Strål
säkerhets
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Swedish Radiation Safety Authority

Author: SSM's Scientific Council on Electromagnetic Fields

Research

2018:09

Recent Research on EMF and Health Risk

Twelfth report from SSM's Scientific Council on Electromagnetic Fields, 2017

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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.

Objective

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 twelfth in this series and covers studies published from

October 2015 up to and including March 2017. 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.

No new health risks have been identified. Whether mobile phone use causes brain tumours or not was mainly addressed using time trends studies in the last two years. The results were not entirely consistent but mainly point towards a lack of association. Some cell and animal studies indicate that EMF exposure may cause oxidative stress even at low exposure levels. It is unclear what relevance this may have when it comes to direct health effects in humans. A striking result was that some studies showed a stronger association between memory functions and radio wave exposure than other usage variables.

The annual report also has a section covering other relevant scientific reports published recently

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Project information

Contact person at SSM: Hélène Asp
Reference no: SSM2017-1339

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This report concerns a study which has been conducted for the Swedish Radiation Safety Authority, SSM. The conclusions and viewpoints presented in the report are those of the author/authors and do not necessarily coincide with those of the SSM.

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Recent Research on EMF and Health Risk

Twelfth report from SSM's Scientific Council on Electromagnetic Fields, 2017

Content

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 then 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 report is number twelve in the series and covers studies published from October 2015 up to and including March 2017.

The composition of the Council that prepared this report has been:

Prof Heidi Danker-Hopfe, Charité – University Medicine, Berlin, Germany
Prof Clemens Dasenbrock, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany
Dr Emilie van Deventer, World Health Organization, Geneva, Switzerland (observer)
Dr Anke Huss, University of Utrecht, the Netherlands
Dr Lars Klaeboe, Norwegian Cancer Society, Oslo, Norway
Dr Leif Moberg, Sweden (chair)
Dr Eric van Rongen, Health Council of the Netherlands, The Hague, The Netherlands
Prof Martin Röösli, Swiss Tropical and Public Health Institute, Basel, Switzerland
Dr Maria Rosaria Scarfi, National Research Council, Naples, Italy
Mr Lars Mjönes, B.Sc., Sweden (scientific secretary)

Declarations of conflicts of interest are available at SSM.

Stockholm in November 2017

Leif Moberg
Chair

Executive Summary

This report reviews studies on electromagnetic fields (EMF) and health risks, published from October 2015 up to and including March 2017. The report is the twelfth in a series of annual scientific reviews which 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.

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. 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. Workers exposed to fields from MRI scanners are also affected by these transient symptoms.

Cell studies

From the studies reviewed during the period of interest it seems that magnetic fields higher than 1 T are able to interfere with cell differentiation, while fields of lower intensity do not affect fundamental cellular processes.

Animal studies

Some teratogenic effects and a decrease in the vascular endothelial growth factor (VEGF) expression were reported in mice after exposure to 10 mT static magnetic field, but not after 1 mT. Using arbitrarily chosen study design and co-exposures, i.e. objectives and justification are missing, some researchers address beneficial health effects of static magnetic field exposure. For example a 16 mT static magnetic field influences the cardiovascular system of hypertensive rats towards normotension. 128 mT static magnetic field (co-) exposures with different test items tested in four different studies resulted in diverging effects without any central theme. Moreover, in all four studies only one 128 mT exposure level was used, and an exposure-response could not be evaluated. Finally, pain reduction due to 20 -204 mT static magnetic field exposure was demonstrated in a specific pain model in mice.

Human studies

Only studies aiming at non-invasive brain stimulation were published which is beyond the scope of this report.

Epidemiology

Transient symptoms experienced by workers exposed to magnetic resonance imaging (MRI) scanners are well established, but there is a lack of knowledge regarding potential long-term health effects. A large registry-based study on MRI scans of pregnant women provided no clear evidence of risk of stillbirth, but evidence of harmful effects to the foetus from the use of Gadolinium contrast medium.

Extremely low frequency (ELF) fields

The exposure of the general public to extremely low frequency (ELF) fields (>0 Hz-300 Hz) is primarily from 50 and 60 Hz electric power lines and from electric devices and wiring 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: Epidemiologically, associations have been observed, but a causal relationship has not been established.

Cell studies

A large number of studies have been published in the period of interest on possible effects of ELF magnetic fields on cell cultures. Although in several cases a difference was recorded with respect to sham-exposed samples, it is mainly related to the cell type investigated and is reversible. It is interesting to note that, among the studies reporting effects, the oxidative stress (and the parameters indirectly related to the redox state of the cells) is the most frequent endpoint affected by the exposure. Most of the studies dealing with combined exposures reported stronger effects compared to treatments with the chemical or physical agents alone. Such effects were either protective or damaging, depending on the experimental protocol adopted. In particular, it seems that the exposure to ELF magnetic fields, given before the chemical or physical treatment, is able to reduce the damage.

Animal studies

Similar to the previous Council report, various studies used one exposure level only and usually in the 1mT range at 50 or 60 Hz. Behavioural and cognitive disturbances were reported again. In addition, a preventive effect of exposure to a 0.5 mT ELF magnetic field on alterations comparable to Alzheimer disease (AD) was demonstrated in an AD mouse model. Testing different exposure levels (2 – 10 mT), oxidative stress increased dependent of the strength of the magnetic field. Two studies reported that a single 30-60 minutes exposure for an electric field of 1 – 10 kV/m may inhibit a stress-induced rise of glucocorticoid (GC) levels in mice, but it strongly depends on the configuration of the electric field exposure system. Other studies using exposures to ELF magnetic fields less than 1 mT gave various results without a clear picture on the reported effects.

During this reporting period, again, none of the animal studies directly addressed childhood leukaemia which is still of relevance in view of the results of epidemiological studies. Two large Italian co-carcinogenicity studies reported on single tumour types only, including hemolymphoreticular neoplasias (HLRN). This limited and selective evaluation of tumour incidences clearly decreases the significance of the studies. In addition, for humans, HLRN of adults are not relevant for childhood leukaemia.

Finally, study designs with 2 to 3 groups with 6 or less animals per group and using one sex only are often not well justified. Such designs easily produce chance findings without any possibility to investigate plausible exposure-response associations. Entitling those little studies as “pilot studies” should be the minimum.

Human studies

Only one human experimental study was found, exhibiting severe limitations and thus does not contribute to the knowledge about acute effects of ELF magnetic field exposure on cognitive performance.

Epidemiology

Of recent studies on residential exposure to ELF magnetic fields and childhood leukaemia, two found decreasing risk estimates over time, but this finding is not consistent across epidemiological studies. Altogether, while it remains an open question as to what caused the decrease of observed relative risks: these studies do not alter the current interpretation of an observed association of residential exposure to ELF magnetic fields and childhood leukaemia yet absence of a causal explanation. Research on other outcomes is scarce and does not indicate new insights for health risk assessment.

Intermediate frequency (IF) fields

The intermediate frequency (IF) region of the electromagnetic spectrum (300 Hz-10 MHz) is defined as being between the low frequency and the radiofrequency ranges. Despite increasing use of IF

magnetic field-emitting sources such as induction cooktops 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 IF electromagnetic fields and no conclusions can be drawn at present. Additional studies would be important because human exposure to such fields is increasing, for example from different kinds of surveillance systems. Studies on possible effects associated with chronic exposure at low levels are particularly relevant for confirming adequacy of international exposure limits.

There were no studies identified in the IF region of the electromagnetic spectrum during the period covered by this report.

Radiofrequency (RF) fields

The general public is exposed to radiofrequency fields (10 MHz-300 GHz) from different sources, such as radio and TV transmitters, Wi-Fi, 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. Recent measurement studies combined with dosimetric calculations have demonstrated that typically 90 to 95% of the absorbed radiation is from personal use of wireless communication devices.

Cell studies

According to the findings from the previous reports, most of the *in vitro* studies reported no effect of exposure to RF fields, except for a few cases where parameters related to oxidative stress were affected. Moreover, the cell type plays an important role in eliciting the effect, if any. In two studies, a protective effect was detected against treatments with chemical or physical damaging agents.

Animal studies

As in previous years, a variety of endpoints has been investigated in relation to exposure of experimental animals by RF fields. A substantial number of studies focused on effects in the brain. Several studies observed changes in gene expression in brain tissue with whole-body SAR exposure of 4 W/kg, a situation for which thermal effects cannot be excluded. A study on the blood-brain barrier showed contrasting results in males and females and is therefore difficult to interpret. Studies on behaviour and memory were also not consistent. One French study showed changes in parameters indicating increased damage in brain tissue, and a reduction in long term memory, after 15 minutes but not after 45 minutes of exposure. Two other studies, with exposures up to 4 weeks, did not observe any such effects in young or old animals. In another study whole-body SARs ranging from 2.2 to 3.3 W/kg resulted in stimulation of object recognition.

Studies investigating oxidative stress have found increased levels in brain and other tissues, even after whole-body SARs as low as 0.0067 W/kg. In studies investigating different exposure durations the oxidative stress levels were reduced after longer exposures. In several studies pregnant animals were exposed and effects in the offspring investigated. Negative effects were observed on the female and male reproductive systems employing low exposure levels (whole-body SARs of less than 0.05 W/kg). Variable results were obtained with regards to developmental endpoints.

All these studies were done on rodents, but there were also three studies on non-mammalian species. In chicken embryos, no effect was observed on survival and gene expression from exposures throughout development, with very low exposure levels, around 0.04 mW/kg. In fruit flies, a 30-minutes exposure resulted in differential expression of 168 genes in oocytes, including genes associated with metabolism, stress and apoptosis. In lizards, long-term exposures resulted in reduction in innate immune reactions, but no effect on acquired immune responses.

Human studies

New results with regard to spontaneous waking EEG are inconsistent. While one study found no effects, two other did. But the two studies with observed effects were not consistent. One study found a decrease in the alpha and beta activity of the brain waves, while the other one found mostly effects in the delta and an enhancement in the beta frequency ranges. Cognitive performance and symptoms were not affected in the studies published in this reporting period, which confirms previous findings. Studies on heart rate variability are not informative due to methodological limitations. Finally, there is a study indicating that the macro-structure of sleep, specifically REM sleep, is affected by RF field exposure during sleep when analysed at an individual level. This, however, needs confirmation.

