

Excluded studies

The following studies have not been considered due to the lack of sham-exposed controls: Patruno et al. (2015), Reale et al. (2014), Hasanzadeh et al. (2014) and Jung et al. (2014).

2.2. Animal studies

In continuation of the last years, studies on brain and behaviour dominated, followed by different papers addressing endpoints like geno- and immunotoxicity, oxidative stress, cancer and physiology. Especially the contradictory results of ELF exposure on brain, behaviour and neurodegenerative animal models should be more elucidated during this reporting period, but as in the previous years, most researchers used one exposure level only.

2.2.1. Brain and behaviour

Fard et al. (2014) investigated the aggressive behaviour in a foot-shock-induced (2 mA, 5 min, 3 s interval) aggression model in groups of five male Sprague-Dawley rats after 50 Hz 0.5 mT ELF-MF exposure alone for 30 d and 8 h/d or concurrent to ip injection of saline, baclofen (as γ -aminobutyric acid (GABA) agonist) and CGP35348 (GABA antagonist). ELF-EMF, baclofen or CGP35348 alone as well as baclofen or CGP35348 in two doses each as well as in combination with ELF-MF did not reveal a significant effect on aggressive behaviour.

Demir et al. (2014) used male Wistar rats with at day 17 pre-implanted electrodes on the dura mater above the cortex for a rat febrile convulsion model. Starting on day 22, febrile convulsion was induced by heating these rats once every two days for a period of 20 days in a 45°C water tank for 4 min or until seizure occurred. Six males each were allocated to the following 6 groups: sham (S), febrile convulsion (FC) without MF exposure, MF without FC, exposure to MF before FC (MF + FC), MF after FC (FC + MF), MF before and after FC (MF + FC + MF). A 50 Hz 5.0 mT ELF-MF was applied to the respective animals for periods of 30 min on /15 min off over 8 hours each day.

In all rats, rectal temperature after febrile seizure induction, seizure latency, seizure duration, and EEG were recorded. The repeatedly induced hyperthermia decreased the seizure latency and duration. This effect was more obvious on seizure duration than on latencies. ELF-MF increased seizure latency, pathologic theta and delta waves. Beta waves, frequently seen in awake animals, were decreased. The negative effect of ELF-MF on brain waves became more evident with prolonged exposure. By contrast, the convulsion durations were significantly decreased.

Elmas and Comlekci (2015) recorded fronto-occipital bipolar EEG in 10 (xylazine/ketamine) anaesthetized female Wistar rats during 50 Hz, 0.3 mT ELF-MF exposure for 2 min. The EEG of the sham group (n=10) was similarly recorded. In addition, heart rate variability (HRV) was determined during EEG recording. Another 10 females each served as nerve donors for an *ex vivo* 50 Hz 0.3 mT ELF-MF or sham exposure of the right sciatic nerve for 30 s in a nerve chamber (for the *ex vivo* exposure of isolated nerves), in order to determine the nerve conduction velocity (NCV). The data did not reveal statistical differences between the exposed and sham group in terms of EEG and HRV data before, during, and after ELF-MF exposure. NCV data (conduction velocities, maximum wave lengths, de-, re- and hyper-polarization times) were not different between exposed and sham exposed nerves.

Li et al. (2014b) investigated whether the post-synaptic brain-specific protein neurogranin (Ng) modified prenatal restraint stress response or prenatal pulsed MF (pMF, 0.11 T, 0.3 ms pulse rise time, 2.4 ms pulse width, 1/min frequency) in the hippocampus of rat offspring. Four groups of six pregnant Sprague-Dawley rats each were tube-restraint, pMF or sham-exposed at gestational days 14–20. The 4th group served as control. The offspring was sacrificed at 1 month. Ng expression was determined by immunohistochemistry and Western blotting. Restraint inhibited Ng expression, especially in females, whereas 0.11 T pMF increased the Ng expression in both sexes. The authors speculated on an association between decreased Ng in offspring hippocampus and deficits in spatial learning and memory. The stimulated Ng expression by “pMFs stress might enhance synaptic growth and remodelling.”

Chung et al. (2015) exposed 10 male Sprague-Dawley rats each for 2 or 5 days to 60 Hz, 2.0 mT ELF-MF, presumably for 24h/d (*Remark: inaccurate description by the authors*). 10 males served as sham controls. Major neurotransmitters in the different areas of the rat brain were investigated. In the striatum and thalamus norepinephrine levels were decreased after 5 days whereas its metabolite VMA increased after ELF-MF exposure. Dopamine was detected in these brain regions only. Serotonin and its metabolite HIAA were significantly elevated in the same brain regions (i.e., striatum and thalamus) and in the hippocampus. Also in the striatum and thalamus and after 5 days ELF-MF exposure, the amino acid neurotransmitters glutamine, glycine, γ -aminobutyric acid were increased whereas ELF-MF decreased the levels in cortex, cerebellum and hippocampus. Finally,

nitric oxide concentrations in striatum, thalamus and hippocampus were elevated after 2 mT exposures. The authors give the weak statement “From our results, we can speculate that there is possible relationship between ELF-MF and neurotransmitters.” Therefore, the mechanisms and consequences remain unknown.

Liebl et al. (2015) investigated the potential long-term effect of 50 Hz, 1 mT exposure on mouse models of Alzheimer’s disease (AD) and amyotrophic lateral sclerosis (ALS). Six to fourteen APP23 mice (developing AD) per group per sex were exposed for 16 months. Spatial learning (water maze) was not affected by 1.0 mT ELF-MF exposure. Studying effects on ALS, disease onset and survival of SOD1^{G85R} or SOD1^{G93A} mice exposed for ten or eight months were different compared to sham-exposed animals. These “two transgenic mouse lines expressing mutant variants of the Cu/Zn-superoxide dismutase (SOD1), namely SOD1G85R and SOD1G93A, develop a progressive phenotype in adult mice resulting in a prominent loss of motor neurons and finally a complete paralysis”. Groups of 52 –76 sham- or 1 mT-exposed ‘ALS mice’ were analysed. Protein aggregation, glial activation and levels of toxic protein species revealed no effect of ELF-MF on those specific AD and ALS relevant processes on a cellular level. Unfortunately, exact numbers of mice per group used for the investigation of the different endpoints at the beginning of the study and at the end, are not given. In addition, the daily duration of exposure is not described.

Liu et al. (2015) used an Alzheimer’s disease (AD) rat model provided by daily ip injection of D-galactose for 42 days + stereotactic hippocampal microinjection of A β ₂₅₋₃₅ peptide fragments on day 43. D-galactose was used for the induction of premature aging, A β ₂₅₋₃₅ for AD-like symptoms. The non-AD groups 1 & 2 underwent similar procedures but received saline. After Morris water maze training, 64 male Wistar rats were divided in 4 groups: (1) control, (2) ELF-MF (50 Hz, 400 μ T, 60 d), (3) AD, and (4) AD+ (ELF-MF). Groups 2 and 4 were ELF-MF exposed for 60 days, groups 1 and 3 were not (sham) exposed. In group 4, the 42 days lasting ip and d43-microinjection were performed in parallel to the ELF-MF exposures during the first 7 weeks. ELF-EMF effects on AD development was studied by applying the Morris water maze (n=9–11/group), histopathological analysis of the hippocampus (n=5/group), and comparative proteomics of the right hippocampus (n=3/group). Anaesthesia and microinjection caused 1–2 deaths per group. ELF-MF lowered weight gain, and partially improved the spatial learning of AD rats. AD typical changes in the hippocampus were lower when ELF-MF exposed. The differential proteomic analysis demonstrated the involvement of several proteins in the above effects. The paper suffers from a weak description of the results.

Raus Balind et al. (2014) determined the effect of 50 Hz 0.5 mT ELF-MF on pituitary adrenocorticotrophic (ACTH) cells in adult rats. In study (1) a short-term exposure of 3-month-old Wistar rats to ELF-MF for 1 and 7 days was used, and in study (2) rats were exposed to ELF-MF from their conception onwards up to 3 months of age. Stereology was applied to immuno-labeled pituitary ACTH cells which were harvested immediately after cessation of exposure. Total number, volume of ACTH cells, the volume of their nuclei and pituitary volume were measured. 0.5 mT exposure for 1 day decreased total number, volume of ACTH cells and their nuclei, as well as the pituitary volume. Only after 7 days the volume of ACTH cells was reduced. Subchronic (~3months) exposure led to a decrease in the volume of ACTH cells and pituitary gland. Based on their results, the authors consider ELF-MF as a potential disruptor of homeostasis in organisms. This very general conclusion should be underlined by results of other independent studies.

Zhao et al. (2015) exposed 3–4 weeks old female ICR mice at 50 Hz 1 mT ELF-MF for 12 h/d, over a period of 1 – 21 days in order to investigate recognition memory task and morphological changes of hippocampal neurons. ELF-MF (50 Hz 1 mT) induced a time-dependent deficit (after 7–10 days) in novel object associative recognition memory (n=15 exposed mice vs. n=15 controls) and also decreased hippocampal dendritic spine density (n=21-31 after 7 and 10 days of exposure or control housing; group sizes for 14 and 21 days not presented). These findings did not correspond to changes in spontaneous locomotor activity and were transient, i.e., the decreases were seen after 7 and 10 days only. Finally, over-expression of hippocampal neuritin, an activity-dependent neurotrophic factor, using an adeno-associated virus (AAV) vector was shown to significantly increase the neuritin level and dendritic spine density. Studied on day 10 only, this increase corresponded to deficits in recognition memory and reductions of dendritic spine density in ELF-MF-exposed mice. This study provides numerous data, sometimes confusingly and incompletely described, and lacks a sham control. Nevertheless the authors claim evidence for an association between ELF-MF exposure, impairment of recognition memory, and resulting changes in hippocampal dendritic spine density. Neuritin prevented this ELF-MF-exposure-induced effect by increasing the hippocampal spine density.

2.2.2. Genotoxicity and/or oxidative stress

Korr et al. (2014) tested the hypothesis that MF exposure at flux densities $\ll 1.5$ mT shows similar results to those in their previous study, in which they found increased unrepaired nuclear DNA single strand breaks (nDNA SSB) only in epithelial cells of the choroid plexus in the brain of 8-wk, 50 Hz, 1.5 mT-exposed NMRI mice. In this new study, groups of 10 seven months old male NMRI mice were exposed continuously for 8 weeks to 0.1 mT or 1.0 mT MF. Controls were left unexposed outside the Helmholtz coils. No increased persisting unrepaired nDNA SSB were observed in the tested epithelial cells of brain, kidney and liver. 1.0 mT MF reduced unscheduled DNA synthesis (UDS) in epithelial cells in the choroid plexus of the fourth ventricle in the brain (EC-CP), in epithelial cells of the cortical collecting duct in the kidney, and reduced mitochondrial DNA (mtDNA) synthesis in neurons of the caudate nucleus in the brain and in EC-CP. It could not be proven whether this result was influenced by the iron transport or storage in these cells. In addition, the authors report that further 20 or 16 mice per group were exposed or control housed, but not investigated, which is confusing.

Saha et al. (2014) reported a linear increase in DNA double-strand breaks (DSB) and apoptosis in the embryonic neuronal stem cell compartment after in utero exposure to 10–200 mGy X-rays. In contrast, no significant induction of DSBs or apoptosis was detected following in utero exposures to ELF-MF (50 Hz, 100 μ T for 2 h on gestational day 13.5 or 300 μ T for 15 h (intermittent 5 min on, 10 min off or continuous) on gestational day 12.5. For the ELF-MF study 3 embryos from each of 3 pregnant C57BL/6 mice per treatment group were analysed. Sham-exposed embryos for each of the different ELF-MF treatments as well as an untreated cage control were additionally used.

Wilson et al. (2015) evaluated the *in vivo* effects of ELF-MF on mutation induction in the germline (sperm) and in blood samples of male 7-week old BALB/c \times CBA/Ca F1 hybrid males which were exposed to 10, 100 or 300 μ T of 50 Hz MF for 2 h, 15 h or sham-exposed. The mutation frequency at the mouse Expanded Simple Tandem Repeat (ESTR) locus Ms6-hm was established in sperm and blood samples by single-molecule PCR. For comparison, ESTR mutation frequency was also studied in samples of male mice exposed to 1 Gy X-rays. ESTR mutation frequency in male hybrids exposed to MFs did not significantly differ from sham-treated controls. A marginally significant increase in mutation

frequency in sperm was not dose-dependent. By contrast, X-rays led to significant increases in mutation frequency.

Woodbine et al. (2015) checked whether exposure to MF before and after exposure to 100 mGy X-rays influenced DSB repair rates. C57BL/6 mouse embryos (of 1-4 mothers per group) were exposed in utero to 50 Hz 300 μ T MF for 3 h before and up to 9 h after exposure to 100 mGy X-rays on gestational day 13.5. Embryos exposed to MF or X-rays alone plus sham exposure(s) served as controls. 1, 3, 6, 9 or 11 h after X-irradiation and/or ELF-MF exposure, the dams were sacrificed, the embryos removed, their head detached from the body, and snap-frozen before cryosectioning and 53BP1 staining. Exposure to MF before and after 100 mGy X-rays did not impact DSB repair in the foetal neuronal stem cell compartment compared to repair rates in only radiation exposed mice.

2.2.3. Cancer

Qi et al. (2015) exposed 24 male and 42 female B6C3F1 mice during the last week of gestation in utero and until 15.5 months after birth to a 50 Hz 500 mG (= 50 μ T) ELF-MF for 12 h/d. 30 male and 32 female controls were observed without exposure. In both sexes and compared to controls, mean body weights of exposed mice significantly decreased. No increased incidence of liver and lung tumours was found. Female ELF-MF-exposed mice developed chronic myeloid leukaemia [3/42 (7%)] compared to 0/32 (0%) in the controls. The diameter of seminiferous tubules in the exposed group (197.4 μ m) was significantly less than in the control (205.7 μ m). According to the researchers, their data support the hypothesis that long-term exposure to 50 Hz magnetic fields is a significant risk factor for neoplastic development and fertility in mice. That conclusion is somehow doubtful because other rodent cancer studies (SCENIHR 2015, IARC 2002) using three different exposure groups, ≥ 20 h/d exposure duration and more animals per group did not demonstrate similar (tumour) findings.

2.2.4. Physiology

Costa and Nogueira Rde (2015) determined in follow-up experiments (SSM, 2013) the influence of 60 Hz 1 mT ELF-MF exposure of different durations on yolk sac vascularization in eggs of Japanese quails. After 2 days of incubation, 3 cm² of the egg shell was removed and the opening re-covered with a PVC film. 20 eggs per group were ELF-MF-exposed from 48 hours of incubation onwards for 2 days. Group 1 was exposed 3 x 2 h per day with 6 h intervals, group 2 for 3 x 3 h/d for 5 h, and group 3 for 3 x 4 h/d with 4 h intervals; group 4 for 24 hours continuously. For the controls the two Helmholtz coils were switched off. Lacunarity analysis was applied to photographs taken of the yolk sac membrane (YSM) vascular network after 1 and 2 days of exposure (72 h, 96 h). The difference of lacunarity values between 72 and 96 h for each surviving embryo was calculated. Up to 14 (of 20) embryos per group died. Nevertheless, the authors stated that 6 and 9 h/d (3 x 2 h and 3 x 3 h) of exposure to 60 Hz 1 mT ELF-MF promoted an inhibition of vascular growth between 48 and 72 h of incubation. 12 and 24 h of exposure had no influence on the vascular network. The entire study is compromised by the high number of embryos which died.

Hori et al. (2015) examined plasma glucocorticoid (GC) levels as indicator for stress response in 50 Hz electric field (EF) exposed male BALB/c mice, including immobilization effect on GC. Groups of n=8 eight week old mice were exposed to 2.5, 5.0, 50, and

200 kV/m for 60 min, and tube-immobilized for 30 min in the second half of the 1 h. A control group and an immobilization-alone group were added. Blood samples were taken immediately after EF exposure. GC levels were analysed by spectrofluorometry. EFs in absence of immobilization did not change GC levels, but they significantly increased in tube-restrained mice. Elevated GC levels due to restraint were reduced by the EF ≤ 10 kV/m. Following EF exposures at 50 and 200 kV/m, GC levels were higher than those observed at 10 kV/m. Supplementary, the effect of EF treatment duration was investigated by comparing exposures of 50 Hz EFs (10 kV/m) for 6, 20, or 60 min. EF exposure for 20 and 60 min suppressed the above immobilization-induced increase in GC levels. Therefore the authors conclude that ELF-EFs alter stress response of mice in a kV/m- and duration-dependent manner.

Kolbabova et al. (2015) addressed the melatonin (MLT) hypothesis assuming that ELF-MF decreases MLT and thereby promotes cancer development. Four 1 month old calves (2 m, 2 f) from each winter (Nov-Dec) and summer (Jul-Aug) experiment were exposed to 50 Hz 0.4 μ T for 35 days in individual wooden boxes. Salivary MLT was measured in exposed and concurrent control calves at 12.00 noon, 10.30 pm, 02.00 pm, and 04.30 pm on days 0, 10, 20, 30 and 35. ELF-MF inhibited MLT secretion in winter, whereas MLT in summer was increased. This season-dependent effect was explained by the ELF-MF influence on serotonin metabolism; therefore future studies should include serotonin measurement.

Lai et al. (2015) tested with their study whether ELF-MF “affect health or not”. Groups of 64 Sprague-Dawley (SD) rats were exposed to 50 Hz 100 μ T ELF-MF, 20 h/d for three months or sham exposed. Body weight was recorded every 2 weeks, food and water intake weekly. Haematology parameters were evaluated before and after the 3 month exposure period. Blood chemistry analysis was run every 4 weeks. The general condition (body weight development, food and water consumption) of the exposed rats was not affected by ELF-MF. Haematological parameters were not significantly altered between the two groups. Similarly, standard blood chemistry (including lipid profile, blood glucose) as well as liver and kidney histology from the ELF-EMF group did not show differences over 3 months of exposure compared with the sham rats. Unfortunately, the authors did not give age and sex of the SD rats. According to the body weight data presented, it is assumed that they started the experiment with 8 week old males.

2.2.5. Immunology

Li et al. (2015a) examined the effect of 50 Hz 5, 10 and 20 mT ELF-MFs after 100 weeks of exposure on hepatic and immunologic functions in 32 male Wistar rats (n=8/group). 10 and 20 mT led to an increase of serum alanine aminotransferase and aspartate aminotransferase. In serum, liver and spleen MDA was elevated, whereas glutathione peroxidase and superoxide dismutase were decreased. The results may indicate lipid peroxidation reactions in liver and spleen tissue after long-term exposure at higher ELF-MF fields. Serum immunoglobulins (IgG, IgA, IgM) were decreased in all ELF-MF exposed rats showing a weakened humoral immune function.

2.2.6. Summary and conclusions on ELF animal studies

Similar to the previous Council report, most studies used one exposure level only and normally ≤ 1 mT at 50 Hz. Again brain function and behaviour addressing neurodegeneration was a topic. Also hypothesis- and mechanism-driven studies were rare.

The animal studies pointed to that ELF-MF exposure in the 1 mT range may interfere with the activity of brain cells, thereby generating behavioural and cognitive disturbances. But contradictory results were obtained by the studies of Liu et al. (2015) at 400 μ T showing increased performance and of Zhao et al. (2015) at 1 mT showing a decrease. In addition, inconsistent results regarding regulation of the different neurotransmitters gave no clear picture. Therefore, potentially underlying mechanisms and consequences remain unknown.

Single papers addressing general health gave no basic news. Unfortunately and due to the lack of an appropriate animal model, none of the studies addressed childhood leukaemia which is still of epidemiological relevance.

The studies are summarized in the following tables:

Table 2.2a Animal studies on ELF-EMF

Endpoint	Reference	Exposure ELF - MF	Duration	Effect
Rodents studies (mostly)				
Brain and behaviour	Chung et al. (2015)	60Hz, 2.0mT	2d & 5d	Changes in the levels of various neurotransmitters in various brain regions.
	Demir et al. (2014)	50Hz, 5.0mT	10-12d, 8h/d, 30min ON, 15min OFF	Increased seizure latency, pathologic theta and delta waves. Beta waves, were decreased
	Elmas & Comlekci, (2015)	50Hz, 0.3mT	2min (EEG) 30s (NCV)	No significant effect on rat nervous system (EEG, nerve conduction velocity [NCV])
	Fard et al. (2013)	50Hz, 0.5mT	30d, 8h/d	No significant effect on aggressive behaviour tested in a rat foot-shock model
	Korr et al. (2014)	50Hz, 0.1, 1.0mT	8wk	In Fe transport-related epithelial cells: 1) No increased persisting unrepaired nDNA SSB, 2) Reduced unscheduled DNA synthesis (UDS) after 1.0mT exposure
	Li, Cheng et al. (2014)	1/min, 0.11T	gd14-20	Prenatal restraint stress decreased and prenatal pulsed MF increased Ng expression in the hippocampus of rat offspring
	Liebl et al. (2015)	50Hz, 1mT	Up to 16mo	No effect of 1.0mT on protein aggregation, glial activation and levels of toxic protein species in AD and ALS mouse models
	Liu et al. (2015)	50Hz, 400µT	60d	Improvement in spatial learning, less AD-typical alterations in hippocampus
	Raus Balind et al. (2015)	50Hz, 0.5mT	1, 7d; In utero +3mo	Decrease in total number, volume of ACTH cells and their nuclei, as well as the pituitary volume
	Zhao et al. (2015)	50Hz, 1mT	12h/d, 1-21d	Decreased recognition memory and hippocampal dendritic spine density after 7-10d (only)
Genotoxicity, oxidative stress	Saha et al. (2014)	50Hz, 100µT or 300µT	2h 15h	No DSBs or apoptosis in the embryonic mouse neuronal stem cell compartment of gd 12.5-13.5

	Wilson et al. (2015)	50Hz, 10, 100, 300 μ T	2 or 15h	No relevant mutation induction in the germline (sperm) and blood samples
	Woodbine et al. (2015)	50 Hz, 300 μ T	3h before & \leq 9 h after 100mGy X-rays	No impact of ELF-MF on DSB repair
Cancer + Fertility	Qi et al. (2015)	50Hz, 500mG	1wk iu + 15.5mo, 12h/d	Chronic myeloid leukaemia in female mice, thinner seminiferous tubules in male mice
Physiology	Elferichi et al. (2015)	128mT SMF	1h/d, 15d	Pseudoanemic effects
	Hori et al. (2015)	50Hz EF 2.5 – 200 kV/m	60min	No influence of EFs on glucocorticoid levels (GC) in absence of immobilization; high GC levels due to restraint were reduced by EFs up to 10 kV/m
	Kolbabova et al. (2015)	50Hz, 0.4 μ T	35d	Melatonin levels in cattle calves increased in winter and decreased in summer
	Lai et al. (2015)	50Hz, 100 μ T	3mo	General health, haematograms and blood chemistry, liver and kidney pathology not affected
Immunology	Li et al. (2015a)	50Hz, 5, 10, 20mT	10wk	Increased liver enzymes and MDA, decreased immunoglobulins
Studies in non-mammalians				
Physiology (Japanese quail)	Costa and Nogueira, (2015)	60 Hz, 1 mT	6, 9h/d	Inhibition of vascular growth in yolk sac membranes;
			12, 24h/d; 1, 2 days	No effect after more than 9 h/d ELF-MF exposure

Excluded studies

Table 2.2b Excluded animal studies on ELF-EMF and main reasons for exclusion

Reference	Reason for exclusion
Mahdavi et al. (2014)	Incomplete data presented
Mahdavi et al. (2015)	Poor description of exposure and dosimetry
Vidal-Gadea et al. (2015)	No health risk relevant data -> Geomagnetic orientation in <i>C. elegans</i>
Wang et al. (2015a)	Clinical application >Neuroprotection of vascular dementia

2.3. Human studies

Since the previous Council report two studies were published, both investigated effects of ELF-MF on brain activity, one with fMRI (Legros et al., 2015) and one with the method of EEG (Gao et al., 2014).

Legros et al. (2015) investigated the effect of a 60 min 60 Hz 3000 μ T MF on brain activation as assessed by functional magnetic resonance imaging. 29 healthy right-handed volunteers (mean age 26.7 ± 1.36 years, the number of females and males in the total sample is not stated) were included. The authors state that the experiment followed a pseudo double-blind design since the experimenter discovered the exposure condition (real or sham exposure) only after the end of direct interactions with the subject. Furthermore participants were investigated in a parallel group design, e.g. they received either sham or real exposure. Functional brain activity was investigated using a 3.0 T MRI scanner. Following a pilot study (n=9) that demonstrates the feasibility to use fMRI to detect subtle changes in functional brain activity with 60 Hz MF exposure at 1800 μ T a study was performed in which two tasks were considered: 1) a finger-tapping task and 2) a mental rotation task besides a rest condition. The MRI session lasted for two hours. An MRI-compatible button press system taped to a glove on the participant's right hand was used to record the response to visual stimuli. For data analyses the numbers of eligible subjects were reduced to 20 (11 in the control group and 9 in the real exposure group: finger-tapping task) and 21 (11 males and 10 females: mental rotation task), respectively. The finger tapping task of the main experiment (60 Hz 3000 μ T vs sham) revealed a significantly higher functional brain activation following real exposure than following sham exposure. This was observed in the contralateral (left) primary somatosensory cortex and in the ipsilateral cerebellum. For the mental rotation task a repeated-measures ANOVA showed a significant time-by-exposure interaction, with a stronger post-exposure deactivation after real exposure as compared to following sham exposure. Exposure had no impact on task performance.

Gao et al. (2014) investigated possible effects of an ELF pulsed magnetic stimulation (1 Hz, 10 mT) on the power of the resting state EEG with eyes closed, as well as on latency and amplitude of the P300 component, which is an event related potential component,

which can be assessed with an oddball paradigm. Real and sham exposure (duration 20 min) was delivered randomized to two separate experimental days separated by one week. The outcome variables were assessed in a pre-post design. The sample consisted of 10 young male subjects (age range 23–27 years). The authors observed an increase in the theta (3.5–7.5 Hz) power in frontal and parietal cortical areas and the low-alpha band (7.5–10 Hz) power in the frontal and occipital cortical area following real exposure. Reaction time in the oddball paradigm was longer after real exposure as compared to sham, the P300-latency was increased at Fz, Cz, and Pz (three of 19 standard locations for EEG recording according to the 10-20-system) and at these locations the P300 amplitude was lower after exposure. However, since information on exposure is not very detailed and since the design was single-blind, the study is considered not to be informative.

2.3.1. Conclusions on human studies

Both studies indicate that ELF-MF may modulate cortical brain activity; results concerning related performance data were heterogeneous.

2.4. Epidemiological studies

In the previous Council report (SSM, 2015) it was concluded that little progress has been made to resolve whether the consistently observed association between ELF-MF exposure and childhood leukaemia in epidemiology is causal or not. Another open question is whether occupational ELF-MF exposure or electric shocks are a risk factor for amyotrophic lateral sclerosis (ALS). Two epidemiological studies discussed in the last report suggested that ELF-MF exposure rather than electric shocks are relevant in that context. Another important topic addressed in the last report was an absence of association for miscarriage and pre-term birth with proximity of place of residence to power lines. However, decreased birth weights close to power lines seen in this study warrants further investigation. Last year little new research on symptoms and ELF-MF was available.

2.4.1. Childhood cancer

Leitgeb (2014a) examined available epidemiological studies on childhood leukaemia and ELF-MF using meta-analytic techniques to explore the presence or the absence of an association. Risk estimates of studies reporting on childhood leukaemia and magnetic field exposure were included. Risk estimates were plotted vs. the number of cases per risk estimate and it was found that the higher the number of cases per risk estimates, the closer to unity the risk estimates were. Based on the assumption that risk estimates based on the highest number of cases are most reliable, he concluded that “a causal link between ELF-MF exposure and childhood leukaemia is no longer plausible and hence that ELF-MF’s classification as possibly carcinogenic needs revision.”

Leitgeb’s approach is, however, flawed. First, it is not clear which risk estimates were considered. It seems that original study results and pooled as well as meta-analysed estimates were mixed, producing multiple counting of study results. In addition, if authors presented results referring to different exposure metrics, all risk estimates were included in the paper. Second, the assumption that risk estimates based on a high number of cases are most reliable is not necessarily true. Detailed exposure assessment may not be feasible in large studies, which may produce non-differential exposure misclassification bias-

ing risk estimates to null (in case of an association). Third and most relevant, Leitgeb did not consider the level of exposure. Obviously, high ELF-MF exposure scenarios are rare and thus risk estimates for highly exposed children groups are based on few cases only. In contrast, risk estimates based on several hundreds of cases can only refer to low exposure groups. Thus, absence of risks for low exposure groups is not informative for the risk of children exposed above 0.3/0.4 μT . In summary, the chosen approach mixes study results in an inappropriate manner and is not suitable to draw any conclusions on the association between childhood leukaemia and ELF-MF exposure.

In Iran, Tabrizi and Bidgoli (2015) performed a case-control study of 22 incident cases of acute lymphoblastic leukaemia (ALL) and 100 healthy controls below 12 years of age to assess the risk of proximity of place of residence to high voltage power lines on the development of ALL. Only children born and growing up in Isfahan were enrolled into the study. Among reasons to exclude cases or controls was if there was “a lack of access to the parents”, or if the child had a moderate or higher socioeconomic position; response rates were not reported. Controls were matched with cases on age (± 5 years). Living near high voltage power lines, using mobile phones, computers, microwave ovens and the use of other electric devices were considered as potentially important environmental factors. Addresses of cases and controls were recorded and matched with locations of factories generating PAH, dioxins, pesticides and other pollutants. Families were considered as exposed if they lived within 4 km of these sources. Parents were asked to fill in a questionnaire that inquired about a range of characteristics, including place of birth of the child, parental ages at delivery, BMI of the parents, educational level, type of occupation, physical activity, birth weight at delivery, familial history of leukaemia, and so on. Prenatal and postnatal exposure to high voltage power lines was analysed for living <600 m versus living ≥ 600 meters of a high voltage power line and expressed as stratified odds ratios, unadjusted for the potential confounders. 4 cases and 3 controls had lived within 600 meters of a high voltage power line prenatally and during childhood, corresponding to an odds ratio (OR) of 3.65 (95% CI 1.69–7.79).

Overall, the study had very low power to investigate any kind of risk factors with just 22 included cases. In addition, it remains unclear why persons with medium or higher socioeconomic position were excluded from the study and the recruitment process of controls is not well described. Apparently addresses of cases and controls were available, but it is not reported that these addresses were used to evaluate the distance of the home to the nearest power line, and what type of power lines these were. All children living within 600 m distance from a power line were classified as “exposed”, although magnetic field exposure is usually at background levels at about 200 m from the power line, even in the case of very high voltage power lines. It seems likely that parents of diseased children were asked for the presence or absence of the sources of different environmental exposures and that the reported elevated OR may thus have been introduced by recall bias.

To assess whether exposure to a 50 Hz magnetic field increases the risk of childhood leukaemia, Salvan et al. (2015) performed a case-control study in Italy, the SETIL study. Incident childhood leukaemia cases (acute lymphoblastic as well as acute non-lymphoblastic leukaemia) aged 0–10 years at the time of diagnosis were included between 1998–2001 from 15 Italian regions, identified by the National Italian Paediatric Cancer Registry AIEOP. Two controls per case were recruited, matched on sex, date of birth (± 15 days) and province of residence, randomly selected from Local Health Authority Rolls. Parents were invited to participate (response rate 55% for cases and 39% for controls), to fill in a questionnaire that assessed a range of potential confounders (e.g.

educational level, parental occupational history, lifelong residential history of the children, child's exposure to chemicals or electrical appliances at home, etc.). Parents who were still living in the home they had lived in a year before the date of diagnosis were invited to participate in an ELF-MF measurement survey. Indoor levels of ELF-MF fields were measured in the child's bedroom, under or close to the bed using an EMDEX II/lite. Both night-time as well as 24-hour measurements were evaluated. Conditional logistic regression analysis was used, adjusting for a range of potential confounders. Exposure was analysed categorically (<0.1 , $0.1-0.2$, >0.2 μT). In total, 713 cases and 1380 controls were included in the study, 24 hour measurements in bedrooms of participants could be performed for 549 cases and 830 controls. Of these, 10 cases and 17 controls fell in the highest exposure category (24 h mean >0.2 μT), which resulted in an OR of 0.79 (0.35–1.79) compared to the low exposure group (≤ 0.1 μT). Odds ratio of the medium exposure category ($0.1-0.2$ μT) was somewhat elevated (OR 1.87, 95% CI 1.04–3.34). Analyses of other exposure metrics and various sensitivity analyses gave similar results.

The SETIL study was carefully performed and analysed taking into account many possible confounders. Another plus of the study was the quantitative exposure assessment in the homes of the children. However, the participation rate for controls was low. Thus, selection bias is of concern. Only few children fell into the highest exposure category and none of the children was exposed to levels above $>0.4\mu\text{T}$, the level above which increased risks were detected in previous pooled analyses. Therefore, despite a number of strong aspects of the study, the study is limited in its ability to confirm or refute the previous assessment of a possible association between higher levels of magnetic field exposures and the risk of childhood leukaemia.

Within the same SETIL study (see above from Salvan et al. 2015), Parodi et al. (2014) reported results from maternal occupational exposures to chemicals and other substances (lead, diesel exhaust, PAHs, chrome and nickel), exposure to ELF-MF fields at home and risk of neuroblastoma. Parental occupational exposures were assigned based on the detailed job descriptions and blind reviewing from industrial hygienists. ELF-MF at home were measured and analysed in line with the report from Salvan et al. The study included 153 neuroblastoma cases and 1044 controls (74.9% and 70.8% of eligible subjects, respectively). Household ELF-MF measurements were obtained for 134 cases and 904 controls. Only five cases were exposed to levels above 0.2 μT and comparing them to children exposed to background levels (≤ 0.1 μT) resulted in a risk estimate close to unity (OR of 0.93, 95% CI 0.32–2.7). Maternal occupational exposures to ELF-MF were not assessed, but exposure to some types of solvents resulted in increased risks of neuroblastoma in the children of exposed mothers. The same strength and limitations of the study apply as for the report by Salvan et al, although overall, the study is in line with previous reports that did not show an elevated risk of central nervous system tumours in ELF-MF exposed children (Kheifets et al., 2010b).

A re-analysis of a case-control study investigating distance to overhead power lines, ELF-MF exposure and risk of acute leukaemia published in 2008 (Abdul Rahman et al., 2008) was published by Hakim et al. (2014). 128 cases were enrolled who received medical treatment due to acute leukaemia at the Universiti Kebangsaan Malaysia Hospital or the Kuala Lumpur General Hospital, Malaysia between 2001-2007. The 128 controls also received treatment in the same hospitals, but due to diseases other than cancer. In the previous study, an increased risk of leukaemia was reported for children who lived within 200 m of an overhead power line (OR 2.30, 95% CI 1.18–4.49). For the current analysis, 30 subjects (12%) were excluded because their home area could not be accessed (e.g.

army area) or because of “wrong coordinates”, which left 108 cases and 118 controls for the analysis. For the remaining participants, MF spot measurements were performed (with an unnamed meter) during daytime “nearby the front door”. In addition, distance to the nearest overhead power line was recalculated with Google Earth, but information on e.g. the voltage level of the lines was not available. Average measured MF levels were 0.14 μT (range 0.01–2.04 μT). 11 cases and 10 controls had exposure values above 0.3 μT , corresponding to an OR of 1.22 (95% CI 0.45–3.37). Proximity of the home to a high voltage power line (<200 m compared to >200 m) was not associated with leukaemia (OR= 0.88, 95% CI 0.35–2.22).

In the current analysis, 9 cases and 11 controls were estimated to live within 200 m of a power line, in the original publication, these numbers were 51 and 31, respectively. While the proportion of children living close to a power line in the first publication was very high and the new data are more compatible with data from other countries, the discrepancy between the two publications remains unexplained. Also, it would have been interesting to learn what the exposure status of those 20 case children and 10 control children was that could not be included in the current publication. Unfortunately, the exposure assessment suffers from incomplete reporting regarding the exposure assessment, in particular the type of the meter, the duration of measurements and distance to the actual homes of the children, and when the measurements were performed, given that this study was published in 2014, but the first cases were diagnosed in 2001 and exposures might well have changed in the time in between. Performing spot measurements, and not 24/48 h measurements or modelling of average exposure levels, may have added to exposure misclassification. In addition, door measurements do not well represent exposure conditions of the apartment or the bedroom of children (Roosli et al., 2011). While in the original analysis, logistic regression was performed adjusted for potential confounders, this was not done in the current analysis, although it was not reported why not. All in all, while the study is compatible with the most recent pooled analysis on childhood leukaemia risk in children exposed to magnetic fields above 0.3 μT compared to levels below 0.1 μT showing an OR of 1.44 (95% CI 0.88–2.36) (Kheifets et al., 2010a), it adds little to the assessment of the association of magnetic field exposure and childhood leukaemia risk.

Bunch et al. (2015) published a case-control study analysing the risk of leukaemia, CNS/brain tumours and other cancers among children residing in the vicinity of 275 or 400 kV high voltage underground cables. 52 525 cases from England and Wales during the period 1962 until 2008 were included, as were one or two controls per case, matched for age, sex and district of birth. Mothers’ residential address at birth was obtained to calculate the distance between the homes for cases and their controls and the cables. Distance of place of residence at birth to the underground cables was categorised in 0–<10, 10–<20, 20–<50, 50–<100, 100–<200, 200–<500 and ≥ 500 meters (reference category). In addition, exposure was modelled and evaluated in categories of <0.1, 0.1–< 0.2, 0.2–< 0.3, 0.3–< 0.4 and ≥ 0.4 μT was used, with <0.1 μT as reference. All analyses were adjusted for socioeconomic status of the census ward. For the analyses by distance, a significant increased risk of CNS/brain tumours (OR 4.12, 95% CI 1.1–15.5) was found in the 20–50 meter band and also for children living within 50 m of a cable (OR 2.32, 95% CI 1.14–4.70). For leukaemia and other cancers, no pattern of risk was observed. A low number of subjects were categorised as exposed in this study (e.g. 9 leukaemia cases, 8 CNS cases and 11 other cases living within 10 m of an underground cable). Thus, one should be cautious when interpreting the risk of leukaemia, CNS/brain tumours and other cancers among children living close to underground high voltage cables. Since

ELF-MF exposure is decreasing rapidly with distance from the cable and reaches background levels approximately after 10 m distance to the cables, exposure misclassification is expected to be considerable. Even if the coordinates of the homes are accurate, estimated distance to the cable has some uncertainty, since floor and direction of sleeping room is not considered in the exposure assessment. In contrast to overhead power lines, underground cables produce no electric fields, no corona ions, have no visual presence etc. – factors that might indirectly influence the observed leukaemia risk. Future studies including underground cables might therefore be of interest to separate potential effects from magnetic field exposure as opposed to such other exposures present in the vicinity of a power line given that exposure assessment can be conducted in an accurate way.