Epidemiology

Whether mobile phone use causes brain tumours or not was mainly addressed using time trends studies in the last two years. The results were not entirely consistent but mainly point towards a lack of association. Whereas these time series studies do not suffer from recall and selection bias, which is of concern for case-control studies, they are vulnerable to secular time trends. Changes in coding praxis or improved diagnostic tools and thus better detection rate may produce an apparent increase or a decrease in the incidence of brain tumours or specific subtypes. The few indications of changing incidence are thus rather attributed to such methodological limitations than actual changes in risk.

Several studies observed decreased semen quality of mobile phone users. Exposure to electromagnetic fields from mobile phones produces heating, and heating can affect sperm quality. However, at levels below standard limits and as encountered under real-life conditions, the extent of heating is too low for such effects and thus the potential underlying biological mechanism remains unclear. The main problem in the available studies is that none of these studies made an attempt to estimate RF field exposure of the testicles, but rely only on mobile phone use. These studies thus cannot solve whether observed associations are due to radiation or other factors related to mobile phone use as such, for example lack of physical activity or higher stress levels. Lack of confounding adjustments in many of these studies remains a strong limitation. Thus, any further studies just addressing frequency or duration of mobile phone use and sperm quality will likely remain uninformative.

Similar issues hold for various observed associations between behaviour and health related quality of life in children and adolescents. Most of the studies observed associations but the underlying causal pattern is difficult to elucidate. A Dutch study that compared effect estimates for sleep outcomes that were hypothesized to be related to RF field exposure (e.g. sleep onset delay, sleep duration, night wakenings) with those a priori not related to electromagnetic fields (e.g. sleep anxiety, sleep disordered breathing) indicates that associations are rather due to other factors related to mobile phone use. The same conclusion was made in a Swiss study that compared effects for cumulative RF field exposure of the brain with usage variables that produces small amounts of RF fields (texting, gaming), because stronger associations were observed for the latter. Strikingly, a different pattern was seen for memory performance, where stronger associations were found for RF field exposure than for usage variables not related to electromagnetic fields. Also the results of a laterality analysis were in favour of a RF field exposure effect. However, other recent studies on cognitive performance and RF field exposure in children and adolescents did not find such an association.

New publications on electromagnetic hypersensitivity, EHS, could not identify physiological characteristics that may help diagnose or develop effective therapeutic options.

In general, study quality was quite heterogeneous in the last two years. On the one hand, many low-quality studies were published which did not fulfil basic quality criteria and were thus excluded from this review. On the other hand, some new approaches are promising to obtain new insights into potential health effects from exposure to RF fields.

A general comment

As in previous years, a number of studies had to be excluded from the evaluation due to poor quality and missing information. Most of the excluded studies 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.

It is very unfortunate that investigators are not adhering to international standards concerning the reporting of their studies, and that journals often do not have an adequate peer-review system that corrects such omissions. There can also be a risk that doing bad quality studies and making people afraid may have some impact on their health and well-being and is another reason why only studies with high quality protocols should be funded, performed and published.

Articles not taken into account in this report, due to insufficient scientific quality, are listed in an Appendix together with the reasons for their dismissal.

Sammanfattning

I rapporten granskas studier av elektromagnetiska fält och hälsorisker, publicerade från oktober 2015 till och med mars 2017. Det är den tolfte i en serie årliga vetenskapliga granskningar som fortlöpande diskuterar och utvärderar relevanta nya data och värderar dessa i förhållande till redan tillgänglig information. Resultatet blir en kontinuerligt utvecklad uppskattning av hälsorisker från exponering för elektromagnetiska fält.

Statiska fält

Exponering för statiska (0 Hz) magnetfält som är mycket starkare än det naturligt förekommande geomagnetiska fältet kan förekomma i närheten av industriell och vetenskaplig utrustning som använder likström, som t.ex. elsvetsutrustning och olika typer av partikelacceleratorer. Den viktigaste källan till exponering för starka statiska magnetfält (> 1 T) är 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 uppleva dessa övergående symtom.

Cellstudier

Av de studier som granskats under rapporteringsperioden framgår att statiska magnetfält starkare än 1 T verkar kunna störa celldifferentieringen, medan svagare fält inte tycks påverka fundamentala cellulära processer.

Djurstudier

Hos möss, som exponerats för 10 mT, har effekter på foster och en minskning av tillväxtfaktorn rapporterats. Vid exponering för 1 mT syns inga sådana effekter. I några studier undersöktes positiva hälsoeffekter från exponering för statiska magnetfält, t.ex. att exponering för fält på 16 mT kan sänka blodtrycket hos råttor med högt blodtryck. Värdet av dessa studier minskas av att varken syfte eller utformning av studierna har närmare angetts. En exponeringsnivå på 128 mT testades i fyra olika studier och gav mycket varierande resultat. I alla fyra studierna användes dock bara en enda exponeringsnivå, vilket innebär att något samband mellan exponering och respons inte kunde utvärderas. I en speciell smärtmodell för möss rapporterades smärtlindring efter exponering för 20-204 mT.

Studier på människa

Endast studier avseende icke-invasiv stimulering av hjärnan har publicerats under rapporteringsperioden vilket ligger utanför de frågeställningar som granskningen omfattar.

Epidemiologi

Det är väl känt att personal som arbetar med magnetfältstomografi (MRI) upplever övergående besvär, men det saknas kunskaper om huruvida det också finns hälsomässiga långtidseffekter. En stor registerbaserad undersökning av gravida kvinnor som genomgått magnetfältstomografi gav inga säkra belägg för ökad risk för missfall. Däremot fann man belägg för skadliga effekter på fostret vid användning av kontrastmedel innehållande gadolinium.

Lågfrekventa fält

Allmänheten exponeras för lågfrekventa (ELF) fält, upp till 300 Hz, i första hand från kraftledningar med frekvenserna 50 och 60 Hz och från elektriska installationer och apparater i byggnader. När det gäller sambandet mellan exponering för lågfrekventa magnetfält och utvecklingen av barnleukemi visar de senaste studierna inte samstämmigt på samband. Inga nya undersökningsmetoder har emellertid använts i dessa nya studier och de har därför samma begränsningar som tidigare forskning.

Därför gäller fortfarande slutsatsen från Rådets tidigare rapporter: I epidemiologiska studier har samband observerats men orsaken till detta har inte kunnat fastställas.

Cellstudier

Under rapporteringperioden har ett stort antal artiklar publicerats som rör möjlig påverkan på cellkulturer från exponering för lågfrekventa magnetfält. Även om skillnader i flera fall registrerats jämfört med oexponerade prover så gäller detta i huvudsak de undersökta celltyperna och är reversibelt. Det är intressant att notera att i de studier som rapporterar effekter, så är det oftast oxidativ stress, och de parametrar som är indirekt kopplade till cellernas redoxtillstånd, som påverkats av exponeringen. De flesta studier rörande exponering av lågfrekventa fält i kombination med kemiska eller fysikaliska agens rapporterade starkare påverkan jämfört med behandling med enbart dessa agens. Sådana effekter kunde vara antingen skyddande eller skadliga, beroende på hur undersökningen var utformad. Framför allt verkar det vara så att exponering för lågfrekventa magnetfält före den kemiska eller fysikaliska behandlingen kan minska skadeverkningarna.

Djurstudier

I likhet med studier granskade i förra årets rapport så används i flera studier bara en enda exponeringsnivå, vanligen på 1 mT-nivån vid 50 eller 60 Hz. Återigen rapporterades beteendemässiga och kognitiva störningar. Dessutom kunde en preventiv effekt av förändringar liknande de för Alzheimers sjukdom påvisas vid exponering för 0,5 mT i en musmodell specifik för Alzheimers sjukdom. När man testade olika exponeringsnivåer (2-10 mT) så ökade den oxidativa stressen med exponeringens storlek. Två studier rapporterade att en enstaka exponering för ett elektriskt fält på 1-10 kV/m under 30-60 minuter skulle kunna förhindra en stressinducerad ökning av glukokortikoid-nivån hos möss. Dock finns det ett starkt beroende av hur exponeringssituationen för det elektriska fältet utformats. Andra studier, där man använt exponeringsnivåer under 1mT, gav varierande resultat utan någon klar bild av rapporterade effekter.

Ingen av de djurstudier som publicerats under rapporteringsperioden bidrar med ny kunskap i frågan om ett eventuellt orsakssamband mellan exponering för lågfrekventa magnetfält och barnleukemi, ett samband som observerats i upprepade epidemiologiska studier. Två stora studier av sam-karcinogenicitet redovisade enbart enstaka tumörtyper, däribland maligna lymfoida tumörer (lymfom, lymfatisk leukemi m.fl.). Denna begränsade och selektiva utvärdering av tumörincidenser minskar studiernas värde. Dessutom, hos människa, är förekomsten av lymfoida tumörer hos vuxna inte relevant för barnleukemi.

Till sist, djurstudier med två till tre grupper med sex eller färre djur per grupp och som endast använder ett kön, är oftast inte motiverade. Sådana studier ger lätt upphov till slumpmässiga resultat utan några möjligheter att undersöka tänkbara exponering-responssamband. Sådana små studier borde benämnas pilotstudier.

Studier på människa

Endast en experimentell humanstudie kunde identifieras och den studien uppvisade allvarliga kvalitetsbegränsningar och bidrar därför inte med någon ny kunskap om akuta effekter på kognitiva funktioner från exponering för lågfrekventa magnetfält.

Epidemiologi

Två nyligen publicerade studier av samband mellan exponering för lågfrekventa magnetfält i bostäder och barnleukemi fann en minskad risk över tid men detta resultat överensstämmer inte med andra epidemiologiska studier. Det är fortfarande en öppen fråga vad som orsakat minskningen av de observerade relativa riskerna. Dessa studier ändrar därför inte den rådande uppfattningen att det finns ett observerat samband mellan exponering för lågfrekventa magnetfält i bostäder och en något förhöjd risk att drabbas av barnleukemi samtidigt som något orsakssamband inte kan beläggas. Det har publicerats få studier om andra utfall än barnleukemi och därför finns ingen ny kunskap som kan ligga till grund för hälsoriskuppskattning.

Intermediära fält

Det intermediära frekvensområdet (300 Hz-10 MHz) av det elektromagnetiska spektret ligger definitionsmässigt mellan det lågfrekventa och det radiofrekventa områdena. Trots en ökande användning av apparater som medför exponering för intermediära fält, som t.ex. larmbågar i butiker och induktionsspisar, så har möjliga hälsorisker utvärderats endast i mycket liten utsträckning. Exponeringsuppskattningen, särskilt för interna elektriska fält, är fortfarande en utmaning för den här typen av exponeringskällor. Mycket få experimentella studier rörande hälsoeffekter från exponering för intermediära fält finns tillgängliga, och inga slutsatser kan dras för närvarande. Fler 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.

Inga nya studier har identifierats i det intermediära frekvensområdet under den tidsperiod som omfattas av denna rapport.

Radiofrekventa fält

Allmänheten exponeras för radiofrekventa fält (10 MHz-300 GHz) från en mängd olika källor som radio- och TV-sändare, trådlösa telefoner och mobiltelefoner och deras respektive basstationer samt från trådlösa datornätverk. Delar av allmänheten känner oro för möjliga hälsoeffekter som skulle kunna orsakas av exponering för radiofrekventa fält. Framför allt har oron för användningen av trådlösa datornätverk i skolor ökat under senare år i en del länder. Nyligen genomförda mätningar och exponeringsberäkningar har visat att den enskilda källa som ger högst exponering är den egna mobiltelefonen.

Cellstudier

I likhet med föregående år rapporterade de flesta cellstudierna inte någon påverkan från exponering för radiofrekventa fält. I några få fall rapporterades att parametrar som hänger samman med oxidativ stress påverkades. Dessutom spelade celltyp en viktig roll för framkallande av den eventuella effekten. I två studier fann man att exponering för radiofrekventa fält hade en skyddande effekt mot påverkan av skadliga kemiska och fysikaliska agens.

Djurstudier

Liksom tidigare år har en mängd olika utfall undersökts vid exponering av försöksdjur för radiofrekventa fält. Ett avsevärt antal studier har fokuserat på effekter på hjärnan. Åtskilliga studier har observerat förändringar i genuttryck i hjärnvävnad, men i de studierna har exponeringsnivån för helkropps-SAR varit 4 W/kg, vilket innebär att värmeeffekter inte kan uteslutas. En studie av blod-hjärnbarriären visade motstridiga resultat för hanar och honor vilket gör den svår att tolka. Inte heller studier avseende beteende och minne visade några samstämmiga resultat. En fransk studie visade förändringar som indikerar skador på hjärnvävnad och en försämring av långtidsminnet. Detta sågs bara efter 15 minuters exponering och inte efter en längre exponering på 45 minuter. I två andra studier, med exponeringstider på upp till fyra veckor, observerades inga sådana effekter, varken hos unga eller gamla försöksdjur. I ytterligare en annan studie, med helkropps-SAR mellan 2,2 och 3,3 W/kg, observerades en stimulering av förmågan att känna igen olika föremål.

Studier avseende oxidativ stress har funnit förhöjda nivåer i hjärna och även andra vävnader, t.o.m. vid så låga exponeringsnivåer som 0,0067 W/kg i helkropps-SAR. I studier som undersökt olika långa exponeringsperioder var nivåerna av oxidativ stress lägre efter längre exponeringar. I ett antal studier exponerades dräktiga försöksdjur och påverkan på avkomman undersöktes. Negativa effekter observerades på fortplantningssystemen både hos honor och hanar vid låga exponeringsnivåer (helkropps-SAR på mindre än 0,05 W/kg). Varierande resultat erhölls för parametrar som rör avkommans utveckling.

De studier som beskrivits gjordes alla på gnagare, men tre studier har även gjorts på andra försöksdjur än däggdjur. För kycklingembryon såg man ingen påverkan på överlevnad eller genuttyck efter exponering under hela utvecklingsperioden. Exponeringsnivåerna var dock mycket låga, runt 0.04 W/kg. För bananflugor resulterade en 30 minuters exponering i olika uttryck för 168 gener i äggceller, inklusive gener som har samband med metabolism, stress och apoptos. För ödlor, slutligen, så resulterade långtidsexponering i en minskning av medfödda immunreaktioner, men ingen påverkan av förvärvad immunrespons.

Studier på människa

Nya resultat med avseende på EEG mätt i vaket tillstånd är motstridiga. Medan en studie inte visar några effekter så gör två andra studier det. Men även dessa två studier är motstridiga sinsemellan. Den ena studien fann en minskning av aktiviteten av hjärnvågorna i frekvensområdena delta och beta, medan den andra i huvudsak fann påverkan i deltaområdet och en ökning av aktiviteten betaområdet. Kognitiva prestanda och symtom påverkades inte i de studier som publicerats under rapporteringsperioden, vilket bekräftar tidigare forskningsresultat. Studier som rapporterade variationer i hjärtfrekvens är inte informativa beroende på metodologiska begränsningar. En studie antyder att sömnens makrostruktur, särskilt REM-sömnen, påverkas av exponering för radiofrekventa fält under sömn när analysen sker på individnivå. Detta behöver dock bekräftas i ytterligare studier.

Epidemiologi

Frågan om användning av mobiltelefon kan orsaka hjärntumörer eller inte avhandlades under de två senaste åren huvudsakligen genom att studera förändringar över tid. Resultaten är inte helt entydiga men pekar sammantaget mot att samband saknas. Dessa tidseriestudier lider inte av minnes- eller urvalsfel, som är problem vid fall-kontrollstudier, men de är istället känsliga för långsamma tidstrender. Förändringar i användning av diagnoskoder eller förbättrade diagnostiska verktyg, och därmed förbättrad upptäcktsfrekvens, kan skapa en skenbar ökning eller minskning i incidensen av hjärntumörer eller olika subtyper av tumörer. De få antydningar som finns om ändrade incidenser hänger därför snarare samman med sådana metodologiska begränsningar än verkliga förändringar i risk.

Ett flertal studier har observerat en försämrad spermiekvalitet hos mobiltelefonanvändare. Det är välkänt att värme påverkar spermiekvaliteten. Exponering från mobiltelefoner kan orsaka värme, men vid exponeringsnivåer under gällande riktvärden och vid nivåer som vanliga användare utsätts för är graden av uppvärmning för låg för att några sådana effekter skulle kunna uppträda. Det finns inte heller några kända biologiska mekanismer som kan förklara en effekt vid mycket låg uppvärmning. Det stora problemet med de aktuella studierna är att det inte gjorts några försök att uppskatta exponeringen av testiklarna för det radiofrekventa fältet, utan man har nöjt sig med ”användning av mobiltelefon”. Dessa studier kan därför inte ge något svar på om de observerade sambanden orsakas av exoneringen eller av andra faktorer som hänger samman med användning av mobiltelefon, som t.ex. brist på fysisk aktivitet eller förhöjda stressnivåer. Frånvaro av justering för möjliga felkällor i form av påverkande faktorer är fortfarande en stor svaghet i många av dessa studier. Därför kommer ytterligare studier gällande spermiekvalitet som bara baseras på frekvens eller tidsperiod av mobiltelefonanvändning knappast att ge någon ny information.

Liknande frågetecken finns för olika observerade samband mellan beteende och hälsorelaterad livskvalitet hos barn och ungdomar. De flesta av studierna fann samband, men det bakomliggande orsaksmönstret är svårt att klargöra. En nederländsk studie jämförde skattningar av olika sömnvariabler, t.ex. insomningsproblem, sömnperiodens längd, vakenperioder under natten, som antogs kunna hänga samman med exponering för radiofrekventa fält med sådana som antogs inte vara påverkade av exponering som orolig sömn, sömnapnéer. Studiens resultat tyder på att sambanden snarare orsakas av andra faktorer som sammanhänger med mobiltelefonanvändning. Samma slutsats kan dras från en schweizisk studie som jämförde effekter från samlad exponering av hjärnan för radiofrekventa fält med användningssätt som ger låg exponering (sms, spel) eftersom man fann starkare samband för den senare typen av exponering. Anmärkningsvärt är att ett annat mönster kunde iakttas för minnesfunktioner, där man fann starkare samband för exponering för radiofrekventa fält än

för användarvariabler som inte har samband med sådan exponering. Även resultaten från lateralitetsanalys, dvs. på vilken sida av huvudet som man håller telefonen, tyder på påverkan från exponeringen. I andra nyligen publicerade studier av kognitiva prestanda och exponering för radiofrekventa fält för barn och ungdomar sågs emellertid inte några sådana samband.

Nyligen publicerade studier av elkänslighet har inte identifierat några fysiologiska egenskaper som skulle kunna underlätta diagnostisering eller utveckling av fungerande terapeutiska alternativ.

Allmänt sett har studiekvaliteten i de epidemiologiska studierna varit mycket varierande under de senaste två åren. Å ena sidan har det publicerats många studier av låg kvalitet, som inte uppfyller fundamentala kvalitetskriterier, och som följaktligen har uteslutits från granskning i den här rapporten. Å andra sidan kan några nya tillvägagångssätt visa sig lovande för att erhålla nya insikter om möjliga hälsoeffekter från exponering för radiofrekventa fält.

En allmän kommentar

Liksom föregående år har det varit nödvändigt att utesluta ett antal studier från granskning beroende på dålig kvalitet och frånvaro av viktig information. De flesta studier som utslutits har saknat, eller lämnat ofullständiga uppgifter om dosimetri, dvs. storleken och fördelningen av exponeringen, eller har saknat oexponerade kontroller. Utan information om dosimetrin kan eventuella effekter inte ställas i relation till exponeringsnivån och utan oexponerade kontroller är det omöjligt att hänföra eventuella effekter till den aktuella exponeringen.