2.4.2. Adult cancer

Kato et al. (2015) reported on a study on thyroid cancer and ELF-MF exposure from use of electric blanket embedded in the Women's Health Initiative Cohort. Between 1993 and 1998, about 90 000 women aged between 50 and 79 years were recruited in 40 centres across the US. Follow-up for incident thyroid cancer was performed until September 2012. At enrolment, participants filled in a questionnaire that provided information regarding demographic and lifestyle information, including electric blanket use. Cumulative electric blanket use was calculated using the reported hours of use per night, months per year and years of usage. Incident thyroid cancer cases were identified by self-report and confirmed with medical records. Analyses were performed using Cox proportional hazard models on nearly 90 000 women, adjusting for potential confounders (race, region, income, height, BMI, hormone use and history of benign thyroid disease). 190 cases were observed during the study period. No indication of an increased risk in relation to electric blanket use was observed (i.e., duration of use in years, total months of use, cumulative number of hours of use).

This is a well-performed, longitudinal and large study. Strengths include the size of the study, prospective study design and that the outcome was assessed as incident cases (not mortality). Weakness of the study include that the exposure information was restricted to the status at baseline. Also, since different types of electric blankets can have different levels of magnetic fields and since settings of the blankets could not be evaluated, a true quantitative analysis of the exposure was not possible. Also, given the advanced age at recruitment, exposure received during more likely sensitive time periods (periods of growth of the thyroid gland) was uncertain, at best. All in all, the study does not provide evidence that exposure to magnetic fields from electric blankets during adult life increases the risk of thyroid cancer in women.

In a population-based nested case-control study based on the Nordic Occupational Cancer Cohort (NOCCA), Talibov et al. (2015) investigated the association between occupational exposure to ELF-EMF, occupational risk of electrical shocks, and acute myeloid leukaemia, (AML). Of 13 435 persons diagnosed with AML between 1961 and 2005 in Finland, Iceland, Norway and Sweden, 5409 cases who did not have a previous history of cancer were included in the analysis. Five controls, totally 27 045 persons, were randomly selected from the NOCCA cohort and matched to each case by year of birth, sex and country. Information on occupation was mainly available on censuses every decade from 1960 to 1990 with some variations between the countries. Occupational information on exposure to ELF-EMF and risk of electrical shocks were assigned to each subject based on census-reported jobs using job-exposure matrices, JEM. Three exposure metrics for ELF-EMF and electric shock were used: 1. Ever exposure to low and/or high levels; 2.

Duration in years of ever low/high and ever high exposure; 3. Cumulative exposure which was expressed in unit years. Employment period was assumed to start at age 20 years and end at either the diagnosis of the case or 60 years whichever came first. Hazard ratios (HR) for ever-high exposure levels of ELF-EMF was 0.88 (95% CI 0.77–1.01) and for electrical shocks the HR for ever high levels was 0.94 (95% CI 0.85–1.05). No statistically significant associations were observed in any of the exposure categories. The large study population, with complete cancer follow-up from high quality cancer registries and the prospective design are advantages of this study. Occupations were reported at the different national censuses, but census information was available between once (Iceland) to a maximum of four (Sweden) time points in the different countries. Therefore, limited data on occupational histories will have introduced exposure misclassification. Overall, the study does not support the hypothesis of an association between occupational exposure to ELF-EMF, occupational risk of electrical shocks, and AML.

2.4.3. Neurodegenerative diseases

Huss et al. (2015) conducted a systematic review on occupational exposure to ELF-MF and risk of Parkinson's disease (PD) (incidence as well as mortality). In total, 11 studies were identified yielding a pooled relative risk of 1.05 (95% CI 0.98–1.13) with some heterogeneity between studies (I-squared: 48%, p-value for heterogeneity: 0.048). Heterogeneity between studies was not explained by the type of exposure assessment (occupational records, census, interview or deaths certificates), the type of study population (general population study vs. industrial cohort) or the type of outcome assessment (death certificates vs. clinical records). In summary, this meta-analysis does not indicate that occupational ELF-MF exposure increases the risk for PD.

Data from the Netherlands Cohort Study on diet and cancer was used to investigate the association between Parkinson's disease (PD) mortality and six occupational exposures (ELF-MF and electric shocks, among others) by Brouwer et al. (2015). The study enrolled 58 279 men and 62 573 women aged 55–69 years in 1986. At baseline, the participants completed a questionnaire on occupational history, dietary habits and other potential risk factors for cancer. For the occupational history, subjects reported whether they had ever had a paid job. If so, type of job, type and name of industry and period of employment for up to five jobs during their lifetime was inquired. Exposure to ELF-MF and electrical shocks at baseline were estimated using job exposure matrices by translating the Dutch coding system to the International Standard Classification of Occupations (ISCO)-68 and ISCO-88. Over the whole time period, 402 male and 207 female PD deaths were identified by means of record linkage until December 2003 (mean follow-up time 17.3 years). Statistical analyses followed a case-cohort approach and accumulated person-years were estimated from a randomly sampled subcohort of 5000 individuals. Data were analysed by means of a Cox model with age as underlying time scale and hazard ratios were adjusted smoking status, non-occupational physical activity and BMI at baseline. Other potential confounders considered but not found to be relevant were: highest level of education attained, alcohol consumption; coffee consumption and tea consumption. Electrical shocks were not found to be related to PD mortality. Based on 39 male cases being ever highly exposed to ELF-MF, a significant association with PD mortality was observed (HR=1.54, 95% CI 1.00–2.36). However, no association for exposure duration or trend in cumulative exposure was seen. Results among women were unstable due to small numbers of high-exposed women. The authors attribute limited weight to these findings because of the absence of a monotonic exposure-response function with either duration or cumulative exposure.

A strength of the study is the objective exposure assessment based on job exposure matrices which is unlikely to create a bias. However, case identification from death certificates is subject to uncertainty. The observed risk increase for ever being highly ELF-MF exposed contradicts most previous studies on occupational ELF-MF exposure as outlined above (Huss et al., 2015) and might be a chance finding given the absence of a consistent exposure-response pattern.

Data from the above mentioned (Brouwer et al., 2015) Netherlands Cohort Study on diet and cancer (NLCS) was also used to determine potential associations between non-vascular dementia-related mortality and occupational exposure to several potential risk factors, including ELF-EMF exposure and electrical shocks (Koeman et al., 2015). 798 male and 1171 female cases were obtained from Statistics Netherlands. Of these cases, information on occupational history and possible confounders were available for 682 men and 870 women. From the subcohort, 2304 men and 1968 women were included into the analyses. Based on the information from the occupational history, job exposure matrices were used to assign ELF-EMF exposure to job titles and the same was done for risk of electrical shocks (background, low or high) with use of the metrics ever/never exposed and cumulative exposure. The analyses were adjusted for smoking, physical activity and body mass index. In women, non-vascular dementia showed significant positive association to ever-high exposure to electrical shocks (Hazard ratio 11.11, 95% CI 3.84–32.16) based on 9 cases but without an exposure-response pattern for cumulative exposure. For men, the corresponding HR was not increased (HR=1.10, 95% CI 0.85–1.42) based on 148 cases. Exposure to ever-low ELF-EMF in men showed a HR of 1.26 (95% CI 1.01–1.57, n=387) and ever-high a HR of 1.40 (95% CI 0.92–2.14, n=333). An increased risk was also seen in men for the 2nd tertile of cumulative ELF-MF exposure (HR 1.74 95% CI 1.29–2.36) with no exposure-response relationship.

Strengths and limitations of the study are discussed above. Analyses in men indicate that occupational exposure to ELF-MF may increase the risk for non-vascular dementia. However, lack of exposure-response associations with cumulative exposure may indicate that the observed association may not be causal. Results for women are not informative because of the small number of exposed cases with subsequent wide confidence intervals. Capozzella et al. (2014) performed a meta-analysis of studies that had reported on amyotrophic lateral sclerosis (ALS) risk among ELF-MF exposed workers. Some quality criteria were used to exclude what was judged to be a low-quality study, and 9 studies were included. The overall risk estimate was 1.33 (95% CI 0.60–3.53) with a low degree of heterogeneity between studies ($I^2=13\%$). The systematic review is thus in line with previous publications (Vergara et al., 2013, Zhou et al., 2012).

The association between ALS, occupational exposure ELF-MF and electric shocks was investigated in a large population-based nested case-control study in Sweden using two electric shock and three MF job exposure matrices (Fischer et al., 2015). The study included participants of the 1990 Swedish Population and Household Census, who were born in Sweden between 1901 and 1970. Follow-up was done via linkages to the Swedish Patient Register, Migration Register, and Cause of Death Register until end of 2010. For each of the 4709 cases included in the study, five control subjects were randomly selected from the study base, individually matched by birth year and sex (n=23 335). Data were analysed using conditional logistic regression matched on birth year, sex, and adjusted for socioeconomic status, education, and region of residence. Overall, no association between ALS and ELF-MF or electric shock was observed. For individuals less than 65 years old,

medium and high electric shock exposure was associated with an increased risk (OR=1.20, 1.02–1.40 and OR=1.22, 95% CI 1.03–1.43, respectively). In an analysis of occupational groups, OR for electric occupations were not increased, but for welders <65 years, the OR was elevated (OR=1.52, 95% CI 1.05–2.21). Risks for welders for all ages combined were not increased. Excluding welders from the analyses had little impact on the association between ALS and electric shock exposures in individuals <65 years. Results were also similar for different job exposure matrices, exposure definitions and cut-points.

In contrast to two large studies published last year (Huss et al., 2014, Vergara et al., 2014), this study indicates that occupational ELF-MF exposure is unlikely to be related to ALS whereas electric shocks may be a risk factor for the working population less than 65 years. This is a large population-based study. Strengths include the prospective collection of exposure and outcome information, both based on records, which makes selection or information bias unlikely. Several job exposure matrices have been included and the results were not sensitive to the used exposure assessment methods. Some non-differential exposure misclassification may have happened because no full occupational history was available although occupational information was available at four time points (censuses 1960 to 1990), or during translation of the original Swedish job coding system to IS-CO88. Such non-differential exposure misclassification is expected to result in an underestimation of the association, if an association exists.

In a population-based case-control study from the Netherlands, Seelen et al. (2014) investigated the relation between residential exposure to ELF-MF and the risk of ALS. 1139 cases with ALS were derived from a population-based case-control study performed from 2006 to 2009 (Huisman et al., 2011). 2864 controls, frequency-matched for sex and age, were randomly selected from patient lists from general practitioners. Residential history of the study participants was collected from a national registry named Municipal Personal Records Database and distance of the home to high voltage (50-150 kV) and very high voltage power lines (220 or 380kV) were calculated on the basis of geocodes of the places of residence and digital maps of the power lines. Exposure was categorised into corridors of various distances from the power lines, where subjects living ≥ 600 meters were considered as reference group. In addition, cumulative exposure in years living within 100 meters from a power line was also computed to detect a possible exposure-response relation. No case occurred within 50 m of a very high voltage power line and only 6 cases within 50 m of a high power line (OR= 1.05, 95% CI 0.40–2.75). There was no increased risk of ALS in the 50–200 m corridor based on 2 (very high voltage power line) and 6 (high voltage power line) exposed cases, respectively. The analyses of cumulative exposure in years showed no exposure-response relationship.

Strength of this study is the register-based design without the problem of recall bias. A common challenge when studying rare diseases is the low number of cases in exposure groups of interest. Exposure assessment is based on distance only, whereas ELF-MF exposure depends on various factors including the currency of the lines. All in all, however, the study is in line with other reports that did not find increased risks of ALS in persons living close to power lines.

2.4.4. Symptoms

A Dutch cross-sectional study of 99 adults addressed the association between exposure to ELF-MF and non-specific physical symptoms (Bolte et al., 2015). Study participants

were selected from a pool of 909 individuals who answered positively to a request sent by email to 3000 persons; participants were selected to achieve a balanced distribution across sex, age groups, socio-economic status and region. Symptoms were inquired using the 16 item somatisation scale of the Four-Dimensional Symptom Questionnaire (4DSQ) and subsequently dichotomised into low and moderately high (score >10). ELF-MF exposure between 40 to 1000 Hz was recorded during 24 hours with a personal measurement device (Emdex Lite) and the collective was divided into a high and low exposure group using the 80-percentile of all measurements (0.09 μ T) as a cut-off. Data were analysed with logistic regression. No adjustment for potential confounders was made, but it was tested whether parameters correlated to ELF-MF shifted the odds ratio by more than 10%. 15 parameters were tested, but the authors reported that none of them acted as either confounders or effect modifiers, except sex. In an analysis of the data from the whole sample, the high exposure group had a crude OR for a moderately high somatisation score of 4.93 (95% CI: 1.24–19.9). As only one man scored moderately high against nine women, a separate analysis was done for the 48 women. The crude OR for women was 8.50 (95% CI: 1.73–46.75).

Personal exposure assessment is a strength of this study, although it is not clear how representative 24-hour measurements are with respect to the exposure of the whole previous week that the symptom questionnaire is referring to. No rationale for the selected exposure cut-point is given. It is also conceivable that participation in the study may have interfered with the behaviour affecting the exposure measurements or with the symptom reporting. Residual confounding may have affected the results: in particular, the most frequently named symptoms were back pain and painful muscles and it is unclear if maybe occupational factors related to (occupational) ELF-MF exposure may have been underlying the symptom reporting. A further limitation is potential selection bias and the small sample size, which prevented from effective evaluation of possible confounding factors. There is no biological mechanism how ELF-MF exposure at such low levels as encountered in this population could induce the listed symptoms. In summary, the evidence retrievable from this small study receives little weight.

Another Dutch cross-sectional survey (Baliatsas et al., 2015) of 5933 adults addressed the association between symptoms and ELF-MF as well as RF-EMF exposure (for the description of the results regarding RF-EMF exposure, see chapter 4.4.5). The number and duration of various non-specific symptoms of ill health was derived from participants' electronic medical records as registered by their general practitioners, and additionally by a written questionnaire. Distance of the place of residence to the closest high voltage power line (of any voltage level between 50–380 kV) was calculated using a geographic information system and was dichotomised as living ≤ 200 m vs > 200 m of a power line. Use of/exposure to electrical devices such as electric alarm clocks, electric chargers, electric blankets or induction hobs was obtained from the questionnaire. In addition, subjective exposure status to different sources of ELF-MF was reported by the participants. Study participants were selected randomly by oversampling areas with high modelled RF-EMF exposure in order to maximize this exposure range. Participation rate was 46%. Linear and logistic regression modelling adjusted for age, sex, education, smoking and alcohol consumption were conducted. Strongest and most consistent associations were observed for subjectively estimated ELF-MF exposure. Objectively calculated distance between place of residence and the closest power line was not associated with symptoms. However, various associations between exposure to electrical devices and number and duration of symptoms were observed. Most consistent was an increased number and duration of symptoms for people with close distance to an electric charger during sleep and

people using an electric blanket. However, sleep quality was not affected for these two exposure sources.

This is one of the largest studies on this subject. Self-reported use and/or exposure to electrical devices may be subject to reporting bias. In addition, the cross-sectional design does not allow investigating the temporal pattern and thus reverse causality is of concern. For instance, people with symptoms may be more likely to use an electric blanket e.g. to relieve back pain or other symptoms. In line with other studies, self-estimated ELF-MF exposure was strongly associated with number and duration of symptoms. The underlying reasons that have to be considered for such an association include reverse causation, placebo effects and reporting bias.

Porsius et al. (2015) used a quasi-experimental design to prospectively investigate whether self-reported cognitive and somatic health complaints (Dutch somatization scale 4DSQ) as well as the belief that a power line could cause these symptoms increase after the construction of a new power line in the Netherlands. A random sample of residents living near (0–300 m, n=229; 300–500 m, n=489) and farther away from the power line (500–2000 m, n=536) participated in the study. Participants were requested to take part in an online questionnaire four times (written questionnaire on request): 1. during construction; 2. power line was visibly finished but not yet operational; 3. two months after the line had been put into operation; and 4. seven months after the line had been put into operation. Occurrence of somatic symptoms during the week prior to the surveys was inquired using the Dutch 4DSQ, a scale of 16 non-specific symptoms such as headaches, dizziness and low back pain. Cognitive problems during the previous week were asked with the six item Cognitive Functioning Scale. Participation rate was related to distance and was 23% for residents living within 300 m and 16% for those living 500–2000 m from a power line for the first survey. Symptom reports did not differ at baseline between the groups but causal belief of negative health effects after exposure to fields from power lines was stronger at baseline for residents in the vicinity of a power line. Between baseline and follow-up, residents living within 300 m from the new power line had a significantly larger increase of cognitive and somatic symptom reports as well as causal belief compared to residents living farther away.

This study demonstrates that the number of symptom reports increases when a new power line is put into operation. The belief that power lines can cause symptoms is already increased during the construction phase, but this may be caused by selective participation, since the participation rate increased with decreasing distance to the power line. It has to be emphasized that the study has not been designed to clarify the role of ELF-MF exposure for the observed symptom increase and ELF-MF measurements have been conducted. Typically, increase in ELF-MF exposure is negligible beyond 100–200 m from a power line and authors state that expected average exposure for that specific power line is below 0.4 μT beyond 55 m. Thus, with respect to causality it would be interesting to see whether and to what extent symptoms increased in this group. However, an analysis restricted to the population living very close to the line and thus with a noticeable exposure increase is not presented in the paper. As an alternative explanation to ELF-MF exposure, placebo and reporting bias has to be considered. The latter implies that risk communication is essential to minimize the health impact of a new power line. The study leaves open whether and for how long the observed difference in symptom reports between the groups will persist. Cross-sectional studies investigating the association between symptoms and distance to existing power line have shown both, associations as well as lack of associations.

The association between sleep quality and occupational ELF magnetic and electric field was investigated by means of a cross-sectional study of electric power plant workers in Zhejiang (China), published by Liu et al. (2014). The study was performed in 2011. From 1073 contacted individuals, 854 workers took part in the study. Reasons for exclusion were retirement, chronic disease or missing information about occupational exposure. During interviews, workers were asked to assess their sleep quality of the past month (good, fair and bad) as well as sleep duration. The electromagnetic field exposure level of participants was measured and assessed by a series of questions pertaining to e.g. occupational exposure hours per day, years and fee of mobile phone subscription. Measurements were taken in the power plant in “main activity areas” of the workers, such as offices, rest rooms or workshops. The authors report the results of the measurements across an “exposed” and “unexposed” group, but it is unclear how workers were classified into these groups. Levels in the exposure group were: mean electric field of 316 V/m (SD: 1212 V/m) and a magnetic field of 6.2 μ T (SD: 14.7 μ T) and for the non-exposure group a mean electric field of 4 V/m (SD: 0.3 V/m) and a magnetic field of 0.1 μ T (SD: 0.02 μ T). For the statistical analyses, these measurement values were not used, but instead, daily occupational exposure duration and occupational exposure duration in years were considered. Logistic models were adjusted for age, sex, smoke, tea drinking, BMI, and work stress. Compared to workers with little daily exposure time (≤ 1.5 hours) risk for poor sleep quality (“fair” and “bad”) was increased for workers with daily exposure duration between 1.5 and 4 hours (OR: 1.68, 95% CI 1.18–2.39) and for workers with >4 hours exposure per day (1.57, 95% CI 1.10–2.24). Duration of occupational exposure and household fee for electricity (as a crude proxy for home exposure) was not related to sleep disturbances.

The exposure assessment method in this study is unclear. In particular, it is not described how “exposure time” was defined, whether any threshold was defined for determining the hours of exposure and how the people from the non-exposure group were treated in the analysis. Given the substantial differences in the magnetic field exposure levels, one would rather expect to see an analysis taking into account the exposure levels than just the hours of exposure per day. Daily exposure duration may be correlated to different job profiles, which may affect sleep differently. This aspect is not discussed in the paper.

2.4.5. Other outcomes

To assess the effect of EMF on selected biomarkers, Wang et al. (2015c) performed a small cross-sectional study in 77 high and 77 low exposed workers in a Chinese power plant. Occupational EMF exposure was based on the job title, job description and measurement data provided by the electric power plant and supplemented by measurements performed by the authors. Of a total of 2138 workers of the power plant, 251 were excluded due to “obvious diseases” and a further 814 persons did not participate. Of the remaining 1073 workers, 77 high and 77 low exposed male workers were matched based on age (± 5 years). Exposed workers were exposed on average more than 4 hours per day and for more than 15 years. Spot measurements at some of the places (e.g. workshop, rest room, office) for a duration of at least 15 seconds and repeated for 5–6 times. Average magnetic field exposures translated into about 15 μ T for exposed workers and 0.02 μ T for unexposed workers, although it is unclear if these values represent time-weighted averages or to arithmetic means of the different measurements taken at various spots. Duration and amount of mobile phone use was assessed with questions regarding since when people had been using mobile phones as well as with a question regarding the monthly fee of

their mobile phones, additionally magnetic field exposure was approximated asking for the electricity bill at home. Blood samples of the workers were taken in the mornings of a day when the workers were off, and were analysed regarding levels of testosterone, estradiol, melatonin, NF- κ -B, HSP70, HSP27, and TET1 with an enzyme-linked immunosorbent assay. Associations of these biomarkers with ELF-MF exposure was evaluated using linear regression adjusting for body mass index, labour intensity, work pressure, sleep quality, smoking, alcohol consumption and tea drinking. Of eight evaluated biomarkers, exposed workers had significantly lower testosterone levels, testosterone/estradiol ratios and lower NF- κ -B levels.

It is somewhat unclear what exposures workers were really exposed to and if there were more differences between high- and low-exposed workers than could be taken into account in the analysis. Although the authors took care to adjust for several potential confounders, at least part of the results may still be affected by residual confounding, in particular short-term effects on the highly temporally variable biomarker levels. A quantitative assessment of the exposure would have helped to evaluate the association between magnetic field exposures and any potential effect on biomarkers.

In another publication from the same author (Wang et al., 2015d) and performed in the same company, serum lipid levels were analysed. Overall, 875 subjects (678 men, 197 women) provided information via questionnaires and blood specimens and were subsequently included in the analysis. Workers were classified into “high” or “low” exposure groups based on job titles and description. Average exposure levels in the “high” exposed group were reported to be 62 μ T and in the “low” exposed group 0.6 μ T. RF-EMF exposure assessment was done via a question of the monthly fee for mobile phones, as described above. Blood samples were taken on a non-working day, in the morning. Blood markers high/low-density lipoprotein cholesterol, total cholesterol and triglyceride were assessed. Analyses were performed adjusting for a range of potential confounders (age, sex, BMI, marital status, educational level, tea and alcohol consumption, smoking, stress at work and “type of workshop”). Differences were observed for low-density lipoprotein cholesterol, but not for the other markers. In essence, the same shortcomings apply as for the other publication.

Li et al. (2015b) performed a cross-sectional study in employees of a power-supply company in Guangdong, China. The aim was to assess markers of oxidative stress in workers exposed to ELF-MF. 700 workers were recruited of which persons with past or present illnesses, or family history of mental or cardiovascular illnesses were excluded. In total, 610 workers were included in the study and were allocated into an exposed or unexposed group, depending on their occupational history. 310 workers regularly performed inspections of transformers and power lines and were classified as exposed, whereas 300 persons working as administrative or logistical staff were allocated to the unexposed group. Blood samples of workers were taken approximately at the same time of day after a working shift. Six different measures of oxidative stress were evaluated: Plasma total antioxidant capacity, Glutathione peroxidase activity, Superoxide dismutase, plasma malondialdehyde concentration, micronucleus cell frequency and micronuclei frequency. ELF-MF measurements were performed with a PMM8053A meter for 2 minutes at multiple spots where exposed workers do their inspection tours, and at 200 additional spots where unexposed workers would be present. 8-hour time-weighted averages (TWA) were calculated based on reported activity logs and exposed subjects were grouped into low (<1.6 μ T, n=92), medium (1.6–7.3 μ T, n=113) or high (>7.3 μ T, n=75) TWA, and in addition into workers who had been exposed for 1–4 or 5 or more years. Oxidative stress parameters

were compared between groups unadjusted for potential confounders using ANOVA or Poisson U-tests. In a sensitivity analysis, analyses were repeated stratified by sex. No differences across groups emerged from any of the analyses.

Strengths of the study include the relatively large study group, the standardised assessment of the blood parameters and the quantitative evaluation of the exposure. A weakness of the study is that it remains unclear how many people were excluded from which groups and for which reason. In particular, the exclusion criterion of “any past or present illness” is rather vague and it is unclear at which stage of the analysis these 90 persons were excluded. Not adjusting for potential confounders is certainly a major shortcoming of the study. All in all, however, the study does not provide evidence of differences in oxidative stress among workers exposed to different levels of magnetic fields. Of note, the study authors reported affiliation with and funding by the electric power research institute Guangdong Power Grid Corporation, but state clearly that they had no conflicts of interest.

A small study on DNA damage was performed in Italy by Villarini et al. (2015), including 21 ELF-MF-exposed welders and 21 unexposed workers, matched on age, sex, residence and smoking habit. In the study, the ELF-MF-exposed workers were electric arc welders, ELF-MF exposure was measured during one whole shift. It was not reported what kind of occupations the unexposed workers had or if they were recruited within the same companies. Blood samples from welders were collected after the end of the work shift after at least four consecutive working days, but it was not reported when unexposed workers were asked to provide the blood samples. DNA damage was evaluated with a comet assay, evaluating tail length, intensity and moment. Statistically significant differences between the groups were found for tail intensity and moment, but not for length. With the incomplete reporting regarding characteristics of the controls, it is unclear if the identified differences could have resulted from other underlying differences between the groups. In addition, welders are exposed not just to ELF-MF but also to welding fumes. Given that welding fumes were not investigated, it cannot be disentangled if they could be underlying the observed effects.

2.4.6. Conclusions on ELF epidemiological studies

New studies on ELF-MF exposure and childhood leukaemia were small and thus do not alter the current interpretation on this subject. In adult cancer studies, no indication for a risk increase was seen in a large cohort study investigating use of electric blankets in relation to thyroid cancer and also not in a large study on occupational ELF-MF exposure and acute myeloid leukaemia. For ALS, a large population-based Swedish study suggested that electric shocks, but not ELF-MF exposure, may be a risk factor for the working population less than 65 years. This is in contrast to studies that appeared last year that suggested it may be the other way around. This question therefore remains as yet unresolved. For non-vascular dementia, a Dutch study provided some indications for an association with ELF-MF exposure. Only few observational studies addressing ELF-MF exposure and symptoms have been published during the last decade and correspondingly, study results are scarce. A large cross-sectional survey found some associations with self-reported exposure to electrical devices. The limitation for the interpretation of this finding is that both outcome and exposure are reported by the same person.

3. Intermediate frequency (IF) fields

Despite increasing use of intermediate frequency magnetic field (IF-MF) emitting sources such as induction cooking and anti-theft devices used in shops, scientific evaluation of potential health risks is scarce. For some of these sources, exposure assessment, especially of induced internal (electric) fields, remains challenging.

3.1. Cell studies

Only one study on the possible effects of IF on mammalian cell cultures was found in the period of interest and is described below and reported in Table 3.1. One more paper was recognized but is not reported due to the lack of sham-exposed controls (Yadegari-Dehkordi et al., 2015).

Koyama et al. (2014) evaluated the potential of a 23 kHz magnetic field of 2 mT for 2, 3, or 4 h to alter the immune response of neutrophil-like differentiated human HL-60 cells. The results of three independent experiments for each condition tested indicated that exposure to a 23 kHz IF magnetic field has no or very little effect on chemotaxis and phagocytic activity.

Table 3.1 *In vitro* studies on IF-EMF

Cell type	Endpoint	Exposure conditions IF	Effect	Reference
Human neutrophil-like differentiated (HL-60) cells	chemotaxis and phagocytosis	23 KHz 2 mT 2, 3, 4 h	No effect	Koyama et al (2014)

3.2. Animal studies

During this reporting period four papers were identified, of which one (Win-Shwe et al., 2015) was a follow-up study to an experiment (Win-Shwe et al., 2013) covered in a previous Council report (SSM 2014). Especially the Japanese studies address the increasing popularity of induction heating (IH) cooking in Japan and Europe.

Ushiyama et al. (2014) explored in rats the effects of 21 kHz sinusoidal MF on standard toxicological parameters complemented by several parameters of immune function. 35 male Sprague-Dawley rats (4–5 weeks old) were split into three groups: Cage-control (CC, n=11), sham (n=12), and 3.8 mT (rms) MF at 21 kHz (n=12) exposure groups. In an acrylic holder restrained animals were exposed for 1 h/day for 14 consecutive days. On day 15 the respective parameters in blood were analyzed. Immunological functions (cytotoxic activity of lymphocytes, chemotactic and phagocytic activity of granulocytes, and CD4⁺ and CD8⁺-T cell frequency were also examined. Body weight, body weight gain, general clinical and hematological parameters as well as immunotoxicity parameters (cytotoxic and phagocytic activity, populations of T cells) were not affected by IF-MF exposure. The significant difference in inorganic phosphorus level between sham and exposure group was still within physiological range. Compared to CC, the lower plasma amyl-

ase activity and lower glucose level in both sham and exposure group was attributed to the restrained stress, not to IF-MF. In their precisely described study, the authors discussed the importance to calculate the induced electric fields for risk assessment, in this study 4.7 V/m for rats at 3.8 mT. This value was only 1.74-fold higher than the ICNIRP “basic restriction value for human exposure to time-varying electric and magnetic fields”. Overall, exposure to 21 kHz sinusoidal IF-MF at 3.8 mT for 1 h/day for 14 days did not affect immune function and clinical pathology parameters in juvenile rats.

Using the same exposure system, [Win-Shwe et al. \(2015\)](#) investigated IF-MF effects during development on neurological and immunological markers in the hippocampus in 3- and 7-week-old male C57BL/6J mice. Pregnant C57BL/6J mice were exposed to IF-MF (21 kHz, 3.8 mT), 1 h/d from day 7 to 17 p.c., i.e. during organogenesis. One control, one sham and one exposure group were used. From six males each, hippocampal samples were obtained on postnatal day (PND) 21. Further groups of six male mice each were treated as follows: (1) control-control (CC), (2) sham-control (SC; sham exposure during organogenesis and control till PND 48), (3) exposure-sham (ES; IF-MF exposure during organogenesis and sham exposure PND 27–48), (4) exposure-exposure (EE; IF-MF exposure during both developmental periods (day 7-17 p.c. & PND 27–48)), and (5) exposure-exposure (ER; same IF-MF exposures as for group 4 but with 1 day recovery). In groups 1) – 4), one hour and in group 5) 24 hours after the last exposure, the mice were sacrificed under deep pentobarbital anesthesia. Using RT-PCR, the expression of mRNA in the hippocampi was examined and microglia activation was studied by immunohistochemical analysis. In these 7 weeks-old IF-MF-exposed mice, the expression levels of the NMDA receptor subunits NR1 and NR2B and the transcription factors (CaMKIV, CREB1), inflammatory mediators (COX2, IL-1 b, TNF- α), and the oxidative stress marker heme-oxygenase (HO)-1 were significantly increased. The expression of the neurotrophins NGF and BDNF did not differ between groups 2-5, but little (not significantly) lower than CC (group 1). According to the authors, the 3-week-old mice did not show this effect (data not presented). Finally, the evaluation of n=2 males per group revealed no difference in microglia activation between groups 1-5.

Summarizing, there are several weaknesses in the study description such as: data on body and organ weights, and on above mentioned mRNA expression levels in the 3-weeks old mice not presented; n=6 males/group from how many dams? (potential litter effect), n=2 out of 6 (?) mice for immunohistochemistry, etc. Therefore the authors conclusion “This study provides the first evidence that early exposure to IF-MF reversibly affects the NMDA receptor, its related signaling pathways, and inflammatory mediators in the hippocampus of young adult mice; these changes are transient and recover after termination of exposure without histopathological changes.” cannot be fully proven.

[Nishimura et al. \(2015\)](#) exposed Sprague Dawley rats (12 per sex per group) to 20 kHz, 0.20 mT (root mean square, rms) or 60 kHz, 0.10 mT (rms) sinusoidal MFs, 22 h/day for 14 days or 13 weeks. Controls were sham-exposed and the experiments were duplicated for each frequency. All examinations after necropsy were blinded and performed under GLP conditions. All rats survived. Throughout the experiments clinical health and body weight developments were within normal limits. Significant differences between MF-exposed and controls in some organ weights and parameters in hematology and clinical chemistry were not repeated in the duplicate experiments. Incidences of histopathological findings reflecting toxicity were sporadic, too. With all the detailed data of a “classical toxicity study”, the authors’ conclusion that the sporadic findings are biologically non-

relevant and should be interpreted as an absence of toxicity in IF-MF-exposed rats is supported.

Lee and Yang (2014) addressed the lack of information regarding the health risk of MFs to aquatic organisms. They used Medaka embryos (*Oryzias latipes*) for studying developmental toxicity *in vivo* due to their optical transparency. Furthermore, the researchers utilized the “light versus dark preference test” (white preference test) for testing behavioural consequences of MF-induced developmental toxicity. Medaka embryos were randomly assigned to four groups that were exposed continuously until hatching to 3.2 kHz of 0.12 (n=27), 15 (n=17), 25 (n=16), or 60 μ T (n=16) IF-MF, respectively. The 0.12 μ T group served as the background control. Images for analysis of several developmental endpoints were taken over all 3 days post fertilization. Number of somites, eye width and length, eye pigmentation density, midbrain width, head growth, and the day to hatching demonstrated faster embryonic development in all three levels (15, 25, or 60 μ T) of IF-MF exposure. Finally, applying the white preference test 4 days after hatch, the hatchlings of the 60 μ T group exhibited significantly higher levels of anxiety-like behaviour as compared to the other groups. Using low MFs and this (new) *in vivo* model, obviously there is a need for a scientific discussion on uncertainties and contradictions to other studies testing developmental effects of (mostly) EL- MFs.

3.3. Human studies

No studies identified.

3.4. Epidemiological studies

No studies identified.

4. Radiofrequency (RF) fields

4.1. Cell studies

Fifteen studies on the possible effects of RF exposure on mammalian cell cultures have been recognized in the period of interest. Among them, eight papers are not presented due to the lack of sham-exposed controls or dosimetry. Therefore, in this section the results of six cell studies are reported (Table 4.1). Apoptosis was the parameter most investigated, but other endpoints have been also examined.

Primary murine Bone marrow Mesenchymal stem cells (BM-MSCs) derived from three male C57BL/6 mice were employed by Wang et al. (2015b) to investigate apoptosis, cell proliferation and cell cycle following pulsed 2.856 GHz RF exposure, SAR=4 W/kg. For each mouse, three cultures were set up: sham-exposed, RF-EMF-exposed and positive control (2.0 Gy γ -ray). The RF pulses were delivered for 6 min at 50 pulses per second, with a pulse width of 500 ns. Apoptosis was assayed 6 hours after the exposure, by flow cytometric technique (Annexin V-PI staining). Cell proliferation was measured 1, 2, 4 and 6 days after the exposure, by means of the MTT assay, while cell cycle progression was assayed 6 hours after the exposure, by flow cytometric technique (PI). Temperature monitoring indicated that RF exposure had no effect on culture temperature. The experiments were carried out blinded. By comparing sham-exposed and RF-exposed samples, no significant differences were detected for all the parameters investigated. Treatment with γ -ray resulted in a significant increase in apoptosis, a significant decrease in cell proliferation and an accumulation of cells in G2 and S phases of the cell cycle, as expected.

Mouse embryonic fibroblasts (NIH/3T3) were employed by Hou et al. (2015) to investigate the induction of apoptosis, oxidative stress and DNA damage after exposure to 1800 MHz RF-EMF, GSM-talk mode, (average SAR = 2 W/kg). The exposure varied from 0.5 to 8 h (5 min on/10 min off cycles) and was carried out in blind conditions. The results of three independent experiments showed that the percentage of late-apoptotic cells was significantly higher in samples exposed for 1, 4 or 8 h than in the respective sham-exposed groups ($p < 0.05$), as assessed by flow cytometry (Annexin-V-FITC-PI method). Exposure duration of 0.5, 2 and 6 h did not induce such an increase. Intracellular ROS levels, measured by fluorescence microscopy and by flow cytometry (DCFH-DA assay) showed a significant increase in cultures exposed for 1, 4 and 8 h ($p < 0.05$), compared to sham-exposed controls. Exposure duration of 0.5, 1.5, 2 and 6 h did not induce such an increase. Gamma foci formation, as a measurement of DNA damage, was not affected after 2, 4, 6 or 8 h RF exposure.