Det är mycket olyckligt att forskare inte håller sig till internationella riktlinjer avseende rapporteringen av sina studier och att vetenskapliga tidskrifter ofta inte har ett adekvat system för faktagranskning som korrigerar sådana misstag. Det finns också en risk att resultat från studier av dålig kvalitet kan skrämma människor och därigenom påverka deras hälsa och välbefinnande. Detta är ytterligare ett skäl till att endast studier med upplägg av god kvalitet ska finansieras, genomföras och publiceras.

Artiklar som på grund av bristande vetenskaplig kvalitet inte granskats i denna rapport har listats i ett appendix tillsammans med orsakerna till varför de uteslutits.

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 and 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 provide 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[1] 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)[2]. 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 exposure to electromagnetic fields has an effect and studies indicating a lack of 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 and the relevance of any experimental biological model used.[3]

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.

[1] Articles are primarily identified through searches in relevant scientific literature data bases; however, the searches will never give a complete list of published articles. Neither will the list of articles that do not fulfil quality criteria be complete.
[2] In the 2017 report, articles not taken into account due to insufficient scientific quality are listed in an appendix and reasons for not being taken into account are indicated.
[3] 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).

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

A large number of studies have been recognized on the effect of static magnetic fields (SMF) in cell cultures, but, following standard quality criteria[4], only three of them were considered.

1.1.1. Development and Reproduction

The effects of 1 and 10 mT static (DC) or 1 and 10 mT 50 Hz sinusoidal (AC) magnetic fields (MF) on vascular differentiation processes were investigated *in vitro* and *in vivo* (Bekhite et al., 2016). For *in vitro* studies, mouse embryonic stem (ES) cells were employed. Embryonic bodies (EB) were exposed/sham-exposed from day 2 until day 8 of differentiation. A significant inhibition of vascular endothelial growth factor (VEGF) protein expression was detected in EBs exposed to 10 mT static or sinusoidal MF, while an increased differentiation was induced following exposure to 1 mT. Furthermore, 10 mT AC or DC MFs displayed a significant increase in apoptosis ($p<0.05$), while no effect was detected at 1mT. ROS formation increased for all the exposure conditions tested ($p<0.05$), but decreased after pre-incubation with free radical scavengers. By using the same exposure system and exposure conditions, the authors obtained similar results from *in vivo* experiments in female BALB/c mice (see section 1.2.1).

To assess whether occupational exposure to gradient magnetic fields (GMFs) emitted by Magnetic Resonance Imaging (MRI) scanners causes biological changes in human cells, cell proliferation and clonogenic potential of human hematopoietic stem cells were evaluated by Iacininoto et al (2016). To this purpose, a customized exposure system, able to reproduce gradient signals measured during MRI routine diagnostic exams, was realized. To mimic exposure at 1.5 T and 3 T MRI scanners, the effect of two GMF exposure protocols were investigated on hematopoietic progenitor (CD34+) cells isolated from peripheral blood samples of six blood donors from the general population, and three umbilical cord blood samples. Cell cultures were exposed or sham-exposed for 72 h. In addition, cultures set up with blood samples from three donors working at 1.5 and 3 T MRI facilities were also examined to compare *in vitro* and *in vivo* exposure.

The results of laboratory exposure on proliferation and clonogenic cell output of cells obtained from blood samples from the general population indicated that GMFs had no effects on cell proliferation, as evaluated after 72 h exposure and after 7 days of culture. Nevertheless, a significant higher output of clonogenic cells was detected with respect to sham exposed samples ($p<0.05$). It was no more detectable after 7 days of culture in samples exposed at 1.5 T, while persisted over time at 3 T, being detectable up to two weeks after exposure ($p<0.05$). At variance, no effects were detected in cells from MRI workers, compared to samples exposed *in vitro* to GMFs and of sham-exposed controls. The higher output of clonogenic cells exposed *in vitro* was confirmed in cells from cord blood samples exposed at 3 T. These findings suggest that GMFs at 3 T influence the mechanisms regulating hematopoietic cell differentiation, without affecting cell proliferation.

1.1.2. DNA integrity and oxidative stress

In order to explore the effect of exposure conditions which likely occur in the framework of MRI clinical procedures, Romeo et al (2016) exposed a human foetal lung fibroblast cell line (MRC-5) to 370 mT magnetic induction under different exposure times. Viability, measured in terms of metabolic activity and membrane integrity, and ROS formation were evaluated in cultures exposed/sham exposed 1 h per day for 4 consecutive days (six independent experiments). Longer exposure duration

[4] See Appendix for excluded studies.

(24 h) was carried out to evaluate DNA integrity in terms of DNA migration and early apoptosis (three independent experiments). No effects were detected for any of the exposure conditions investigated.

1.1.3. Conclusions for static magnetic field cell studies

Although in the last year a large number of papers have been published on the effect of SMF on cell cultures, in most of them no sham-controls have been assessed. Therefore, since the comparison between exposed and not exposed samples have been carried out with respect to negative controls, such papers have not been included in the analysis. From the studies considered in the period of interest (Table 1.1.1) it seems that static magnetic fields stronger than 1 T are able to interfere with cell differentiation, while magnetic fields of lower intensity do not affect fundamental cellular processes.

Table 1.1.1 – *In vitro* studies on exposure to static magnetic fields

Cell type	Endpoint	Exposure conditions ELF-EMF	Effect	References
Mouse embryonic stem (ES) cells	differentiation	SMF (DC), 1, 10 mT 50 Hz l (AC), 1, 10 mT 6 days	inhibition of VEGF protein expression and increased apoptosis at 10 mT; Increased differentiation at 1 mT. Increased ROS formation in all cases.	Bekhite et al. (2016)
Human hematopoietic progenitor (CD34+) cells	Proliferation, clonogenic output	1.5, 3 T 72 h in vitro MRI workers	In vitro exposure: Higher output of clonogenic cells, reverted after 7 days from 1.5 T exposure, but not at 3 T. Workers: No effects No effect on proliferation.	Iacininoto et al. (2016)
Human foetal lung fibroblasts (MRC-5)	viability, proliferation, ROS formation, DNA integrity	370 mT, 1 h/day for 4 days 24 h	No effect	Romeo et al. (2016)

Abbreviations: AC: alternating current; DC: direct current; MRI: magnetic resonance imaging; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor.

1.2. Animal studies

In the previous reports only single studies on SMF effects were found whereas during this reporting period eight animal studies were identified. One study addressed developmental effects, another effects on the physiologically important metals Cu and Zn in main organs after 1mT and/or 10 mT, a third the effect of 16 mT static magnetic fields (SMF) on hypertension. A fourth experiment investigated the 20-204 mT SMF-effect on pain. Finally, all four remaining studies examined physiological and co-exposure effects of 128 mT SMF.

1.2.1. Development and Reproduction

In female BALB/c mice, n= 10/group, the effect of sham, 1 and 10 mT static (DC) or 1 and 10 mT 50 Hz sinusoidal (AC) magnetic fields (MF) on embryonic development was investigated (Bekhite et al., 2016). Exposure for 20 days and 8 h/d during the entire gestation period to 10 mT MFs increased resorptions and dead foetuses. 10 mT led to reduced crown-rump length and fresh weight, to less blood vessel differentiation and resulted in histopathological changes together with decreased vascular endothelial growth factor (VEGF) protein expression in lungs, liver, kidneys and eyes. From day 2 until day 8 of differentiation, embryonic bodies (EB), derived from pluripotent mouse embryonic stem cell line CCE were exposed for 8 h/d to sham, 1 and 10 mT static (DC) or 1 and 10 mT 50 Hz sinusoidal (AC) MFs using the same exposure system. ROS production and apoptosis increased, vascular marker and VEGF expression decreased after 10 mT MF exposure. In summary, VEGF was

demonstrated as an important mediator during embryonic development and is linked to malformation and decreased blood vessel formation after 10 mT of both SMF and ELF-MF exposures.

1.2.2. Physiology

De Luka et al. (2016) exposed groups of 10 male 6 month-old Swiss mice to 1 mT SMF for 30 days. Group 1 was sham-exposed to the ambient geomagnetic field of 40 µT, group 2 to an upward oriented and group 3 to a downward oriented SMF of each 1 mT. Basically irrespective to the orientation, 1 mT SMF entailed a decreased concentration of Cu in brain, of Cu and Zn in liver, and of increased Zn in brain, whereas Cu in spleen was not affected.
The authors' general conclusion that the "specific changes…in the Cu and Zn content in the examined organs…presumably could be attributed to protective…effects of SMF" is not necessarily resulting from the data of this too small experiment examining three organs and using one exposure level only.

Milovanovich et al. (2016) tested the biological effects of a 128 mT SMF but discriminated between upward- and downward-orientation. The small experiment used 3 groups of 9 male 9-10 weeks old Swiss mice: 1) sham, 2) downward-, 3) upward-orientated 128 mT exposure for 5 days, 1 h/d between 8-12 am. Blood, spleen, liver, brain and kidneys were obtained for further blindly performed analyses. No differences were seen between the groups in body weight or food consumption. Exposure of both SMF orientations resulted in a decrease of total white blood cells and of granulocytes in serum and spleen. Nonspecific pyelonephritis and an increase in serum HDL (high density lipoproteins) was observed additionally for both orientations. Upward-orientated SMF led to edema of the brain and increased spleen cellularity, whereas downward-orientated SMF caused inflammatory (periportal) liver infiltration. Summarizing, in blood and organ tissue pro-inflammatory effects were observed, partially depending on the SMF-orientation.

Tasic et al. (2017) of the same Serbian research group exposed groups of 17 twelve-week old male spontaneously hypertensive (SHR) rats for 30 days to 1) upward-oriented or 2) downward-oriented SMF of 16 mT intensity. Group 3 was sham-exposed. After the 30 day exposure period all SHR rats were surgically equipped with a femoral arterial catheter for blood pressure recording followed by a 2 day recovery period, arterial blood pressure was recorded. For a quantitative detection of noradrenalin a blood sample using the femoral catheter was obtained after blood pressure recording. Up- and downward-oriented SMF significantly reduced arterial blood pressure as well as plasma noradrenalin levels and increased the sensitivity of the baro-receptor reflex. A reduction in heart rate was seen in downward-oriented SMF only. The experimental set-up and results demonstrate that a 16 mT SMF influences the cardiovascular system towards normotension.

In continuation to studies of previous years of the Tunisian research group Ferchichi et al. (2016) treated male Wistar rats with a single intraperitoneal (ip) injection (1.1 mg/kg body weight) of silica-coated gold nanoparticles (GNP) and exposed them to 128 mT SMF for 14 days (1h/d). Four groups of 6 rats were used: 1) control (0.1 mL saline), 2) GNP, 3) SMF, 4) GNP+SMF. The study focussed on effects in lungs only. As demonstrated by fluorescence microscopy, co-treatment (GNP+SMF) increased accumulation of GNP in lungs. Light microscopy detected in GNP- lungs a slight, and in GNP+SMF-lungs marked hyperplasia of BALT (bronchus-associated lymphoid tissue) and alveolar compression. In lung homogenates the oxidative stress was assessed by measuring malondialdehyde (MDA) levels. These increased in the order SMF, GNP, GNP+SMF treatment, whereas a fall of CuZN-superoxide dismutase, catalase and glutathione peroxidase activities was seen in the same order. In this small study SMF increased the accumulation and inflammatory reaction of GNP in lungs and reinforced oxidative stress.
Unfortunately, the same parameters were not tested in other main organs (liver, kidneys, spleen, and testes) but discussed on the basis of other literature data.

In a further study from Tunisia Ghodbane et al. (2015) investigated the effect of 128 mT SMF-exposure for 5 days (1 h/d) on oxidative stress and apoptosis in rat brain and liver. In addition, the assumed dietary protective effect of selenium (Se) and vitamin E supplementation was tested in male

Wistar rats. Six males per group were assigned to 1) control (sham), 2) Se (0.2 mg/L Na_2SeO_3 in drinking water for 4 weeks), 3) Vit E (150 mg/kg by gavage for 5 days), 4) SMF, 5) Se + SMF, 6) Vit E + SMF. SMF increased the catalase (CAT) activity in liver and induced hepatocyte apoptosis. CAT and apoptosis were not induced in brain. MDA in brain and liver was unaffected by SMF. Co-exposures of Se and vit E restored liver CAT activity but did not reduce hepatocyte apoptosis. Again, in this small study only one field-strength and two main organs were selected. Such a pilot data set cannot give any information on a potential exposure level-dependency.

Lahbib et al. (2015) presented a 3rd and very similar 5-day study from the same group using this time vitamin D for co-exposure. 24 male 50-70 g Wistar rats formed groups of 6 rats each: 1) sham control, 2) vit D (1600 IU/100g by oral gavage (*per os, po*) during 5 days), 3) 128 mT SMF, 4) co-exposure (SMF + once po vit D after the fifth SMF exposure of 1 h/d). Compared to control, plasma glucose and insulin levels decreased after SMF exposure more than after co-exposure. In addition, the pancreatic islet area decreased after SMF exposure only but was similar in control, vit D and co-exposed groups. In rat pancreas, the expression of the glucose transporter GLUT2 failed but was detected in the other, especially co-exposed group(s). Finally, vit D alone did not substantially affect the tested parameters.
Unfortunately, the paper suffers from some incomplete experimental details (e.g. the time of day for vit D gavage and decapitation of the animals for blood collection, and inaccurate description of results (i.e. inconsistencies between text and figures). Once again, this small study should be looked at with reservations.

Zhu et al. (2017) studied in adult male BALB/c mice the effect of a 20-205 mT SMF, produced by NdFeB magnets, on pain and expression of P2X3 receptors in trigeminal ganglion (TG). P2X3 receptors are involved in initiation and maintenance of pain. In this study pain originated from an experimental tooth movement (ETM) induced by springs between teeth. Three groups (n=6/gr) were used for pain levels: 1) SMF + ETM, 2) ETM, 3) control. Exposure started after ETM and lasted up to 14 days, >22 h/d. Pain levels were evaluated by the Mouse Grimace Scale (MGS) 4 h, 1, 3, 7, 14 d after ETM. Also 4 h, 1, 3, 7, 14 d after ETM subgroups of n=8 mice were sacrificed for collection of TG and subsequent detection of P2X3 by immunohistochemistry and Western blotting; i.e., 40 mice each for 4) SMF + ETM, and 5) ETM. Eight non-treated mice served as 7) controls. The peak of pain levels was seen 3 days after ETM, thereafter decreased. SMF reduced the pain at the time-points 4 h, 1 and 3 days but not after 7 and 14 days. Expression levels of P2X3 were significantly lower after 4 h, 3 and 7 days. In conclusion, the applied 20-204 mT SMF reduced pain and down-regulates pain-relevant P2X3 receptors in TG in this specific pain model.

1.2.3. Summary and conclusions on static magnetic field animal studies

Some teratogenic effects and a decrease in vascular endothelial growth factor (VEGF) expression were reported in mice after exposure to a 10 mT static magnetic field, but not after a 1 mT exposure. Using arbitrarily chosen study design and co-exposures, i.e. objectives and justification are missing, some researchers address beneficial health effects of SMF, e.g., 16 mT SMF influences the cardio-vascular system of hypertensive rats towards normotension. 128 mT SMF co-exposures with different test items tested in four different studies resulted in diverging effects without any central theme. Moreover, in all four studies only one 128 mT exposure level was used, and an exposure-response could not be evaluated. Finally, pain reduction due to 20 -204 mT SMF exposure was demonstrated in a specific pain model in mice.

Table 1.2.1 Animal studies on exposure to static magnetic fields

Endpoint in rodents	Reference	Exposure SMF	Duration	Effect
Development & Reproduction	Bekhite et al. (2016)	1, 10mT; In addition 50 Hz, 1 & 10mT	20 d gestation period, 8h/d	Malformation(s), VEGF decrease at both 10mT (SMF &

		ELF-MF		ELF-MF) exposures
Physiology & Pathophysiology	De Luka et al. (2016)	1mT	24h/d, 30 d	Liver: Cu↓, Zn↓; brain: Cu↓, Zn↑; spleen: Zn↓ Cu↔
	Tasic et al. (2017)	16mT, up-/down-ward oriented	24h/d, 30 d	Blood pressure reduction in SHR rats
	Ferchichi et al. (2016)	128mT +gold NP	1h/d, 14 d +1.1 mg/kg ip	Oxidative stress in lungs re-inforced, GNP accumulation & inflammation increased
	Ghodbane et al. (2015)	128mT +Se or +Vit E	1h/d, 5d + 0.2mg/L dr.-w. or + 50 mg/kg/d, 5d 1h/d, 5d + vit D (1600 IU per 100g bw) po	CAT and apoptosis in liver increased, but not in brain, MDA in brain and liver unaffected by SMF. Co-exposures of Se and Vit E restored liver CAT, but no reduction in hep. apopotosis
	Lahbib et al. (2015)	128mT	1h/d, 5d	SMF: Blood glucose ↑, insulin↓, islet area ↓, no GLUT2 expression in pancreas. Partly restoration after single vit D gavage.
	Milovanovich et al. (2016)	128 mT upward- & downward	>22h/d, 14d	WBC↓, Lymphocytes (serum) ↓, granulocytes (spleen) ↓, kidney & liver inflammation, Brain edema
	Zhu et al. (2017)	20-204 mT		Pain ↓, P2X3 receptor down-regulation after exp. tooth movement

Abbreviations: ↑= increase (d); ↓=decrease (d); CAT: catalase; Cu: copper; ELF-MF: extremely low frequency magnetic field; GLUT: glucose transporter; GNP: gold nanoparticles; MDA: malondialdehyde; SE: selenium; SHR: spontaneously hypertensive; SMF: static magnetic field; VEGF: vascular endothelial growth factor; Zn: zinc; WBC: white blood cell count.

1.3. Human studies

During this reporting period two human provocation studies with static magnetic fields were published (Kirimoto et al., 2016, Nojima et al., 2016). Both investigated possible effects of transcranial static magnetic field stimulation (tSMS) as a new non-invasive brain stimulation technique. Since this topic is beyond the scope of this report, they are not discussed here.

1.4. Epidemiological studies

The previous SSM report (SSM, 2016) concluded that epidemiological studies confirmed associations between magnetic resonance imaging (MRI) work and experiencing acute symptoms. Evidence on potential long-term effects was scarce. One study suggested that traffic accidents of MRI workers should be studied in more detail and no effects on behaviour were seen in small children that underwent a single MRI examination as foetus in another study.

1.4.1. Symptoms

Zanotti et al. (2015) performed a small survey among 17 physicians who had been working more than one month, but less than one year with MRI scanners. The physicians were on average 33 years old, 9 were men and 8 were women. All attended a postgraduate school in radiology. Participants filled in a questionnaire on MRI-related symptoms. 94% reported ever having experienced symptoms when working with MRIs; these were primarily unusual drowsiness/tiredness, concentration problems, headaches, sleep disorders, nausea, illusion of movement and dizziness/vertigo. The majority of the symptoms was reported to appear after about 15 minutes working in the scanner room and to disappear about 30 minutes after exposure had ceased, although it is somewhat unclear how that could be the case for sleep disorders. Most of the radiologists reported a regression of the complaints after about 1-2 months after starting work in the MRI room, suggesting some form of adaptation.
This is a very small study on symptoms in radiologists working with MRI scanners. A limitation is self-reported outcomes combined with self-reported exposures. The results are, however, in line with previous symptom reports. Note that some studies report a much lower prevalence of symptoms, which is likely due to different time frames that symptoms are inquired for (e.g. ever having experienced symptoms when working with an MRI, symptoms during the past year, or symptoms that occurred during the last work shift). Additional factors may be related to the fact that radiologists in the beginning of uptake of MRI work may report more symptoms.