Neural cell apoptosis induced by RF-EMF exposure at a frequency of 2.856 GHz was investigated by Zuo and co-workers (Zuo et al., 2014). Differentiated PC12 cells were exposed for 5 min in a rectangular waveguide. The temperature of the cell cultures was monitored and the highest temperature increase was less than 0.5 °C during the exposure period. PE was measured by ANNEXIN-V/PI assay after exposure at an average power density ranging from 10 to 100 mW/cm². In three independent experiments, apoptosis resulted in a significant increase at 6 h after 30 ($p < 0.01$), 50 ($p < 0.05$) and 100 mW/cm² ($p < 0.01$), but no significant difference was seen in 10 mW/cm² exposed cultures with respect to sham controls. Moreover, the time course of radiation-induced apoptosis showed that 6 h was the peak time of apoptosis after exposure. To confirm the observed

effect, several parameters strictly related to apoptosis were investigated at 30 mW/cm². The exposure induced chromatin condensation and apoptotic body formation (Hoechst 33342 staining), increased DNA fragmentation (TUNEL staining; $p < 0.01$), depolarization of mitochondria membrane (JC-1; $p < 0.01$), increased expression of Bax, cytochrome-C, cleaved Caspase-3 and PARP, decreased expression of Bcl-2. Moreover, the activity of caspase 3 increased significantly ($p < 0.01$). The treatment with DEVD, a caspase 3 inhibitor, significantly inhibited the increase of cleaved PARP and caspase 3 activity ($p < 0.05$). All the biological assays were carried out blinded. Such results indicated that the experimental conditions adopted were able to induce apoptosis in neural cells that is via mitochondrial-dependent caspase-3 pathway.

To investigate activation of microglia and astrocytes, Lu et al. (2014) exposed mouse microglial N9 cells and astroglial C8-D1A cells to intermittent (5 min on, 10 min off) 1800 MHz GSM-modulated RF-EMF for 1 to 24 h at a SAR of 2.0 W/kg. Temperature monitoring indicated culture temperatures of $37 \pm 0.2^\circ\text{C}$ during RF-EMF exposure. The results of three independent experiments carried out blinded showed increased transcript expression of the pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α in microglia and increased expression of IL-6 in astrocytes at 6-24 h after RF EMF exposure ($p < 0.05$). Corresponding changes in the protein levels of these cytokines were also measured in the supernatants of the RF-EMF-exposed cultures. The authors also observed an increased expression of iNOS protein levels in microglia and COX2 in astrocytes at 3-24 h following RF-EMF exposure. Phosphorylated STAT3 protein levels and DNA-binding activity were both increased in microglia cells at 3-24 h following RF-EMF exposure relative to the sham control group. Pre-treatment with Stattic (a STAT3 inhibitor) attenuated the RF-EMF-induced increase in cytokine release and p-STAT3 protein expression in microglial cells, but not astrocytes. The authors concluded that RF-EMF differentially induced pro-inflammatory responses in microglia but not astrocytes and involved differential activation of STAT3 in microglia and astrocytes. Lipopolysaccharide was used as a positive control for cytokine expression.

Duan et al. (2015) investigated the induction of genotoxic effects by 1800 MHz RF-EMF on a mouse spermatocyte-derived GC-2 cell line, and compared the results with those obtained on cultures exposed to 50 Hz ELF-EMF (see section 2.1). Cell cultures were exposed to 1800 MHz RF-EMF in GSM-Talk mode (SAR of 1, 2 or 4 W/kg). After 24 h of intermittent exposure (5 min on and 10 min off) the alkaline comet assay and immunofluorescence against c-H2AX foci were applied to evaluate the induction of DNA strand breaks. Moreover, the FPG-modified comet assay, suitable for oxidative DNA base damage evaluation, was also employed. By comparing exposed and sham-exposed cultures, no effect was detected in terms of both comets (3 independent experiments) and foci formation (4 independent experiments). On the contrary, the FPG-modified comet assay revealed a statistically significant increase in DNA fragmentation ($p < 0.05$) when 4 W/kg SAR was tested, suggesting oxidative DNA base damage. Cells treated with hydrogen peroxide and etoposide showed a significant increase in comet parameters and foci formation, respectively (positive controls).

Kumar et al. (2015) excised long bones (femur and tibia) from Sprague Dawley rats and exposed them at both 900 and 1800 MHz. In particular, 900 MHz exposure, continuous wave (CW), was 90 min long at 2 and 20 W/kg SAR, while 1800 MHz exposure, CW and pulse modulated (PM), was 120 min long at 2.5 and 12.4 W/kg SAR. To test the effect of 900 MHz, 24 rats were used to extract 48 long bones, randomly assigned to the following groups (12 bones per group): sham exposed, RF exposed at 2 W/kg, RF exposed at 10

W/kg and positive control (treatment with concanavalin-A, ConA). The effect of 1800 MHz was evaluated on 72 long bones from 36 rats. The following six groups were tested: sham exposed, CW at 2.5 W/kg, CW at 12.4 W/kg, PM at 2.5 W/kg PM at 12.4 W/kg and positive control (12 bones per group). Temperature measurements were performed at the beginning and at the end of each exposure period and a slight, not significant increase was recorded in exposed samples. After exposure, the lymphoblasts were extracted, cultured for 72 hours and assayed for proliferation rate, by means of the Trypan blue staining, and genotoxicity, by applying the alkaline comet assay. The results did not indicate any significant change in cell proliferation and DNA damage for all the experimental conditions tested, while treatments with ConA induced a significant increase in both parameters investigated, as expected.

Habauzit et al. (2014) exposed primary human keratinocytes to millimeter wave (60.4 GHz) RF-EMF for 3 h at an average incident power density of 20 mW/cm² (corresponding to an average SAR of 594 W/kg over the cell monolayer). Temperature monitoring identified a 6.7 °C increase (to 42.5 °C) in exposed cells, compared to sham controls. Microarray analysis identified 789 significantly differentially expressed genes with a fold change of 2 or greater. To determine whether these genes were altered by RF-EMF or by sample heating the authors repeated these experiments with culture temperatures similar to that of the sham control. In the latter case, no significant differences in gene expression were identified. RT PCR validated the heat shock positive control response and the RF-EMF induced heat shock response on a variety of heat shock and stress response protein transcripts.

4.1.1. Summary and conclusions on cell studies

The new *in vitro* studies confirm the previous Council conclusions: several endpoints have been investigated and in most cases no effect of the exposure was detected. Nevertheless, in some investigations, effects on parameters related to apoptosis have been reported, although transient. Several studies have been recognized but not considered due to the lack of sham-exposed samples, dosimetry, or temperature control.

The studies are summarized in the following tables:

Table 4.1a *In vitro* studies on RF-EMF

Cell type	Endpoint	Exposure conditions RF-EMF	Effect	Reference
Primary murine Bone marrow Mesenchymal stem cells (BM-MSCs)	Apoptosis, proliferation and cell cycle	2.856 GHz Pulsed 4 W/kg SAR 6 min.	No effect	Wang et al. (2015)
Mouse embryonic fibroblasts (NIH/3T3)	Apoptosis, oxidative stress and DNA damage	1800 MHz, GSM-talk mode 2 W/kg SAR 0.5 – 8 h (5 min on/10 min off cycles)	Increased apoptosis and ROS formation after 1, 4 and 8 h RF exposure; no effect after 0.5, 2 and 6 h. No effects on DNA damage.	Hou et al. (2015)
Differentiated Rat neuronal cells (PC12)	Apoptosis, oxidative stress, DNA damage	2856 MHz 10-100 mW/cm ² 5 min	No effect at 10 mW/cm ² . Increased apoptosis at 30, 50 and 100 mW/cm ² at 6h post RF-exposure. At 30 mW/cm ² alteration of all the parameters investigated.	Zuo et al. (2014)
Mouse microglial (N9) and astroglial (C8-D1A) cells	Protein and mRNA: variety of cytokine genes, iNOS, COX2 Phosphorylation: STAT3	1800 MHz, GSM 2 W/kg SAR 1-24 h (5 min on/10 min off) Co-treated with Stattic	Increased IL-1 β , iNOS (microglia) and IL-6, COX2 mRNA (astrocytes) Increased expression levels of p-STAT3 in microglia (3-24 h), attenuated by Stattic.	Lu et al. (2014)

Mouse male germ (GC-2) cells	DNA damage	1800 MHz, GSM-Talk 1, 2, 4 W/kg SAR 24 h (5 min on/10 min off)	No effect with comet assay, no H2AX foci formation; Increased DNA fragmentation with FPG-modified comet assay	Duan et al. (2015)
Rat bone marrow lymphocytes n=48 (900 MHz) n=72 (1800 MHz)	DNA damage, cell proliferation	900 MHz, CW SAR 2 and 20 W/kg 90 min 1800 MHz, CW and PM SAR 2.5 and 12.4 W/kg 120 min	No effect.	Kumar et al. (2015)
Primary human keratinocytes	mRNA	60.4 GHz 20 mW/cm ² (average SAR 594 W/kg over the cell monolayer)	All effects observed due to heating	Habauzit et al. (2014)

Abbreviations: COX2 - Cyclooxygenase-2; FPG - Formamidopyrimidine DNA-glycosylase; H2AX – Histone-family member; iNOS – inducible nitric oxide synthase; ROS – Reactive Oxygen Species; STAT – Signal transducer and activator of transcription.

Table 4.1b Excluded *in vitro* studies on RF-EMF and main reasons for exclusion

Reference	Reason for exclusion
Lee et al. (2014)	No sham controls
Kazemi et al. (2015)	No sham controls
Zuo et al. (2015)	High SAR level and no T° control during the exposure
He et al. (2014)	No dosimetry performed
Li et al. (2014c)	No dosimetry performed
Naziroglu et al. (2015)	No sham controls
Xiong et al. (2015)	No dosimetry performed
Zhu et al. (2014)	No dosimetry performed; no sham controls

4.2. Animal studies

In the period covered by this report, 33 animal studies on a variety of topics were identified. However, 13 of these had to be excluded, mainly because of inadequate or missing dosimetry. These studies are listed in table 4.2.

4.2.1. Brain and behavior

Deshmukh et al. (2015) exposed groups of 6 male 60-days old Fisher rats to 900 MHz RF fields at a whole-body SAR of 0.60 mW/kg, 1800 MHz fields at a SAR of 0.58 mW/kg or 2450 MHz fields at a SAR of 0.67 mW/kg, for 2 h/day, 5 days/week over a period of 180 days. At the end of the exposure period the memory of all rats was tested and the brains were removed and heat-shock protein (HSP) and DNA damage were assessed. Both learning and memory were impaired after the exposures, with no difference observed between the frequencies. This was also the case for spatial memory, with an increasing effect with increasing frequency, but differences between frequencies were not tested, only between each type of exposure and sham exposure. The same pattern was seen with an increase in HSP levels in the exposed groups: a significant difference from the sham-controls and an increasing trend with increasing frequency, but again this was not tested. DNA damage, assessed with the comet assay, was increased in all exposed groups, with more damage in the 1800 and 2450 MHz groups compared to the 900 MHz group.

Tang et al. (2015) exposed male Sprague Dawley rats to 900 MHz fields for 3 h/day during 14 or 28 days. The SAR in the brain was 2 W/kg and the whole-body SAR was 0.016 W/kg. At the end of the exposure periods, they tested in separate groups spatial memory (n=9), blood-brain barrier permeability (n=12), ultrastructure (n=3), expression of the stress-response protein heme oxygenase-1 (HO-1) using immunohistochemistry (n=6), and of two enzymes (mkp-1 and p-ERK/ERK) potentially involved in the regulation of HO-1 (n=6). In the group exposed for 28 days, spatial memory was impaired and there was obvious ultrastructural damage, which were not found in the sham- and 14-days-exposed groups. In both exposed groups there was an increased permeability of the blood-brain barrier, an increased expression of HO-1 and of mkp-1 and a decreased expression of p-ERK/ERK, with larger effects in the longer exposed group. These observations indicate a duration-dependent effect of the exposure on the brain and brain function, and suggest that this involves the stress-response protein HO-1 and the mkp-1/ERK pathway.

Zhang et al. (2015) exposed CD-1 mice during pregnancy day 3-18 for 12 h per day to a 9.417 GHz RF field with an intensity of 200 V/m. They provide an SAR level of 2 W/kg, but fail to indicate how this was determined. Five weeks after birth, the offspring was tested in groups of 8–12 for behaviour. Mice that were exposed during pregnancy showed increased anxiety-related behaviour and decreased depression-related behaviour. Male mice also showed decreased learning and memory, but female mice did not.

Masuda et al. (2015b) implanted a closed cranial window in the skull of male Sprague Dawley rats (n=8–10 per group) in order to measure several inflammation-related micro-circulatory parameters in the cortex of the brain. They then exposed the animals to a 1437 MHz RF field at a SAR in the target area of 2 W/kg for 50 min. They did not observe any significant differences between exposed and sham-exposed groups in hemodynamics, plasma velocity, vessel diameter or leukocyte adhesion to endothelial cells in any microvessel, nor in permeability of the blood-brain barrier.

In a parallel study of the same group, Masuda et al. (2015a) implanted a closed cranial window in the skull of 4 or 8-week old male Sprague Dawley rats (n=9–13 per group) in order to measure blood-brain barrier permeability using fluorescent dye extravasation. No effects were found in either group, nor were any immunohistological changes observed. Jeong et al. (2015) exposed mice transgenic for a rapid development of amyloid β plaques, thus being a model for the development of Alzheimer's disease (AD). The female 1.5 month-old transgenic mice and their wild type counterparts were exposed in groups of 7–11 to 1950 MHz fields for 2 h/day, 5 days/week during 8 months. Although the whole-body SAR was 5 W/kg, the maximum increase in body temperature was only 0.5 °C. After the exposure, memory impairment in the exposed transgenic animals was decreased compared to that in the sham-exposed group. Histopathological analysis of the brains indicated that the development of amyloid β plaques and other, associated parameters was decreased in the exposed animals. No such changes were observed in wild type animals. The authors suggest that RF exposure might be beneficial since it slows down the development of AD.

Sahin et al. (2015) investigated the effect of 900 MHz RF exposure on hippocampal neurons in young Sprague Dawley rats. They exposed 8-week old male animals in groups of 6 for 1 h/day during 30 days at a power density of 0.49 W/m². They calculated a whole-body SAR of 0.024 W/kg, but the method cannot be verified. The number of pyramidal neurons in the cornu ammonis of the hippocampus was found to be lower in the exposed compared to the sham-exposed animals.

Dasdag et al. (2015b) exposed restrained adult male Wistar rats (7 per group) to a GSM 900 MHz signal for 3 h/day, 7 days per week during 12 months. The brain SAR_{10g} was 0.114 W/kg, the brain SAR_{1g} was 0.143 W/kg, and the WBA SAR was 0.0369 W/kg. After the last exposure the brains were removed and the levels of 5 different microRNAs were investigated. According to the authors, these are small non-protein-coding RNA molecules. They play critical roles in growth, differentiation, proliferation and cell death by suppressing one or more target genes. More than 50% of microRNAs are found in cancer-associated regions of the genome or in fragile sites; this suggests that microRNAs have important roles in the pathogenesis of neoplasia. They can act as key regulators in gene expression networks, can influence many biological processes and also show promise as biomarkers for disease. One of the microRNAs, mo-miR-107, was decreased, while the levels of the four other remained unchanged. Downregulation of this microRNA has been found in gliomas and other tumours, and with neurodegenerative diseases such as Alzheimer's.

In a parallel study of the same research group, Dasdag et al. (2015a) exposed restrained adult male Wistar rats (8 per group) to a 2.4 GHz Wi-Fi signal continuously during 12 months. The brain SAR_{10g} was 0.001030 mW/kg, and the WBA SAR was 0.000141 mW/kg. After the exposure the brains were removed and the levels of 5 different microRNAs were investigated. The expressions of two of the microRNAs were decreased: miR-106b-5p and miR-107, while the levels of the three others remained unchanged. Downregulation of miR-107 has been found with neurodegenerative diseases such as Alzheimer's, while that of miR-106b-5p has been found with several types of cancer and type-2 diabetes.

4.2.2. Genotoxicity, oxidative stress

Cao et al. (2015) investigated the circadian rhythm of the plasma concentrations of three antioxidants, melatonin, glutathione peroxidase and superoxide dismutase in 8 week-old male Sprague Dawley rats. The animals (6 per group) were exposed or sham exposed to a 1.8 GHz field for 2 h per day for 32 days, on different times of the day (3, 7, 11, 15, 19 and 23 h GMT) at a whole-body SAR of 0.05653 W/kg. There was a 12 h light-dark cycle, 7–19 and 19–7 h (GMT), respectively. After the last exposure, the plasma concentrations of the antioxidants were determined at six different time points over 21 h and the daily changes compared between exposed and sham-exposed groups (n=6 per group), making it a rather complicated study. The circadian rhythms of each of the three antioxidants were altered in some of the RF-exposed groups compared to sham-exposed animals. For melatonin a decrease was observed in the amplitude of the groups treated at 15 and 23 h GMT. In these and other groups there were also shifts in the rhythm, but no results of statistical testing of these were provided. In the groups exposed at 3 and 23 h GMT the levels of melatonin were lower than in the sham-exposed group over the entire period. For glutathione peroxidase, the amplitude was decreased in the groups exposed at 3, 7 and 23 h GMT. In all but the 23 h GMT group a shift in rhythm is seen, but again no results of statistical testing of these were provided. For superoxide dismutase the amplitude was decreased at 3, 11, 19 and 23 h GMT (also at 7 h GMT, but this seems not correct). A shift in rhythm is seen at 7, 11, 15, 19 and 23 h GMT, again without results of statistical testing. In the groups exposed at 3, 11, 19 and 23 h GMT the levels of superoxide dismutase were lower than in the sham-exposed group over the entire period, taking into account the rhythm shift. The presented data show effects of the exposure on all three antioxidants, but the analysis of the data could have been better.

Zong et al. (2015) exposed 12–14 week old male ICR mice (8 per group) to 900 MHz RF fields for 4 h/day during 7 days at an SAR of 0.05 W/kg. The animals were either killed immediately after the last exposure or treated with bleomycin 4 h later and killed after 20 min. In blood leukocytes primary DNA damage and bleomycin-induced damage as well as its repair kinetics were determined, while oxidative damage was assessed by measuring levels of malondialdehyde and superoxide dismutase in plasma, liver and lung tissue. No effects were observed in animals treated with RF alone. Bleomycin resulted in increased DNA damage in leukocytes. This was mitigated by preceding RF exposure and the difference was maintained during the repair of the damage in the 2 h following bleomycin treatment. Bleomycin also resulted in increased malondialdehyde and superoxide dismutase in plasma, liver and lung. Preceding RF treatment reduced the malondialdehyde level in liver and that of superoxide dismutase in lung.

Bodera et al. (2015) exposed male Wistar rats in groups of 8 to 1800 MHz RF fields for 15 min per day during 5 days at a SAR varying from 0.024-0.028 W/kg. In half of the groups, an inflammation in a paw was generated by injection of complete Freund's adjuvant. Each arm of the study included a sham-exposed group, a group treated with EMF only, a sham-exposed group treated with the painkiller tramadol and a group treated with EMF and tramadol. After the treatment, the level of malondialdehyde as the end-product of the lipid peroxidation was assessed in blood, liver, kidneys and brain. In both healthy animals and in those with inflammation, no effects of EMF alone on malondialdehyde were observed in liver and kidney, while in blood and brain the levels were increased. The effects of the combined EMF/tramadol treatment were assessed against the sham controls. This should have been done, however, against the sham+tramadol group, so the effect of EMF in the tramadol-treated groups cannot be evaluated. The study shows an

indication for an effect of EMF exposure on lipid peroxidation in blood and brain, but not in liver and kidney.