Fatahi et al. (2017) performed a survey in 8 research institutions across Europe where 7T MRI scanners were used. Of 116 invited technical personnel, 66 (56%) filled in a questionnaire inquiring about exposure as well as about health symptoms. Regarding exposure, years of experience working with 7T MRI scanners was asked, as were work practices such as presence during image acquisition in the MRI room, how often and how long they usually stayed in the MRI room, and working hours per week. Regarding health, exposure-related symptoms were asked, as well as perception of safety in the work environment. Participants were on average 31 years old (SD 7 years). 92% of the participants reported ever experiencing any symptoms. At least half of the participants had ever experienced vertigo, metallic taste, headache, fatigue, feeling of instability or involuntary muscle contraction when working with MRI scanners. More symptoms were reported in workers who reported presence during image acquisition in the MRI room. Nevertheless, all except one participant felt that working with MRI was relatively safe (85% of the participants felt “moderately” or “very safe” when working with the MRI scanners).
The study indicates that technicians working with MRI scanners often perceive exposure-related symptoms. This is in line with previous studies. Technicians will be exposed to static fields when being close to the scanner, in addition to time-varying gradient fields when moving around the scanner. During image acquisition, workers may be additionally exposed to stray fields from scanning (kHz range, plus possibly some low-level RF-fields). This study thus adds the observation that more symptoms were reported in technicians who were present during image acquisition which could be related to the stray fields during scanning. Workers of research institutions are an interesting collective because such facilities have installed stronger scanners (7 T) than most clinical institutions, so the type of scanners this study was targeting.

A survey on vertigo including work-shift measurements was reported by Schaap et al. (2016). 234 participants from 15 clinical and research facilities in the Netherlands were included. Employees working with MRI scanners during the days of the visits in 2011 were invited to participate. All included persons performed static and time-varying magnetic field measurements. Vertigo as well as work practices and potential confounders were asked for in a diary. 100 persons contributed data for more than a single day. Vertigo was reported by 20 participants, occurring in 22 out of 33 shifts of affected participants. Of six exposure metrics, reporting of vertigo was significantly associated with all metrics, but best predicted with full-shift time-weighted average of time-varying magnetic fields. The authors discuss that due to the correlation of all exposure metrics, it remained impossible to clearly disentangle effects from the different types of exposure. This, however, means that prevention of vertigo in affected workers could thus be based on any of the exposure metrics.

Particular strength of the study includes the relatively large data base with individually measured exposure for participants. Regarding vertigo, there seem to be workers who are much more likely to be affected compared to others, equally exposed, co-workers. The reasons for that remain unclear.

1.4.2. Reproduction

Ray et al. (2016) evaluated all mother-child pair births in Ontario, Canada that resulted in live birth or stillbirth between April 2003 and March 2015. Two types of exposures were evaluated: (Cohort 1) Any MRI that was performed during the first trimester of the pregnancy, or (Cohort 2), a Gadolinium-based contrast-enhanced MRI that was performed during pregnancy, independent of trimester of the pregnancy. In cohort 1, five adverse birth outcomes were evaluated: stillbirth after 20 weeks gestation and including 28 days after birth, congenital anomalies excluding children with a concomitant chromosomal disorder, neoplasm, vision loss, hearing loss. For cohort 2, the authors evaluated next to the five outcomes of cohort 1 also nephrogenic systemic fibrosis (NSF), a rare disease that has been associated with gadolinium exposure. About 1.4 million births were evaluated, of which 5 654 had an MRI during first trimester exposure, and 394 had a gadolinium-enhanced MRI. The authors took account of a range of potential confounders in their statistical analysis by calculating propensity scores and using these scores to weigh the risk estimates. In cohort 1, HRs for the above listed outcomes were not statistically significantly elevated. Risk of stillbirth in cohort 1 was 1.68 (95% CI 0.97 to 2.90), but in cohort 2, this risk was 3.70 (95% CI 1.55 to 8.85). Fewer than five NSF events occurred, which resulted in low power to evaluate the association. Within cohort 2, risk of any rheumatologic, inflammatory, or infiltrative skin condition was elevated if gadolinium-enhanced MRI was performed during the first trimester (adjusted HR, 1.41; 95% CI, 1.11-1.79).
This is a well-performed large registry-based study, health outcomes were selected based on a priori considerations of potential health effects. Because residents of Ontario receive universal healthcare, this registry should cover all births that occurred in this time period in Ontario, and the registry also includes relevant additional information, such as information on SEP or age of the mother, but also maternal health-related conditions. A particular challenge for this type of study is reverse causality in the sense that the reason for receiving an MRI investigation during pregnancy may also affect the unborn child. This study used up to date methods (propensity score and inverse probability weighting) do deal with such potential bias. Unfortunately, different types of MRI scanners that translate into differences of exposure levels could not be evaluated in this study. Gadolinium use during pregnancy is discouraged, but this study provides evidence of a harmful effect to the foetus from the use of the contrast medium.

1.4.3. Conclusions on epidemiological studies

Transient symptoms experienced by workers exposed to magnetic resonance imaging (MRI) scanners are well established, but there is a lack of knowledge regarding potential long-term health effects. A large registry-based study on MRI scans of pregnant women provided no clear evidence of risk of stillbirth, but evidence of harmful effects to the foetus from the use of Gadolinium contrast medium was provided.

2. Extremely low frequency (ELF) fields

2.1. Cell studies

Twenty-eight papers have been described in this section, dealing with the effect of ELF fields alone and in combination with chemical or physical agents.

2.1.1. Differentiation

Ma et al. (2016) investigated effects of extremely low frequency magnetic fields (ELF-MF) (50 Hz, 1 mT) exposure on neuronal differentiation of embryonic neural mice stem cells. They found that four hours of exposure per day for one, two and three days increases cell proliferation ($p<0.01$ vs. sham). When the exposure was carried out during the induced differentiation to neuronal cells (cells treated with specific growth factors), an increased development of neurons was detected. In particular, the development of astrocytes was not affected, while exposed neurons developed longer neurites, with more branching points ($p<0.01$ vs. sham), without inducing cell apoptosis. An increase of a specific calcium channel in the cell membrane, whose absence eliminated all effects of the ELF-MF on the differentiation process, suggests that exposure to ELF-MF influences cellular calcium concentration, which in turn affects neuronal development. All the reported results refer to five duplicate independent experiments. According to the authors, it is not clear whether this has positive or negative implications.

2.1.2. Neurodegeneration

To investigate the association between exposure to ELF-MF and neurodegeneration Benassi et al. (2016) used human neuroblastoma cells (SH-SY5Y) exposed to an ELF-MF (50 Hz, 1 mT) for up to three days. By comparing exposed and sham exposed samples a slight increase of reactive oxygen species (ROS) production was detected ($p<0.05$), although cell proliferation and viability were not affected. Moreover, to evaluate if a correlation exists between Parkinson's disease (PD) and ELF exposure, SH-SY5Y cells were also treated with the neurotoxin MPP^+ (1-methyl-4-phenylpyridinium), a specific *in vitro* Parkinson's disease model. Treatments with MPP^+ alone induced ROS increase and cell death via the activation of caspase 3/7, the induction of p53 downstream gene expression, as expected. When cells were pre-exposed to ELF-MF the effect of MPP^+ was significantly enhanced ($p<0.05$). The addition of antioxidants restored the levels of ROS measured in sham exposed cultures. The results of this study suggest that ELF-MF exposure alone does not induce neuronal damage, but could promote the development of neurodegenerative diseases in the presence of additional environmental factors.

2.1.3. Neuronal activity

Three studies aimed to investigate the effect of ELF-MF exposure on neuronal activity.

de Groot et al. (2016) evaluated the effect of chronic exposure to ELF-MF on primary rat cortical neurons. Cell cultures were exposed for 7 days to block-pulsed with a main frequency of 50 Hz and different magnetic field intensities (1–1000 μT rms) to assess viability, calcium homeostasis, neurite outgrowth and spontaneous neuronal activity. When exposed cultures were compared to sham-exposed ones, cell viability was not affected for any of the exposure conditions adopted. Depolarization- and glutamate-evoked increases in intracellular calcium concentration ($[Ca^{2+}]i$) were slightly increased at 1 μT, while both basal and stimulation-evoked $[Ca^{2+}]$ (intracellular calcium concentration) show a modest inhibition at 1000 μT (94% vs. sham; $p<0.05$). Neurite length was unaffected up to 100 μT, but increased at 1000 μT ($p<0.05$). However, neuronal activity appeared largely unaltered following

chronic ELF-MF exposure up to 1000 μT. The authors concluded that the effects detected were small and essentially restricted to the highest field strength (1000 μT).

The effect of a 50 Hz ELF-MF on the activity of gamma-aminobutyric acid A (GABAA) receptors, was investigated by Yang and co-workers on cerebella granule neurons (CGNs) isolated from rats (Yang et al., 2015). Cells were exposed at 0.2 or 1 mT flux density for 30 to 120 minutes before assessing the current amplitudes (ion flux) upon administration of the neurotransmitter GABAA. After 60 min exposure at 1 mT an increase of about 20 % in the amplitude of GABAA currents was recorded in exposed cells compared to sham exposed ones ($p<0.05$), but no effect was detected for shorter exposure duration. For lower values of flux density (0.2 mT) an increase of only 10 % was recorded after 1 h exposure ($p>0.05$), while for longer exposure duration (2 h) the results obtained were comparable to the one recorded at 1 mT. Cellular signaling cascades possibly involved in the effect were also investigated following 1 h exposure at 1 mT by using specific activators and inhibitors: the protein kinase C was activated by the exposure, while activation or inhibition of the enzyme protein kinase C mimicked or abrogated the increased current amplitudes. The authors concluded that since 1 mT of exposure is not experienced by the general public and occasionally in occupational settings, the significance of their results is more applicable to biological mechanisms than population health risk assessments.

The effect of pulsed magnetic fields (PMFs) on amplitude of evoked compound action potential (CAP) from the segments of sciatic nerve was investigated by Ahmed and Wieraszko (2015). PMFs were applied for 30 min at 0.16 Hz and intensity of 15 mT and induced an enhanced amplitude of CAPs ($p<0.005$). Moreover, treatments with lidocaine and tetrodotoxin, two antagonists of sodium channel, reduced CAP amplitude of about 50%. Such a reduction was reverted when PMFs were applied after chemical treatments. Action potential was also modified by treatment with high potassium concentration, and veratridine: also in this case the effect was modified by exposure to PMFs. Neither inhibitors of protein kinase C and protein kinase A, nor known free radical scavengers had any effects on PMF action. On the whole, these results suggest that PMFs could modulate neuronal excitability at least partially through interactions with sodium channel.

2.1.4. Immune system

Golbach et al. (2015) used neutrophils isolated from human blood that, upon chemical *in vitro* activation, produces 'NETs' (neutrophil extracellular traps). NETs lead to increased antimicrobial properties as well as autoimmune diseases like lupus erythematosus and arthritis. Therefore, their formation can results in beneficial or detrimental effects. The authors employed a custom-made exposure system and an irregular combination of four block waves with frequencies of 320, 730, 880 and 2600 Hz (300 μT field intensity). Non-activated and phorbol 12-myristate 13-acetate (PMA)-activated cells were exposed for different times, depending on the target investigated. Exposures from 1 to 4 h were carried out to investigate NET formation, which resulted in enhanced activated neutrophils after 4 h exposure ($p<0.05$ compared to sham exposed cells), but not in non-activated cells. The elevated NET formation correlated well with increased antimicrobial properties, tested in an *in vitro* system. PMA, a potent inducer of NET formation, mimics a pathogenic stimulation in neutrophils by intracellular protein kinase C-activation. Combined treatments with PMA and EMF resulted in a synergistic effect on NET formation, suggesting that EMF modulates the PMA-induced signalling pathway downstream of protein kinase C- activation. In particular, the authors provide first evidence that low frequency electromagnetic fields enhance NET formation via an NADPH-oxidase-dependent mechanism, possibly by up regulated production of reactive oxygen species.

Luo et al. (2016b) examined the effects of six hours exposure to 50 Hz (250 μT, 500 μT, or 1 mT) MFs on the expression of inflammatory factor genes and a cluster of differentiation 69 (CD69) in mouse prime splenic lymphocytes activated by para-Methoxyamphetamine (PMA) and ionomycin. Cells were isolated from the spleen of 10 healthy Kunming mice and the levels of interleukin-2 (IL-2), IL-4, interferon-gamma (IFN-γ), GATA binding protein 3 (GATA-3) and T cell-specific T-box

transcription factor (T-bet) were assessed. Moreover, the expression of CD69 was also investigated. No differences were detected compared to sham-exposed controls. In this study, the effect of *in vivo* exposure was also investigated (see section 2.2.6).

2.1.5. DNA damage

Four studies investigated the effect of ELF-MF fields on DNA damage.

The effects of 24 h exposure to 50 Hz magnetic field, 10 and 30 μT field intensity, were investigated by Kesari et al. (2016) in two mammalian cell lines: human SH-SY5Y neuroblastoma cells and rat C6 glioma cells. To this purpose, micronuclei (MN) were assessed as a measure of genotoxicity, and cytosolic and mitochondrial superoxide concentrations as indicators of changes in reactive oxygen species (ROS). Co-exposures with menadione (MQ, a provitamin, precursor of vitamin K) were also carried out: following 24 h exposure, cell cultures were treated for 3 h with MQ. The results of three independent experiments carried out on SH-SY5Y cells indicated that a significant increase of MN frequency was induced only by exposure at 30 μT, either in presence and in absence of MQ ($p<0.05$). No effects were detected in C6 glioma cells. When the effect of exposures were evaluated in terms of free radical production, a statistically significant increase of the cytosolic superoxide level and production of mitochondrial superoxide was detected in C6 cells, but not in SH-SY5Y cells. Such an increase was more pronounced at 10 μT ($p<0.001$) than at 30 μT ($p<0.05$). Combined treatments did not induce variation with respect to samples treated with MQ alone. Multifactorial statistical methods were employed for data analysis. According to a number of their previous results, the authors write that their findings suggest that the threshold for biological effects of ELF-MFs is 10 μT or less.

In a further study, the same research group evaluated possible changes in proteins involved in DNA damage responses (c-H2AX, Chk1, p-Chk1, p21,p27, and p53) and in cell cycle distribution induced by ELF-MF, given alone or in combination with menadione (Luukkonen et al., 2017). To this purpose, they pre-exposed human SH-SY5Y neuroblastoma cells to a 50 Hz, 100 μT MF for 24 h prior to a 1 h or 3 h menadione treatment at different concentrations (from 0 up to 25 μM). In 3 independent experiments, no effects on the distribution of cell cycle stages were observed when cell cycle analysis was performed after the 24 h MF exposure followed by a 1h menadione treatment. However, after 3 h menadione treatment, increase in the G1 phase was observed ($p<0.05$), accompanied with a decrease in the S phase ($p<0.01$). This effect was also observed without menadione (0 concentration). When changes in proteins involved in DNA damage responses were investigated, a systematic decrease in MF-exposed vs. sham groups was seen after the 1 h menadione treatment in p21 level ($p<0.05$). This effect was not observable in the samples exposed to menadione for 3 h. No effects were observed in the level of any other protein studied. Furthermore, treatment to menadione for 1 or 3 hours resulted in a significant ($p<.001$) dose-dependent increase in DNA damage assayed by the Comet assay, as expected. The damage was significantly decreased only in cells that were pre-exposed to MF for 24 h and treated for 1 h with menadione ($p<0.05$). No effect was detected when menadione treatment was 3 h long.

Zhu et al. (2016) investigated the induction of DNA damage in human lens epithelial cells (HLE). Cell cultures were exposed to 50 Hz MF, at 400 μT field intensity for 2, 6, 12, 24 and 48 hours and the induction of double strand breaks and DNA fragmentation was measured by means of the phosphorylated form of histone variant H2AX (ϒH2AX) foci formation (5 independent experiments) and the alkaline comet assay (3 independent experiments). For each endpoint investigated, appropriate positive controls were also provided. Compared to sham-controls, no statistically significant differences were detected for all the field intensities investigated.

A study was conducted to evaluate the effect of pulsed magnetic fields (PMF) exposure on DNA methylation. Epigenetic processes, including DNA methylation, are a molecular interface mediating the interaction between genome and environment. Changes in global genome methylation have been reported in association with several environmental factors, but no studies are available on the effects

of ELF-MF on DNA methylation in human cells. Giorgi et al. (2017) investigated the DNA methylation levels of the L1 5′UTR region, which is commonly investigated as a surrogate for global genome methylation. Human neural cells (BE(2)C) were exposed for 24 and 48 hours to a PMF (50 Hz, 1 mT) alone or in combination with oxidative stress (hydrogen peroxide given during the first 1h of exposure). For each experimental condition, three independent experiments were set-up. After 24 h of PMF exposure, a significant increase in the methylation level was found, compared to sham-treatments ($p<0.05$). Such an increase was not detected at 48 h exposure. When samples treated with hydrogen peroxide were compared to control cultures a decrease was recorded after 24 h ($p<0.05$) but not for longer times (48 h). Combined treatments exhibited significantly less methylation as compared to samples exposed to PMF alone for 24h ($p<0.01$), which was less pronounced after 48 h exposure ($p<0.05$). On the whole, the results obtained indicate that exposures to the single agents PMF and hydrogen peroxide induced weak variations of DNA methylation levels. However, the combined exposure leads to a significant decrease of DNA methylation levels, although most of the changes were transient, suggesting that cells can restore homeostatic DNA methylation patterns.

2.1.6. Oxidative stress

Calcabrini and co-workers (Calcabrini et al., 2017) evaluated the induction of oxidative stress by 1, 2 or 4 hours exposure to 50 Hz at flux density ranging from 25 to 200 μT. Healthy human keratinocytes (NCTC 2544 cells) were employed as an *in vitro* model. Cells were exposed and sham-exposed for 1 h at 25, 50, 100, 150 and 200 μT. The ROS formation was evaluated soon after, while viability was tested 24 h after exposure. The results of three independent experiments indicated that an increase in ROS formation was induced only at 50 and 100 μT ($p<0.01$). Cell viability did not vary with respect to sham-exposed samples for any of the exposure conditions examined. A significant increase in ROS production was also observed after 2 h at both 50 and 100 μT ($p<0.05$), while no effect was recorded after longer exposure times (4 h). Cells were also exposed to 50 and 100 μT in presence of o-Phenanthroline (o-Phe, a ROS inducer) or Rotenone (Rot, a ROS inhibitor). Combined treatments for 1 h with 50 μT and o-Phen reduced ROS production to control levels, while no differences were detected between cells treated with Rot alone and Rot + MF, suggesting that ROS generation induced by MF is not at the mitochondrial respiratory chain level. Several antioxidant enzyme activities were also investigated 1, 2 and 4 h after 50 and 100 μT exposure. In most cases a statistically significant variation was recorded after 1 h at 50 μT with respect to sham samples ($p<0.05$). However, all the observed alterations reverted to controls after 24 h of recovery, confirming the transient effect and the rapid recovery of standard conditions without dangerous effects on cell health. The authors concluded that the observed effects, although reversible, vary according to the density and duration of cell exposure and a greater cell vulnerability is shown at 50 μT.

Zeng et al. (2017) evaluated the effects of different patterns of ELF-MF exposure (single and repeated) on primary cultured hippocampal neurons at different developmental stages by assessing viability, apoptosis, genomic instability, autophagy and oxidative stress. Cells were isolated and cultured in vitro. The experiments were carried out after 7 or 14 days *in vitro* (DIV7 and DIV 14, respectively). For exposure, a 50-Hz 2-mT ELF-MF was given once for 30 min, 8 h, or 24 h (single exposure) or was repeated 30 min or 8 h/day for 7 days (3 independent experiments for each condition). Single exposures did not affect viability for any of the experimental conditions investigated. On the contrary, repeated exposures resulted in a significant decrease of DIV 14 viable cells ($p<0.05$). DIV7 cells significantly decreased the viability only after 8 h repeated exposures ($p<0.05$), indicating that changes in exposure time and stage influence the effect of ELF-MFs on cell viability. Repeated exposure at DIV7 induced no significant changes in ROS formation compared to sham samples, while a statistically significant increase was recorded in DIV 14 cells ($p<0.05$). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is mainly responsible for the ROS generation associated with neuronal death. Since the authors also detected a higher level of Nox2 (NADPH oxidase 2) expression (an isoform of the NADPH oxidase) after repeated exposure for 8 h/day in both DIV7 and DIV14 cultures compared to sham-exposed cells ($p<0.05$), they suggested that Nox2 expression is an important factor in producing ROS during repeated ELF-MF exposure. Neither 30 min nor 8 h per day

repeated exposure induces DNA damage, evaluated as foci formation, apoptosis, or autophagy. As stated by the authors, the observed effects in terms of oxidative stress do not have severe adverse biological consequences, maybe due to compensatory mechanisms, at the translational or posttranslational level.