4.2.3. Cancer

Lerchl et al. (2015) performed a replication of the study by Tillmann et al. (2010) that found an increased incidence of ENU-induced liver tumours when the animals were exposed to RF fields. Also in the current study, ENU was administered to pregnant mice, which were subsequently exposed to a UMTS signal for 23.5 h per day during the entire pregnancy, and the offspring continued to be exposed up to a total exposure period of 72 weeks. Exposure levels were WBA SARs of 0.04, 0.4 and 2 W/kg and 96 animals per group were used. They observed an increased incidence of bronchoalveolar and hepatic tumours and lymphomas, without an exposure-reponse pattern, however. Bronchoalveolar carcinomas and lymphomas were only increased with 0.4 W/kg, while bronchoalveolar adenomas were more increased with 0.04 and 0.4 W/kg than with 2 W/kg.

4.2.4. Fertility

Odaci and Ozyilmaz (2015) exposed 6-8 week-old male Wistar rats (8 per group) to a 900 MHz RF field for 1 h per day during 30 days. The whole-body SAR was 0.025 W/kg. After the last exposure, the testes were removed. The right testicles were histologically analysed and the left ones were used for assessment of catalase, superoxide dismutase, malondialdehyde and glutathione. A decrease in seminiferous tubule diameter and epithelium thickness was observed, as well as an increase in apoptotic cells. Compared to sham-exposed animals the malondialdehyde, superoxide dismutase and catalase levels were increased, while no effect was observed on glutathione. This gives some indication of increased oxidative stress.

4.2.5. Physiology

Fasseas et al. (2015) exposed wild-type and aging- or stress-sensitive mutant *Caenorhabditis elegans* worms to signals from an 1800 MHz GSM mobile phone (E-field 5.53 V/m), a 2400 MHz Wi-Fi router (E-field 2.1 V/m) and a 1900 MHz wireless DECT phone (E-field 3.75 V/m) and checked for effects on growth, fertility, lifespan, chemotaxis, short-term memory, oxidative stress and apoptosis. Exposure to the GSM signal was for 30 min, 1 or 3 h and to the other two sources for 30 min, 1, 3, 6 or 24 h. No effects were observed on any of the parameters investigated in any of the worm strains. The number of worms exposed per group is not provided.

Cheng et al. (2015) exposed groups of 6 male Sprague Dawley rats aged 6 weeks to pulsed electromagnetic fields at 100 kV/m for 10^4 , 10^5 or 3×10^5 pulses, presumably at 250 MHz (they provide no frequency, but refer to a paper of Minamitani et al. (2007)). They sacrificed the animals after 12, 24, 48 or 96 hours and examined the hypophysis for ultrastructural damage and for expression of heat shock protein 70 (HSP70). At the light microscopic level, no damage was observed, but ultrastructural damage was seen at 12 h after exposure. This damage increased with increasing number of pulses and with increasing time after exposure. HSP70 expression was investigated in the group that received 3×10^5 pulses. It was found to be significantly increased at 12 h following exposure; thereaf-

ter it gradually decreased again, but was still higher than in the sham-exposed group at 96 h after exposure.

4.2.6. Immunology

Ohtani et al. (2015) exposed Sprague Dawley rats during pregnancy (n=12) and after birth (4 pups per dam) for 20 h/day during 63 consecutive days from the start of pregnancy. The RF was a 2.14 GHz W-CDMA signal and the whole-body SAR in both the pregnant dams and the pups after birth was set at 0.2 W/kg. No changes were observed in the numbers of CD4/CD8 T cells, activated T cells or regulatory T cells among peripheral blood cells, splenocytes and thymocytes. Expression levels of 16 genes associated with the Th1/Th2 balance were analyzed in spleen and thymus tissue. Three genes, Il4, Il5 and Il23a, were upregulated in the thymus, but no increased expression of the IL-4 protein was observed. The authors conclude that no adverse effects of long-term RF-EMF exposure on immune function was observed.

4.2.7. Summary and conclusions on animal studies

The newest animal studies on the effects of exposure to RF fields again show some indications for an increase in oxidative stress, even with exposure to a SAR as low as 25 mW/kg, but the findings are not consistent. Increased oxidative stress might lead to health effects, for instance by increasing DNA damage, which may lead to a higher risk of cancer. One study found effects, including increased DNA damage, in brain tissue after exposure to SARs as low as 0.58 mW/kg. This is an extremely low exposure level and in order to verify these findings, the study should be replicated. The replication of a study that found an increased risk of cancer led to similar results, but these were inconsistent in that they did not show an increased risk with increasing exposure level. A concern regarding the study design is that the very specific experimental conditions cannot be extrapolated to human exposures.

Unfortunately, as in previous years, a number of studies had to be excluded from the analysis. Most of them provided no or incomplete dosimetric information, or failed to include a sham-exposed group of animals. Without dosimetric information any effects cannot be related to an exposure level and without a sham-exposed group it is not possible to attribute any effects to the actual EMF exposure. Studies lacking this information are a waste of money and effort and should not have passed the peer-review system.

The studies are summarized in the following tables:

Table 4.2a Animal studies on RF-EMF

Endpoint	Authors	Frequency	Exposure	Effect
Rodents studies				
Brain and behaviour	Deshmukh et al. (2015)	900, 1800, 2450 MHz	WBA SAR 0.60, 0.58, 0.67 mW/kg	Impaired learning, memory. Increased brain HSP. Increased brain DNA damage
	Tang et al. (2015)	900 MHz	Brain SAR 2 W/kg, WBA SAR 0.016 W/kg	Impaired memory. Increased BBB permeability. Increased stress-response protein
	Zhang et al. (2015)	9.417 GHz	200 V/m (SAR 2 W/kg)	Increased anxiety, decreased depression, decreased learning, memory (males)
	Masuda et al. (2015a)	1437 MHz	SAR 2 W/kg	No effect hemodynamics, plasma velocity, vessel diameter, leukocyte adhesion, BBB
	Masuda et al. (2015b)	1437 MHz	SAR 2 W/kg	No effect BBB, immunohistology
	Jeong et al. (2015)	1950 MHz	WBA SAR 5 W/kg	Increased memory Alzheimer mice, decreased plaques; no effect wildtype
	Şahin et al. (2015)	900 MHz	PD 0.49 W/m ² (WBA SAR 0.025 W/kg)	Decreased pyramidal neurons hippocampus
	Daşdağ et al. (2015a)	900 MHz	Brain SAR _{10g} 0.114 W/kg	Decreased miR-107, no effect 4 other mRNAs
	Daşdağ et al. (2015b)	2.4 GHz WiFi	Brain SAR _{10g} 0.001030 mW/kg	Decreased miR-106b-5p and miR-107, no effect 3 other mRNAs

Genotoxicity, oxidative stress	Cao et al. (2015)	1.8 GHz	WBA SAR 0.05653 W/kg	circadian rhythms of three antioxi- dants altered in some exposed groups
	Zong et al. (2015)	900 MHz	WBA SAR 0.05 W/kg	Decrease bleomy- cin-induced DNA damage leuko- cytes; no effect RF alone.
	Kumar et al. (2015)	900, 1800 MHz	WBA SAR 2, 10 (900 MHz), 2.5, 12.4 (1800 MHz) W/kg	No effect geno- toxicity and pro- liferation lympho- blasts from bones
	Bodera et al. (2015)	1800 MHz	WBA SAR 0.024-0.028 W/kg	Increased lipid peroxidation in blood and brain, not in liver and kidney
Cancer	Lerchl et al. (2015)	2100 MHz UMTS	WBA SAR 0.04, 0.4, 2 W/kg	Increased inci- dence ENU- induced lung and liver tumours and lymphomas; no dose response
Fertility	Odacı & Özyılmaz (2015)	900 MHz	WBA SAR 0.025 W/kg	Degradation of testicular tissue. Increased oxida- tive stress.
Physiology	Cheng et al. (2015)	Pulsed 250 MHz	100 kV/m	Increased ultra- structural damage hypophysis. In- creased HSP70 expression hy- pophysis.
Immunology	Ohtani et al. (2015)	2.14 GHz W- CDMA	WBA SAR 0.2 W/kg	No changes in CD4/CD8 T cells, activated T cells or regulatory T cells. Il4, Il5 and Il23a, upregulated in thymus, no increased expres- sion of IL-4 pro- tein.

Non-mammalian animals				
Physiology (flatworm)	Fasseas et al. (2015)	1800 MHz GSM, 2400 MHz Wi-Fi, 1900 MHz DECT phone	E field 2.1-5.53 V/m	No effect growth, fertility, lifespan, chemotaxis, short-term memory, oxidative stress, apoptosis

Table 4.2b Excluded animal studies on RF-EMF and main reasons for exclusion

Reference	Reason for exclusion
Narayanan et al. (2015)	Incomplete dosimetry.
Salunke et al. (2015)	Incomplete dosimetry; exposure level not provided.
Ozgun et al. (2015)	Exposure not determined.
Hanci et al. (2015)	No sham-exposed group.
Shokri et al. (2015)	Exposure level not provided.
Sehitoglu et al. (2015)	Exposure level not provided.
Bakacak et al. (2015)	Assesment of SAR level not provided.
Aydogan et al. (2015a)	No sham-exposed group.
Aydogan et al. (2015b)	No sham-exposed group.
Sieron-Stoltny et al. (2015)	Inadequate exposure system; incomplete dosimetry.
Eris et al. (2015)	Exposure level not provided.
Rafati et al. (2015)	No information on frequency, type of signal and exposure level.
Mortazavi et al. (2015)	Exposure level not provided.

4.3. Human studies

Since the last Council report six human provocation studies were published with waking EEG (two), sleep EEG (one), cognition (one), and physiological parameters (one) as outcomes. One study looked at a cognitive performance and physiological parameters in subjects with idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) and non-IEI-EMF controls.

4.3.1. Sleep EEG

In a study which aimed to investigate inter-individual variability and intra-individual stability of EMF effects, Lustenberger et al. (2015) analysed exposure effects on the power of all-night NREM sleep EEG in 20 young male subjects (mean \pm SEM: 23.3 \pm 0.5 years). Participants were exposed twice for 30 min prior to sleep with exposure sessions two weeks apart. Each session consisted of a sham (SH) and field (FD) exposure. In a randomized, double-blind crossover design subjects had one of the two condition orders: SH1 - FD1 - SH2 - FD2 or FD1 - SH1 - FD2 - SH2. The 900 MHz exposure (modulated at 2 Hz) with a peak spatial SAR_{10g} of 2 W/kg was delivered by a planar patch antenna.

The lateral cortex was exposed to a peak spatial SAR value averaged over 1 g of tissue (psSAR_{1g}) of up to 2.12 W/kg \pm 12%, the corresponding 0.62 W/kg \pm 35% of the thalamus indicates limited RF penetration depth of 900 MHz. EEG was recorded at 128 sites with a high density EEG cap. The power spectrum was analysed with regard to the spindle frequency range (13.75-15.25 Hz) and the delta-theta frequency range (1.25-9Hz), which have been shown to be affected in previous studies by the same working group. There was no exposure effect on sleep variables. Exposure led to an increase of the power in the delta-theta frequency range in several fronto-central electrodes, however, when controlling for multiple testing there was no significant cluster of electrodes. In this study no effects of exposure on the EEG in the spindle frequency range was observed. The observed effects were not reproducible within subject, i.e. effects which were seen in the first night of exposure were not seen in the second night of exposure. These authors claim that their results do not provide any evidence that some subjects were more susceptible/sensitive to the specific RF-EMF exposure used in their study and that it remains unclear whether a biological trait exists that predicts how subjects' brains would react to EMF exposure. Furthermore there was no exposure effect on subjective sleep quality and mood in the morning.

4.3.2. Waking-EEG

Given that previous research has repeatedly, but not consistently shown that radiofrequency, electromagnetic fields influence the resting state alpha activity (8–12 Hz) of the waking EEG Ghosn et al. (2015) studied this hypothesis in 26 healthy young subjects (23.5 \pm 3.1 years; 13 females and 13 males) in an eyes-open and an eyes-closed condition. Participants were carefully selected to minimize variability introduced by heterogeneity of the sample, e.g. by handedness or smoking. Furthermore, all females were studied in the follicular phase of their menstrual cycle to avoid any interference with the EEG. Real (2 W peak power, 250 mW average, SAR_{10g}: 0.49 W/kg) and sham exposure were delivered by a commercial mobile phone in a double-blind, counterbalanced cross-over design in sessions one week apart. The study also considered factors that are known to influence the alpha activity (salivary cortisol, caffeine and electrode impedance) and heart rate. EEG was recorded at 29 electrodes. This methodologically sound study, in which a possible interference with between exposure and EEG recording was also considered, showed that during real exposure alpha activity was significantly lower in the closed eyes condition (in all but 3 electrodes). This effect persisted during the post-exposure assessment. There were no differences in salivary cortisol and caffeine as well as in heart rate. Also the electrode impedances were not different between exposure conditions. Unfortunately the authors do not communicate their results concerning the eyes-open condition. One might speculate that the differences were not present in the eyes-open condition. Differences in the recording situation (eyes-open vs eyes-closed) might explain some of the inconsistencies observed in earlier studies on the resting state waking EEG.

Eggert et al. (2015) investigated effects of two levels of TETRA (385 MHz) exposure (maximum SAR_{10g} in the head 1.5 W/kg and 6.0 W/kg) as compared to sham in 30 healthy young male subjects (18 - 30 years), who were potential users of the TETRA communication standard on slow cortical potentials (SCPs). In this randomized, double-blind cross-over study exposure was delivered by a body-worn antenna, which was especially designed for this study, positioned at the left side of the head and mimicking the use of a TETRA portable communication device. Details concerning exposure are published separately by Schmid et al. (2012). Subjects had altogether nine test sessions (three per exposure condition) in which three SCPs were assessed: clock monitoring task

(CMT), contingent negative variation (CNV) and Bereitschaftspotential (BP). For CMT and CNV related performance parameters were assessed. The results indicate that there were neither exposure-related differences in the slow cortical potentials nor in the related performance parameters.

4.3.3. Cognitive functions and symptoms

In the same study, effects of TETRA exposure on divided attention, selective attention, vigilance and working memory as well as on mood, well-being and somatic complaints were analysed (Sauter et al., 2015) (25.4 ± 3.1 years). Working memory was assessed in a 0-back, 1-back, 2-back and 3-back task. Mood, well-being, subjective somatic complaints, divided and selective attention, as well as working memory in the 0-back and 3-back task were not affected by TETRA exposure. In the vigilance task lower reaction times, e.g. faster reactions, were observed for both exposure levels as compared to sham. Inconsistent effects have been observed for the 1-back and 2-back working memory tests. While mean reaction times were higher under both exposures in the 1-back condition they were lower in the 2-back condition. Furthermore, the number of correct reactions was higher under 1.5 W/kg exposure and lower in the 6 W/kg exposure condition as compared to sham. Overall, the results are not indicative of a negative impact of short-term TETRA exposure on cognitive functions and well-being in healthy young men.

Malek et al. (2015) investigated possible effects of a GSM and UMTS base station exposure (1 V/m) on cognitive performance in four tests: reaction time, rapid visual processing, paired associate learning and spatial span and on the physiological parameters body temperature, heart rate and blood pressure in 200 subjects (100 with IEI-EMF and 100 with no IEI-EMF). The authors state no exposure effects were observed in either group. The description of this single blind study is not detailed enough to contribute to the scientific discussion of RF-EMF effects.

4.3.4. Other outcomes

Soderqvist et al. (2015) investigated effects of a RF exposure delivered by a GSM test phone on biomarkers analysed in blood serum of 24 young subjects (12 females and 12 males, 18–30 years). The duration of exposure is not clear (30 min according to the abstract 60 min according to the text). Participants had three sessions at least one week apart. Three exposure conditions were assigned to the experimental days (SAR_{10g} : 2 W/kg, SAR_{10g} : 0.2 W/kg and sham) in a randomized crossover counterbalanced design. Blood samples were drawn at arrival, after 30 min of rest (these two samples were used for habituation), 60 min of rest, immediately after exposure and 60 min after the end of exposure. Three biomarkers were analysed: S100 β , which among others may be involved in the Ca^{2+} fluxes, transthyretin (TTR), which is a serum transport protein, and β -trace protein, an enzyme involved in the prostaglandin D2 synthesis. None of these three biomarkers was affected by RF exposure. This study leaves several open questions, e.g. the underlying mechanism for the exposure-independent changes in the concentration of the biomarkers, which might affect the experiment if not adequately controlled. Furthermore the study design was single-blind.

4.3.5. Summary and Conclusion on human studies

Consistent with previous studies the sleep study found an effect of the NREM-EEG power of the sleep-EEG. However, deviating from previous findings, the spindle frequency range was not affected. In this study effects were observed for the slow activity (delta and theta frequency ranges). In this study with 128 electrodes no significant cluster of electrodes could be observed when controlled for multiple testing. Furthermore effects could not be replicated within subjects. The waking EEG studies showed a decreased alpha activity in the resting state EEG-activity recorded with eyes closed and no effects on slow cortical potentials and related performance parameters. Except for vigilance in one study, cognitive performance was not affected and conflicting results have been observed in a working memory task. Effects on mood, well-being, somatic complaints, subjective sleep quality and physiological parameters, which were addressed in single studies, have not been observed.

4.4. Epidemiological studies

Regarding RF-EMF exposure, studies discussed in the previous report were in line with older studies. Uncertainty remained in relation to long term mobile phone use and brain tumours. Many studies showing associations between sperm quality and mobile phone use were of low quality and could not be used to evaluate a potential association with RF-EMF exposure. Several studies cross-sectionally observed associations between mobile phone use in adolescents and symptoms, but whether this was a causal association could not be derived from these studies.

4.4.1. Pregnancy outcomes

Based on data of approximately 100 000 singleton births from the Norwegian Mother and Child Cohort Study (1999–2009), Baste et al. (2015) investigated the effects of maternal mobile phone use during pregnancy and paternal mobile phone use prior to conception on the offspring. The cohort was linked to the Norwegian Medical Birth Register to obtain information about all singleton pregnancies. Studied reproductive health outcomes were congenital malformations, perinatal mortality, low birth weight, preterm birth, born small for gestational age and preeclampsia during pregnancy. Information about maternal mobile phone use was collected prospectively in week 15 and 30 of pregnancy by means of a written questionnaire (participation rate: 39%); paternal mobile phone use was inquired around week 15 only. Analyses adjusted for parity, maternal and paternal age, maternal smoking during pregnancy, and paternal smoking habits did not yield an association between maternal mobile phone use and adverse pregnancy outcomes except a slightly reduced risk for preeclampsia (RR=0.89; 95% CI 0.82–0.96 for medium exposure and RR=0.89; 95% CI 0.80–0.98 for high exposure). Regarding paternal mobile phone use, two associations were identified although not consistently so: Fathers' estimated testis exposure (defined as hands-free use with the mobile phone in front or in the trouser pocket or on the belt) use was associated with a borderline increased risk of perinatal mortality (RR=1.77; 95% CI 1.00–3.15), and exposure of the head or testes from mobile phone was related to a decreased risk of preeclampsia during pregnancy (RR=0.73; 95% CI 0.54–0.99).

A positive feature of this study is the prospective design. The mothers provided exposure information at a time when they could not possibly know about potential reproductive

outcomes. In addition, the large sample size with more than 100 000 births included in the analysis (and almost 75 000 with paternal information) is an asset. However, it remains unclear how relevant maternal mobile phone use is for foetal exposure, since exposure of a foetus to RF fields from a mobile phone is minimal during maternal mobile phone calls. Carrying a mobile phone close to the belly when travelling might be a more relevant exposure situation than making a call. Furthermore, the study cannot make any statements about the impact of radiofrequency electromagnetic fields on spontaneous abortion occurring before gestational week 15.

In Beijing, China, Zhou et al. (2015) conducted a survey to determine several potential risk factors of early spontaneous abortion, including EMF exposure from several sources. The study population consisted of 34 417 cases of pregnant patients seeking medical attention in an obstetrics- and gynaecology hospital in Beijing during the period 2000–2013. From the study population 32 296 questionnaires including general personal information, obstetrical history, family history and living environment and habit were collected. The spontaneous abortion rate in the total sample was 3%. Of different EMF sources, the authors assessed self-reported living distance from base stations, use of mobile phones, microwave oven, induction cookers, and electric blankets. Among the EMF sources of interest, the authors found a significant increased risk for spontaneous abortion among women having mobile base station within 100 meters from their residence ($P < 0,001$). No increased risk was observed for the other EMF sources.

It is well known that distance as such, and in particular self-reported distance, is not a valid proxy for exposure (Beekhuizen et al., 2014, Frei et al., 2010). In addition, missing exposure information from the other EMF sources make this study uninformative regarding a potential effect of high- and low frequency electromagnetic fields on spontaneous abortion. The study population is not well defined and possibly does not include healthy mothers. In summary, the study is not adequately designed to provide any information for risk evaluation.

In Iran, Mahmoudabadi et al. (2015) performed a case-control study to evaluate the association between mobile phone use and risk of spontaneous abortion. 292 women with miscarriage in the first 14 weeks of their pregnancy in the age group 18–35 years with singleton natural pregnancies were recruited from several hospitals in Teheran. As controls, 308 pregnant women at 14 weeks gestation from the same hospitals were matched with maternal and paternal ages, duration since last delivery, educational level, occupation and history of previous abortions. Other matching criteria were not further defined factors such as gravidity and family relationship. Women with chronic diseases were excluded. No information was provided regarding participation rate. Information about the use of mobile phones during pregnancy was obtained through personal interviews. Factors like average calling time per day, location of the telephone when not in use, use of hands-free, use of other applications, and the specific absorption rate (SAR) of the participants' mobile phone were considered. Combining the SAR with duration of calling time per day was given the term "effective SAR". All mobile phone exposure metrics investigated, except use of hands-free devices, were significantly correlated to the risk of spontaneous abortion ($p < 0,001$). A logistic regression analysis of the association between spontaneous abortion and effective SAR showed an odds ratio of 1.11 (95% CI 1.07–1.16).

The limited information regarding selection of participants and poor exposure assessment are severe limitations in this study. Selection bias is a serious concern if mothers are

asked about potential risk factors after having just experienced a spontaneous abortion, and the same accounts for reporting bias. The calculated “effective SAR” value has not been validated and is unlikely to be correlated with actual exposure, since SAR reported from the manufacturer is measured when the telephone emits at maximum strength. Under normal conditions, the actual SAR is far below maximum levels and depends on many factors. In addition, an explanation on how a telephone not in use or used as a gaming tool can affect the foetus need an explanation. Observing similar risks for such behaviours that are not, or only marginally, related to RF-EMF exposure of the foetus suggests that other factors than the exposure from the mobile phone are underlying the observed effect.

Results of an Iranian case-control study were reported by Zarei et al. (2015). Mothers of 77 children referred to a speech treatment centre in Shiraz, Iran, as well as 35 healthy control children were included in the study but it was not reported how these control mothers were recruited and what their participation rate was. Included children were between 3-5 years old and their mothers were interviewed regarding sources of RF-EMF exposure, including mobile phones, mobile phone base stations, Wi-Fi, cordless phones, laptops and power lines. It was not explained, however, how exposure data were summarised and what kind of statistical analysis was performed. The authors reported that call time and months used mobile phones was associated with speech problems, but the direction of the association was not reported. In addition, average duration of daily call time, cordless phone use and CRT (unexplained abbreviation, possibly cathode ray tubes?) was reported not to be associated with speech problems in the offspring. This is a badly reported study, with incomplete information on nearly all study procedures, from inclusion of participants, to the definition of what a speech problem is, the way the exposure assessment was operationalised and how the analysis was done. The study therefore does not add to our understanding of potential effects of electromagnetic field exposure on health effects on the offspring.

4.4.2. Adult cancer

Leitgeb (2014b) conducted a review on available epidemiologic studies of brain cancer and mobile phone use. He plotted any risk estimates provided in the literature reporting on mobile phone use, in particular risk estimates versus cumulative call time, number of calls or time since first use. For all these exposure indices risk estimates tended to be increased at the upper end (so at higher levels of the evaluated exposure proxies), although increase was substantially stronger for the former compared to the two latter indices. This pattern has been previously described and discussed in other meta-analyses and review articles. The paper of Leitgeb does not bring any new argument on the on-going controversy whether this pattern is due to bias (in particular recall bias) or whether it reflects a true causal association. In addition, the same principal shortcomings as for the paper regarding ELF-MF exposure and childhood leukaemia apply (Leitgeb 2014).

Hardell and Carlberg (2015a) evaluated time trends in brain tumour incidence and mortality in Sweden. According to the author, the underlying reason for this undertaking was that null findings of the cancer registry (reporting no increase in brain tumours over time) had been used to dismiss findings of some case-control studies showing increased risks of brain tumours in persons with frequent mobile phone usage.

Three different data sources were used to assess changes over time: The Swedish Cancer registry (that evaluates incidence of new cases), the Swedish National Inpatient Registry

(evaluating hospital discharge data of patients treated in hospital) and finally the Swedish Death Registry (evaluating mortality). Five different types of tumours were assessed in the Inpatient Registry and the Death Registry: The International Classification of Diseases, version 10 (ICD10) codes D32: benign neoplasm of meninges; D33: Benign neoplasm of the brain and other parts of the central nervous system; D42: Neoplasm of uncertain or unknown behaviour of meninges; D43: Neoplasm of uncertain or unknown behaviour of brain and central nervous system, and C71: malignant neoplasm of the brain. In the Cancer Registry, ICD 7 code 193.0 was analysed, which includes malignant neoplasms of the brain. Note that the authors explain this code to include also benign tumours, although this contradicts the named code as such.

Of these registry data, time trends over the years 1998–2013 were analysed. For the Inpatient Registry, number of patients per 100 000 was reported, but these data were not adjusted for age, which is problematic, given the increasing aging of the population. For the mortality data, age-adjusted death rates per 100 000 and for the cancer registry age-adjusted incidence data were reported. In all three data sets, joinpoint regression analysis was performed to check if any trend over time in these data had changed at a particular point in time. If such a joinpoint was detected, then trends until that time point and after that time point were reported.

For D32 and D33 (so benign neoplasms of meninges, brain and central nervous system), no changes were detected in the Inpatient Registry, but the Death Registry recorded statistically significant decreases over time. For D42, the Inpatient Registry reported a statistically significant decrease over time; mortality data were not reported for this outcome. D43 had a joinpoint in 2007 for both inpatient as well as mortality data: In the Inpatient Registry, data for the time period 1998–2007 showed no significant trend over time, but an annual increase of 4% was observed for the time period between 2008–2013. Death registry data showed an annual decrease of 7% between 1998–2007 but an annual increase of 23% between 2008 and 2013. For malignant neoplasms of the brain, no change over time was detected in the Inpatient Data and the Cancer Registry, but the mortality data reported a statistically significant annual decrease of about 1%. The authors argue that given the increase in recent years of D43, the null findings of the cancer registry should not be used to dismiss the potential link between mobile phone use on brain tumour risk.

There are several issues with the analysis also discussed in a letter to the editor (Ahlbom et al. 2015, Hardell and Carlberg, 2015c). In particular, the steady increase in life expectancy has led to an increase in total numbers of occurring cancers because as people get older, the chances to get cancer also increase. The reported number of inpatients that were not age adjusted should therefore be interpreted with caution. In addition, it is unclear if repeated admissions to a hospital are counted several times, and whether it is possible to differentiate between primary and secondary tumours (metastases). In the mortality data, coding practice seems to have changed in that there was a decrease of malign brain tumours (code C71) in about the same amount as there was an increase of D43, the neoplasms of unknown behaviour. Reason for that is that autopsies have strongly decreased over recent years in Sweden and therefore the type of tumour was more often unknown. Given the interest in mobile phone use and brain cancer, it would have been informative to exclude those tumours that did not appear in the brain (D43.4 spinal cord, and D43.7 and D43.9: other or unspecified parts of the central nervous system), but this was not done. These data sources are therefore not informative regarding a potential association between mobile phone use and brain tumours.

Cancer registry-reported numbers should have the highest value, given that these data are checked against other data sources. All in all, small changes in coding practice may change considerably the number of reported cases in any of the evaluated databases which then may introduce apparent trends over time. However, previous reports evaluating trends in brain tumour incidence pertained to reports from a range of different countries, which appear to be overall consistent in showing no increase in brain tumour risks. Kim et al. (2015b) carried out a time series analysis with New Zealand Cancer Registry data from 1995 to 2010. No increase of temporal trends of age standardised incidence rates for malignant brain tumours (glioma) was found at ages 10–69. Temporal and parietal lobe sites were examined separately as they are located in the area of maximum mobile phone exposure, but no increase over time was found in these locations either. Separate gender specific analyses for age groups with 20 year intervals found a significant decrease of brain tumours in males aged 10–29, as well as significant increases in women aged 30–49 and men at people aged over 70, but increases were somewhat stronger for glioma occurring at any site, compared to glioma at temporal or parietal sites.

In summary, this study does not indicate that malignant brain tumours have increased following the introduction of mobile phones. Only about 180 tumours have occurred in New Zealand annually, thus this study cannot significantly detect potential small changes in the incidence rates. Small changes would be expected if only rare subtypes were causally affected by mobile phone exposure, or if only persons with very intensive mobile phone use had an increased risk. The study can also not make any conclusions regarding latency periods of more than 15 years, because less than 10% of the population had a mobile phone subscription before 1995. From 2007 onwards, the number of mobile phone subscriptions exceeded the number of inhabitants in New Zealand.

Grell et al. (2015) adapted a point process model developed in the context of studies investigating spatial aggregation of a disease around a source of potential hazard, and applied it to a subset of the INTERPHONE data to analyse the spatial distribution of brain tumours within the head and the exposure from RF-EMF caused by regular mobile phone use at the preferred side of the head. In total, 478 glioma cases out of 2710 INTERPHONE cases were used for this analysis. Reason for exclusions were, i) no localisation information (n=1180), ii) no estimates for the origin of the tumour or estimation of the tumour origin included several voxels (1-cm cubes) (624), iii) non-regular mobile phone use (346), iv) no side preference for mobile phone use (60), and v) missing information about the preferred side of use (22). The statistical analyses showed that distance to the preferred ear for mobile phone was associated with the location of brain tumours in mobile phone users. When covariates were added to the model, cumulative call time was not found to be relevant for the distance relation.

This is an innovative approach to analyse brain tumour data with localisation information, which is based on the assumption that the origin of brain tumour is correlated with the extent of RF-EMF exposure. It cannot, however, reveal potential indirect consequences of RF-EMF exposure. Such a case-only analysis is not subject to selection bias, which is a concern for the case-control analysis of INTERPHONE. One important parameter used for the point process model is self-reported preferred side of the head for mobile phone use. There is indication in INTERPHONE and other case-control studies that such statements after the diagnosis are subject to recall bias. Cases are more likely to state that the side of the head where the tumour is located was the preferred side for calling. Such recall

bias may explain the observed correlation between distance to the preferred ear for mobile phone and the intensity of brain tumours. This aspect is not discussed in the paper. Based on material from the Finnish part of the Interphone study, Shrestha et al. (2015) evaluated the risk of pituitary tumours in relation to exposure from mobile phones. This population-based case-control study was based on cases aged 20–69 years identified through five neurosurgery departments during November 2000–September 2002. 80 cases (participation rate 77%) were included in the analyses. Controls were identified from the national population register using 1:3 frequency matching. Among controls, a participation rate of 42% was achieved. Information regarding exposure was obtained through personal interviews. The proportion of regular mobile phone users, defined as at least one call per week for 6 months, was 68% for cases and 84% for controls. A statistically significant reduced risk was seen among ever-regular mobile phone users (OR 0.39, 95% CI 0.21–0.72). Reduced risk estimates were also found in relation to duration, cumulative hours of use and cumulative number of calls. For persons with a long duration since first use (10 or more years), risk was also not increased (OR=0.69, 95% CI 0.25–1.89).

A likely explanation for the reduced risk estimates is selection bias among controls where participation rate was considerably lower than for cases, probably yielding an over-representation of mobile phone users. This phenomenon has also been observed among controls in other countries participating in the Interphone study. As all studies with similar design, self-reported exposure assessment is always a limitation to consider. All in all, the lack of positive association between the risk of pituitary tumours in relation to exposure from mobile phones is in line with the few previous studies (Benson et al., 2013, Schoemaker and Swerdlow, 2009, Takebayashi et al., 2008) on this subject.

Carlberg and Hardell (2014) conducted a survival analysis of the glioma patients of their previous case-control studies in relation to the use of mobile- and cordless phones (summarised as “wireless phones”). A similar study with identical design with cases diagnosed between 1997–2003 (Hardell and Carlberg, 2013) has been evaluated in the 2013 SSM report (SSM, 2013). 427 new cases were added to this new study compared to the previous one, and the latency period (time since first use) was increased from >10 years to >20 years. This study included 1678 cases diagnosed between 1997–2003 and 2007–2009 with a malignant brain tumour. The cases were followed up from the date of diagnosis until death or until December 18, 2013. For glioma, the overall hazard ratio (HR) and confidence interval for wireless phone use was similar as for the paper from 2012, 1.1 (95% CI 0.9–1.2) for any duration of exposure. The risk of dying increased with longer latency time. For a latency of >20 years the hazard ratio was 1.7 (95% CI 1.2–2.3), whereas in the previous analysis including a hazard ratio of 1.3 (95% CI 1.03–1.7) >10 years latency time was reported.

The use of proxy interviews with next-of-kin for deceased patients is a limitation of this study, although the authors stated to have made some adjustment for this. However, it is not clear how this was done. In the new analyses hazard ratio was only slightly elevated for the 10 to 15 year and 15 to 20 year latency group (1.1, 95% CI 0.9–1.4 and 1.1, 95% CI 0.8–1.4, respectively). In the first paper of 2012 a statistically significant risk was observed for this latency group.

Two pooled analyses of earlier sets of data on use of mobile- and cordless phones (wireless phones) and risk of glioma and meningioma were published by Hardell and Carlberg (2015b) and Carlberg and Hardell (2015). No new data are presented and these papers just combine previous analyses on glioma (Hardell et al., 2006b, Hardell et al., 2013) and

meningioma (Carlberg et al., 2013, Hardell et al., 2006a). These studies were already evaluated in previous Council reports (SSI, 2007:4, SSM, 2014) and will not be discussed here again.

4.4.3. Reproduction

In a sample of 106 male patients (mean age 35 years) of a fertility clinic, the association between mobile phone use and semen quality was investigated (Zilberlicht et al., 2015). After exclusion of non-eligible participants due to chronic or acute medical conditions (e.g. long-standing diabetes mellitus, hypertension, varicocele, orchitis), smoking (>more 10 pack years) and a high level of alcohol consumption (>1 litre of alcoholic beverages per day), semen quality from 80 individuals was analysed with respect to volume, concentration, motility and morphology. Different aspects of mobile phone use were collected by means of questionnaires. Data were analysed using multivariate logistic regression modelling. The proportion of participants with abnormal sperm concentration was higher for those study participants who reported to talk >1 hour per day or who reported to talk while charging the phone (adjusted for smoking status). Distance of mobile phone from groin, when not in use, was not related to semen concentration. No univariate associations were found between age, residential area, occupation, number of children or years of education and thus were not considered in the multivariate model.

The sample size in this study is small and the recruitment process of this patient collective unclear. Thus, potential selection bias cannot be excluded. Mobile phone use is self-reported, which is a limitation. Exposure of testicles is relatively low when talking on the phone and thus it is difficult to interpret the results in terms of RF-EMF exposure effects. In particular, it is not obvious from an exposure perspective, why talking when charging has an independent effect, in addition to talking duration. Thus, other factors related to mobile phone use cannot be excluded as a potential cause for the observed associations. Given the many factors that were evaluated, the observed effect could also be chance findings. There is a need for dosimetric studies to reveal the factors that are related to testicle's exposure in order to improve the exposure assessment in any study addressing male fertility

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

In chapter 2.4.4 the results of ELF-MF exposure and symptoms from a Dutch cross-sectional survey of 5933 adults have been described (Baliatsas et al., 2015). Here the results from this study with respect to RF-EMF exposure are presented. Exposure to mobile phone base station radiation and broadcast transmitter emissions were estimated with a propagation model (ECOLOG). Exposure from DECT cordless phones and other people's mobile phones was derived from a previous study evaluating exposure for a range of different activities, such as being at a train station (Bolte and Eikelboom, 2012). For various exposure metrics (sources) the 90th percentiles were between 0.07 (radio/TV) and 0.22 V/m (mobile phone base stations). Subjective exposure to all RF-EMF sources combined was inquired by means of a questionnaire. None of the modelled RF-EMF exposure sources was related to the occurrence of symptoms, whereas consistent associations of self-reported RF-EMF exposure with all symptoms were observed.

In addition to the aspects discussed in chapter 2.4.4, a strength of the RF-EMF analyses is the objective exposure assessment based on modelling. However, the explained variance

by the models is quite low (for all models <30%) and the exposure gradient is small despite oversampling potentially highly exposed subjects. Own duration of mobile and cordless phone use was not considered in this analysis, which is likely to be more relevant for personal exposure than the small observed differences for the environmental sources (Roser et al., 2015). Thus, it remains open whether the observed lack of associations reflects indeed true absences of associations or whether it is caused by the large uncertainty in exposure assessment and the lack of a relevant exposure gradient in the collective. The consistent association pattern observed for subjective RF-EMF exposure is in line with previous studies and demonstrates the relevance of placebo effects and reporting bias in this field of research. It further shows that the study is sensitive enough to capture strong effects if present.

Lamech (2014) described the symptom pattern in a case-series study of 92 residents of Victoria (Australia) who had complained about adverse health effects after the rollout of smart meters in 2006 until August 2013. The age of the respondents varied between 6 and 74 years, 63% were female. Most common symptoms were insomnia, headaches, tinnitus, lethargy and cognitive disturbances. This study is purely descriptive, no links with exposure were made and the study therefore cannot establish a causal link between the occurrence of these symptoms and the installation of smart meters. Smart meters emit only during very short time periods during the day (Tell et al., 2013) and RF-EMF exposure levels from smart meters are generally very low and rapidly decreasing with distance (Tell et al., 2012).

A Chinese cross-sectional study a total of 7102 adolescents (participation rate: 92%) investigated the association between mobile phone use and attention deficit (Zheng et al., 2014). Participants were recruited from four schools in south-western China (grades 7–12, age range: 12–20 years). Inattention was assessed by the teacher and was based on nine questions regarding inattention descriptions; adolescents scoring at least six of the nine with a “yes” were classified as having inattention. Questions about different mobile phone use behaviours such as calling or using the mobile phone for entertainment were answered by the adolescents. Data were analysed by logistic regression models adjusted for age, sex, area of residence (urban/rural) and whether living close to a mobile base station (with the question “is there a mobile phone base station around your home or school?”). Inattention was significantly associated with mobile phone ownership, the duration of using mobile phones for entertainment per day, the position where pupils kept their mobile phone during the day and whether the mobile phone was turned off or not during night. Time since first using a mobile phone or mean call duration per day was not associated with attention deficits.

Since call duration is most relevant for RF-EMF exposure in this study and no association was seen for this exposure variable, the results suggests that observed associations with various aspects of mobile phone use are rather not caused by RF-EMF emissions from the mobile phone. Other explanations include reverse causality which would occur if extensive use of mobile phones for entertainment may be the consequence of inattention and not the other way round. Alternatively, there may be a lack of recreation due to extensive usage of mobile phones for entertainment. The strength of this study is the large sample size, high participation rate and the fact that inattention was assessed by the teacher and mobile phone use by the students, thus reducing information bias. However, the cross-sectional design of the study does not allow drawing conclusions about the timing of exposure and effect.

In another cross-sectional survey from the same research group (Zheng et al., 2015) the association between mobile phone use and self-reported well-being was assessed in 746 children (participation rate: 94%). Participants aged 9–12 years were recruited from two primary schools in Chongqing, China. Mobile phone use and symptoms (HBSC, Health Behaviour in School Aged Children) were assessed by a written questionnaire, filled in by the children. Data were analysed by means of logistic regressions adjusted for sex, age, rural/urban residence, academic stress, daily exercise and having a recent cold or flu. Fatigue was associated with years of mobile phone usage (OR for > 1 year: 1.85; 95% CI 1.07–3.22) and daily duration of mobile phone calls (OR for >10 min/day: 2.98; 95% CI 1.46–6.12). The other symptoms (headache, dizziness, sleeping problems, feeling low and heart beating fast) were not associated with years of mobile phone usage and daily duration of mobile phone calls, although for the latter non-significant exposure response associations were seen for all symptoms except “heart beating fast”. The high participation rate is an asset of this study. However, the cross-sectional design is a limitation for the interpretation of the results. Amount of mobile phone use reported by young children is expected to be inaccurate. No attempts have been made to disentangle RF-EMF exposure from other factors associated with mobile phone use. Thus, it is unclear whether and to what extent the observed association is due to RF-EMF exposure or due to other factors such as sleep deprivation due to nightly mobile phone use (Schoeni et al., 2015) or blue light exposure from the smart phone screens (Chellappa et al., 2013).

4.4.5. Other outcomes

To assess the effect of mobile phone use on selected hormones, Geronikolou et al. (2015) described an experimental study performed within different groups of higher or lower degree of mobile phone users. Between January and February 2011, 28 healthy primary and high school students were included into the study. Children with an infection in the month before the study, a chronic disease, obesity or chronic medication intake were excluded from the study, but the response rate and number of excluded children was not reported. Mobile phone users were divided into occasional (group A) and regular phone users (group B). Children underwent the Trier Social Stress Test (consisting of 3 minutes preparation time followed by a free speech and mathematical task in front of an audience). 20 minutes later, children were exposed to mobile phones by talking to their parents for 5 minutes, holding a 2 or 3G phone to their left ear. Five salivary cortisol level samples were taken throughout the experiment: At baseline, 10 and 20 minutes after the stress test, and 10 and 20 min after the phone call. Two-way ANOVA for repeated measurements was applied, not adjusting for any confounders. At baseline, the mobile phone user group had much higher salivary cortisol levels than the occasional user group. Cortisol levels stayed approximately the same over consecutive tests in group B, but were reduced over tests in group A.

A striking difference between the two groups was that group B was on average two years older than group A, 13–14 compared to 11–12 years, respectively. 33% of group B, and 19% of group A were girls. Given the very large difference in baseline cortisol levels in group A compared to group B, it is unclear why the authors did not at least account for age and sex differences in the analysis. In addition, the applied mobile phone exposure is not well described. The authors write that SAR differences across children were avoided, but simultaneously report that 2 and 3G phones were used. 2 and 3G phones, however, have largely different exposure profiles, given dissimilarities in the signal and output power regulation of the corresponding mobile phones. The authors mention that occasional users of mobile phones had lower self-reported mobile use compared to regular

users, but actual levels of frequency and duration of mobile phone use were not reported. Given the shortcomings of the design of the study and the analysis of the results, it is not possible to interpret the study results as to any mobile phone-related exposure effects.

A French retrospective cohort study evaluating causes of death among navy personnel exposed from radar transmitters was reported by Dabouis et al. (2015). All navy personnel (only from the mainland) who had served between 1975 and 1995 were included into the study, follow up for causes of death was performed from 1975–2000. Women, personnel of the aviation branch of the navy, and people who had served less than 200 days on board of a navy vessel were excluded from the study, which left 39 850 persons for the analysis. Probabilistic linkage was used to link with the death registry, and 1185 deaths were identified. Duration spent on board and tasks of the personnel were evaluated for the exposure assessment. The population was classified as the “radar group”: Personnel with tasks above the main deck, and a “control group”: personnel with tasks below the main deck. Measurements on one vessel were performed on 50 spots above the deck (numerical assessment of maximum exposure spots, as well as typical location spots of personnel), and on 10 spots below the deck. Exposures in 4 different frequency bands were assessed: High frequency (2–30 MHz), Radar L (1.3–1.35 GHz), S (2.9–3.2 GHz) and X (9.38–9.45 GHz). It is unclear how exactly the measured values were combined in the exposure assessment. Age standardized mortality rate ratios were calculated. Total mortality was not different between the groups; deaths due to respiratory causes were somewhat lower in the “radar group” compared to the “control group”, although 40–44% of causes of death were unknown in these two groups, respectively.

This is a relatively large study on navy personnel likely exposed to radiofrequency fields and radar from the vessels they served on. Strengths of the study are the cohort design including all navy personnel who had worked on the vessels over a period of two decades. Given that about 11% of the population could not be linked to mortality files and another 40–44% lacked information regarding causes of death, the analysis regarding specific causes of death certainly has to be interpreted with care. Another weakness of the study is that no further information regarding educational level or lifestyle was available on the vessel workers, e.g. the reduced mortality rate ratio due to respiratory causes might well have been due to a lower proportion of smokers in the “radar group”. It is unclear to what kind of personal exposure levels the performed spot measurements translate to. Emissions from radar transmitters are highly pulsed and cannot be compared with other RF-EMF sources from a biophysical point of view. All in all, the study does not provide evidence for an increased risk of death in navy personnel employed above compared to employed below the main deck.

A survey on mobile phone use and auditory brainstem-evoked potentials (ABR) in volunteers was reported by Gupta et al. (2015). The ABR test can be used for auditory threshold estimation, determining hearing loss type and degree, and auditory nerve and brainstem lesion detection. Between June 2014 and January 2015, 100 participants were recruited at the Medical College of Faridkot, India. Participants were between 18 and 30 years old, had no clinical evidence of a hearing disorder and were divided into ever (n=67) and never (n=33) mobile phone users. The mobile phone user group was then subdivided by duration of GSM mobile phone use into 1–5 (n=40), or more than 5 years (n=27) duration of use. Within the user-group, another subdivision was made based on cumulative use of more or less than 1 hour per day. Of auditory brainstem-evoked potentials, latencies, interpeak latencies and amplitudes of waves were assessed and between-group comparisons were made using ANOVA, not adjusting for potential confounders.

No differences between the 4 different mobile-phone user groups and the non-user group were observed.

The authors did not report participation rate and also not how many people were excluded due to some kind of hearing disorder. It is unclear how the exposure groups were really defined, especially whether the “cumulative use” of mobile phones was based on current use, or use over the whole assessment period. It is unclear why only GSM users were included and what was done with participants reporting to use smartphones (phones working primarily on UMTS). Not adjusting for potential confounders is certainly a shortcoming of the study. All in all, however, the study did not provide an indication of differences in ABR across different user groups of mobile phones.

Shrivastava and Saxena (2014) recruited 100 healthy volunteers aged 18–22 years to investigate the effects of long-term mobile phone users on melatonin excretion. The participants were grouped into high users (>2 h/day) and low users (≤ 2 h/day). From each group 30 students were randomly selected and serum melatonin was sampled three times in the same day (morning, noon, and evening). Data were compared with non-parametric tests (Mann Whitney U test) without adjusting for potential confounders. According to the authors, a statistical difference between the groups was observed for the evening values (55.1 pg/ml in high users vs. 47.6 pg/ml in low users). However, differences were much higher for noon values (90.7 pg/ml vs. 58.0 pg/ml) whereas morning values were similar. This study is uninformative regarding an effect of mobile phone use on melatonin levels, since melatonin levels are temporally highly variable and other, potentially relevant group differences were not considered in the analyses (e.g. 38% males in the high user group and 64% in the low user group). Light, an important factor for melatonin secretion, was controlled for by just telling the students to stay under dim light and no further information was reported about when the students went to bed and switched off lights. Finally, mobile phone use on the day preceding the test was not inquired.

Shivashankara et al. (2015) conducted a pilot survey in India to assess the levels of salivary enzymes, protein and oxidant-antioxidant system among mobile phone users. During April and September 2013, 257 volunteering students aged 18–24 years at a medical college in Mangalore, India, were asked to fill in a questionnaire regarding information about their mobile phone use, health condition, and tobacco and alcohol consumption. After excluding persons with particular health conditions (fever, malaria, jaundice on the past month, were on medications such as antibiotics or who regularly consumed antioxidant supplements and multivitamins in the past month) and regularly users of alcohol and tobacco products, 40 men and 31 women were categorised into two exposure groups based on the duration and frequency of use of mobile phones. The category “less mobile phone users” had used a mobile phone less than two years and had a weekly use of mobile phones of less than two hours. “Heavy mobile phone users” had used a mobile phone more than four years and reported a weekly use of two or more hours. It is unclear what happened to the participants who did not belong to either group, and how many people returned the questionnaire. Included participants were invited to a saliva test in the morning and before any mobile phone calls. Five parameters were measured in saliva: total protein, lactate dehydrogenase, amylase, lipid peroxidation and glutathione as well as malondialdehyde. The salivary levels of malondialdehyde and activities of amylase and lactate dehydrogenase were significantly higher among “heavy users” compared to “less users”. Insufficient exposure assessment, lack of considering confounders and the small sample size makes the study difficult to interpret and to judge whether other factors than mobile phone use are a more plausible explanation for the observed effects.

In another Indian survey, Gulati et al. (2015) investigated the genotoxic effect of RF-EMF based on distance from base stations. The studied population included 116 individuals residing near mobile phone base stations (50–400 meters) and 106 controls residing further away from the base stations (>800 meters). There is no information how the studied population was selected, how participants were approached and what the response rate was. Participants provided blood samples that were analysed with a comet assay. Power density of the 1800 MHz frequency band only was measured in the vicinity of the actual base stations, with no relation to the participants. The authors report more tail moment observed in the comet assay in the exposed population. This is a weakly reported study regarding most study procedures. In addition, distance to mobile phone base stations is not related to exposure and lack of individual exposure information make this study uninformative.

In another Indian survey, Singh and Kapoor (2015) conducted a survey to determine the effect of EMF exposure from radar transmitters on plasma catecholamine concentration among radar operators. 166 males in the age group 20–48 years working in the Indian army were categorised into three different groups depending on their radar exposure: one unexposed control group containing 68 persons, one group of 40 persons exposed to the frequency range 8–12 GHz (group I) and one group of 58 persons exposed to frequency range 12.5–18 GHz (group II). EMF measurements were taken at various spots, and resulted in a power density for exposure group I from 0.24–0.77 W/m² and from 0.1 to 15.6 W/m² for exposure group II. For exposure group II, a significant decrease in plasma adrenaline level was observed. For exposure group I, an increase in plasma adrenaline level compared to the controls was observed. Using the same material and methods, Singh et al. (2015) attempted to determine the effect on plasma melatonin and serotonin levels. A significant decline in plasma melatonin and a significant increase in plasma serotonin were found in exposure group II compared to controls. Lack of adjusting for confounding variables and crude exposure assessment are severe limitations and thus the study is not informative in terms of possible effect on plasma catecholamine, plasma melatonin and plasma serotonin from the exposure to EMF from radars.

Balakrishnan et al. (2014) conducted a survey in India to evaluate whether the serum concentration of heat shock protein (HSP) 70 and C-reactive protein (CRP) among frequent users of mobile phones was higher compared to infrequent users. 120 persons working in an IT sector and using mobile phones for more than 5 five hours every day were categorised as frequent mobile phone users. 102 persons using a mobile phone less than half an hour per day were characterised as infrequent users. Self-reported subjective symptoms and specific absorption rate of the phones were recorded. Blood samples were taken and serum C-reactive protein and gene expression levels of the hsp70 were compared between the groups. Both markers were significantly different among frequent mobile phone users compared to infrequent users.

Lack of adjusting for confounding variables, limited information regarding selection of participants and poor exposure assessment are severe limitations and thus the study is not informative in terms of possible effects from the exposure to EMF from mobile phones on concentration of C-reactive protein and hsp70.

In India, Sevi et al. (2014) evaluated auditory evoked potentials among 173 mobile phone users. As a proxy for duration of mobile phone use, age group was used. Because mobile

phone use as such was not evaluated, no conclusions can be drawn regarding effects of EMF exposure on the evaluated outcome.

In Iran, Jarideh et al. (2015) performed a survey to evaluate the effects of exposure from airport radars on short-term memory and reaction time. The studied population included 32 employees aged 27–64 years working in an airport control and approach tower located 500 meters from a radar transmitter, and 29 controls “not working near the radar system”. There is no information how the studied population was selected, except that they were volunteers. Power density at the working place was apparently measured, but the methods were not reported. Participants performed a memory test and a reaction time test. Potential confounders were not accounted for in the analysis. No significant differences in short-time memory and reaction time were observed between the two groups. The poor exposure assessment combined with not taking into account potential confounders makes it impossible to interpret the study regarding effect of radar exposure on short-term memory and reaction time.

4.4.6. Conclusions on epidemiological studies

A new large Norwegian study did not indicate that mobile phone use of the mother during pregnancy is a risk for adverse effects regarding reproductive health. However, to answer the question whether RF-EMF exposure of the foetus is related to adverse pregnancy outcomes, more sophisticated exposure assessment methods are needed. Regarding mobile phone use and brain tumour risk, little new data was published and several papers deal with reanalyses of already published data. As a consequence, little has changed in the rating of the evidence. Studies on symptoms confirmed previous findings pointing to an absence of association with exposure from fixed site transmitters, although non-differential exposure misclassification remains a challenge for these studies. With respect to self-reported mobile phone use, associations with symptoms have been reported in studies of children and adolescents. However, associations were not restricted to call duration but also to other aspects of mobile phone use such as using them for entertainment. This indicates that other factors than RF-EMF exposure such as sleep deprivation due to nightly mobile phone use, blue light from the smart phone screens or lack of recreation due to overuse might be relevant in that context. There is an increasing number of low quality studies which are uninformative for health risk assessment.

5. Recent expert reports

5.1. Final Report Summary - ARIMMORA (Advanced Research on Interaction Mechanisms of electroMagnetic exposures with Organisms for Risk Assessment)

<http://arimmora-fp7.eu/uploads/FRPubSum.pdf> 2015

Executive summary

1. Background

Exposure to extremely low-frequency magnetic fields (ELF-MF) was evaluated in an International Agency for Research on Cancer (IARC) Monograph as 'possibly carcinogenic to humans' in 2001, based on increased childhood leukaemia risk observed in epidemiological studies, while the evidence of carcinogenicity in experimental animals was considered "inadequate" and the supporting evidence from mechanistic studies "weak".

2. Objectives & Consortium

In response to the call FP7-ENV-2011.1.2.2.2, the project ARIMMORA was formed aiming to scrutinize the underlying biophysical mechanisms and to clarify a possible causal relationship between ELF-MF exposure and cancer, especially childhood leukaemia. The consortium consists of ten world-leading competence centres in the fields of epigenetics, ERK signalling cascades, leukaemia *in vivo* models, *in vivo* toxicology, and EMF-sensitive animal models as well as in exposure assessment, biophysical modelling, and risk assessment.

3. Methods & Results

1) Novel experimental and computational techniques were developed and applied to close knowledge gaps in the exposure assessment of children to ELF-MF. The personal exposure studies in Switzerland and Italy demonstrated that the mean exposure of the children is below 0.1 μT , and a small proportion, ca. 1–4% of children, are exposed to magnetic field levels $>0.3 \mu\text{T}$. The high exposure group is best defined by the bedroom exposure, i.e., neither daily activities nor exposures to near-field sources significantly contribute to the integrated exposure. To assess the induced E-field of near-field sources, a novel instrument that directly translates the measured amplitude and gradients to locally induced fields was developed. In addition, the transformation matrices for comparing *in vitro* and *in vivo* experiments with child exposures to facilitate the correct interpretation of experiments for this project and any future studies have been developed. 2) Novel and improved *in vitro* and *in vivo* exposure systems have been developed to maximise the exposure quality. 3) Novel instrumentation that allows not only assessment of the ELF-MF exposure but also the induced E-fields for any far- and near-field. 4) A major contribution was the development of a new transgenic mouse model in which the human gene associated with the most common childhood leukaemia (B-cell acute lymphoblastic leukaemia, B-ALL) is expressed. Results of preliminary experiments, in which one (of 30) of the ELF-MF exposed mice developed B-ALL — compared to none among the 65 control animals — allow the frequency of leukaemia development in the mouse model to be estimated. 5) Findings in several independent *in vivo* experiments showed decreases of CD8⁺ T-cells related to ELF-MF exposure. 6) Small differences in epigenetic modifications were observed in human haematopoietic stem cells exposed to ELF-MF. 7) A feasibility study

based on the findings of the microscopic considerations showed that the radical pair mechanism is a possible candidate for the observed ELF-MF effects on signalling pathways.

4. Conclusions

Despite the several breakthroughs achieved, members of the ARIMMORA consortium concluded in the ARIMMORA risk assessment (applying the IARC Monograph program evaluation scheme) that the relationship between exposure to the agent ELF-MF and the risk of childhood leukaemia is considered consistent with the “IARC Group 2B” classification of possibly carcinogenic to humans. This category is the result of the limited evidence of carcinogenicity in humans and inadequate evidence of carcinogenicity in experimental animals. There was only weak supporting evidence from mechanistic studies. However, the new mechanistic insight from ARIMMORA experiments points to future research and could provide a step-change in future assessments that could be accomplished with one or two follow-up research projects.

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

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

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

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