Osera and co-workers (Osera et al., 2015) investigated whether a short and repeated pulsed EMF (PEMF) could induce beneficial effects triggering adaptive responses against an oxidative insult in SH-SY5Y cells, used as a neuronal cellular model. The exposure was for 30, 15 or 10 minutes, for a total of 4 treatments over 7 days, or continuously for 72 h. In a first set of experiments, the effect of PMF exposure alone was evaluated on mitochondrial activity. Continuous exposures of 72 h to a PEMF (75 Hz, 2 mT) induced a significant decrease in mitochondrial activity, compared to sham-exposed cultures ($p<0.001$; 9 experiments). Such a decrease, although less pronounced, was also recorded when cells were intermittently exposed for 30 min ($p<0.01$) or 15 min ($p<0.05$) over a period of 7 days. Intermittent exposures of 10 min, on the contrary, did not affect basic cellular functions, such as mitochondrial activity, cell proliferation and apoptosis ($p>0.05$). Therefore, to evaluate the effect of combined exposures, cells were pre-exposed for a 40 min overall (four times a week, 10 min each) and, 24 h after the last exposure, were treated for 10 or 30 minutes with hydrogen peroxide (HP), a well-known oxidative stress inducer. Samples treated with HP alone were also included in the study design. No effect on mitochondrial activity and cell number was detected after 10 min HP treatment, given alone or in combination with PEMFs., A 30 min treatment with HP, on the contrary, induced a reduction in mitochondrial activity in all cases ($p<0.05$), while the cell number decreases in cells treated with HP ($p<0.05$) but not in pre-exposed samples. To evaluate the role of pre-exposures in protecting cells from oxidative stress, protein kinase Cα (PKCα) expression, ROS formation and Mn Superoxide Dismutase (MnSOD) activity was recorded. A reduction in PKCα expression in cells treated for 10 and 30 min with HP was detected ($p<0.05$), but such a reduction was not induced in pre-exposed samples. The ROS production was increased in 30 min HP treated cells with respect to cells pre-exposed and HP-treated ($p<0.05$). Finally, MnSOD activity was higher in all the PEMF-exposed samples, with or without HP treatment ($p<0.05$), suggesting that PEMFs up-regulate antioxidant defences. These results contribute to shed light on the protective role of electromagnetic fields against cytotoxic agents.

2.1.7. Cell proliferation

Cell proliferation was addressed in four studies.

Falone and colleagues (Falone et al., 2016) investigated whether the hyperproliferative response of SH-SY5Y human neuroblastoma cells that is evoked by a long-term exposure (5, 10 or 15 days) to 50 Hz, 1 mT ELF magnetic field, could be supported by re-programming of energy metabolism, as well as by an improvement of the enzymatic defenses towards methylglyoxal (MG), a cancer-static and cytotoxic compound endogenously produced mainly by glycolysis. Their findings show that the increase in the proliferation rate of MF-exposed SH-SY5Y cells is associated to an adaptive metabolic response that is aimed at both decreasing the endogenous MG production and activating the main MG-targeting detoxification mechanisms. A long-term exposure to the ELF-MF increased ($p<0.001$ vs time-matched sham-exposed cells) the specific activity of glyceraldehyde 3-phosphate dehydrogenase, which avoids the accumulation of MG precursors within the glycolytic process. In addition, the specific enzymatic activity of glyoxalase 2 (GLO2), the rate-limiting enzyme in the two-step detoxification of MF, was significantly increased by the long-term ELF-MF exposure ($p<0.05$ vs time-matched sham-exposed cells). Such observations were confirmed by the fact that SH-SY5Y cells that were exposed to the ELF magnetic field for 15 days showed reduced level of argpyrimidine, a reliable marker of specific MG-dependent protein damage. With regard to energy supply re-wiring, the authors unraveled a novel role of mitochondria in mediating the metabolic response of cancer cells to ELF-MF. In fact, neuroblastoma cells that were treated with the long-term ELF-MF showed enhanced mitochondrial function, as assessed by both increased activity of citrate synthase and enhanced mitochondrial oxygen consumption ($p<0.05$ and $p<0.01$, respectively, with respect to time-matched

sham-exposed cells). Such findings were supported by the increased protein level of the master regulator of mitochondrial biogenesis anti-peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α) ($p<0.01$ vs time-matched sham-exposed cells). Collectively, the study reported evidence that a 50 Hz, 1 mT ELF magnetic field affects the biology of neuroderived malignant cells by inducing complex cytoprotective adaptations that may confer survival and proliferative advantage to cancer cells. Such responses were associated with improving defense against endogenous pro-glycating processes, as well as with a more efficient handling of the metabolic supply.

Martinez et al. (2016) investigated the proliferative response of the human neuroblastoma cell line NB69 to a 100 μT, 50 Hz magnetic field. To this purpose, they evaluated cell cycle progression and the involvement of two signal transduction pathways for cell proliferation (p38 and c-Jun N-terminal (JNK) kinases). Cell cultures were exposed either intermittently (3h/day for 3 days) for 24, 42 or 63 hours, or continuously for periods of 15 to 120 minutes, in the presence or absence of p38 or JNK inhibitors. Following 24 h exposure, a statistically significant increase in cell proliferation was detected in exposed samples compared to sham controls ($p<0.01$; six independent experiments). The effect was not detected for longer exposure duration (in later stages of growth), as expected. When the p 38 inhibitor was added, a reduction in cell proliferation was recorded, but no difference was detected between sham- and MF-exposed samples, indicating that the MAPK-p38 pathway is involved in such a response. Treatments with the JNK inhibitor resulted in a significantly decreased cell number in sham-exposed cells, but such a decrease was less pronounced in MF-exposed cultures ($p < 0.001$), suggesting that the MF-induced proliferative response would not be mediated by activation of the JNK pathway. In addition, cell cycle-regulating proteins were also modified after two hours of exposure, and a transient activation of the two proliferation-related pathways was observed already after 15 minutes. Furthermore, to evaluate the involvement of reactive oxygen species (ROS) in the activation of the field-induced proliferative response, the antioxidant N-acetylcysteine (NAC) was used as ROS scavenger. NAC blocked only the field effects on cell proliferation and p38 activation.

To evaluate the effects of long-term exposure on cell behaviour An et al. (2015) intermittently exposed/sham-exposed Balb/c mouse embryo fibroblasts (Balb/c 3T3 cells), to a 50 Hz MF at 2.3 mT. The exposure was 2 hours per day, 5 days per week for 11 weeks. At the end of the exposure period, cells were collected and cell morphology, viability, cell cycle and apoptosis was examined. Moreover, the protein level of proliferating cell nuclear antigen (PCNA) and CyclinD1 and malignant transformation were also measured. The results of at least three independent experiments indicated that long-term exposure did not induce changes in cellular and nuclear morphology, apoptosis and transformation. At variance, cell viability was significantly decreased compared to sham exposed samples ($p<0.05$). Cell cycle distribution also changed after 11 weeks exposure: the percentage of exposed cells in S phase significantly decreased and cells in G2 phase significantly increased ($p<0.05$). Moreover, the protein level of PCNA and CyclinD1 significantly decreased ($p<0.05$). These data suggest that long-term exposure to a 50Hz PF-EMF could affect cell proliferation and cell cycle by down-regulation the expression of PCNA and CyclinD1 protein.

Lee et al. (2015) investigated whether exposure to 60 Hz ELF-MF would affect cell proliferation in four cell lines: MCF10A, MCF7, Jurkat, and NIH3T3 cells. To this purpose, they measured cell number, DNA synthesis rate and cell viability. Moreover, they also investigated cell cycle distribution and gene expression profile in MCF-7 cells. MCF10A cells were exposed to 0.1, 0.5, or 1.0 mT for 4 h and cell number was recorded after 1, 2 , 3 and 4 days after exposure (three independent experiments for each condition investigated). The cell proliferation rate was unaffected at 0.1and 0.5 mT but a significantly lower number of cells was detected at 3 and 4 days after 1mT exposure ($p<0.05$), as compared to sham-exposed cells. To better investigate the phenomenon, cell proliferation was also measured in MCF7, Jurkat, and NIH3T3 cells, at 3 days following exposure to 1mT 60Hz for 4 and 16 h. After 4 h and 16 h ELF-MF exposures, there was a significant decrease in the number of MCF10A cells ($p<0.05$). In MCF7 cells, the relative cell numbers were also significantly decreased at 3 days after either 4 or 16 hours MF exposure, compared to sham-exposed control ($p<0.05$). However, the proportion of dead cells was unaffected by the exposure. No effects were detected in Jurkat and NIH3T3 cells. The analysis of cell viability and DNA synthesis rate showed a significant decrease at 3

days after ELF-MF exposure in both MCF10A and MCF7 cells ($p<0.05$), while no effects were found in Jurkat cells. NIH3T3 cells showed a significantly decreased cell viability ($p<0.05$), but DNA synthesis was unaffected. Furthermore, MCF7cells were also employed to investigate the effect of 2 mT exposure for 16 h. At three days after exposure, a lower number of cells was detected in exposed samples compared to sham-exposed ones ($p<0.05$) and cell cycle resulted delayed ($p<0.05$), while apoptosis was not affected. Experiments to evaluate the gene expression profile showed that PMAIP1, a gene involved in apoptosis and survival regulation, was the only up-regulated. The authors suggested that ELF-MF could induce a delay in cell cycle progression via regulation of PMAIP1 gene expression in a cell line specific manner.

2.1.8. Apoptosis

A study by Feng et al. (2016) investigated the of 50 Hz ELF-MF exposure (200, 400, 1000 or 2000 μT) on the regulation of apoptosis in a human amniotic (FL) cell line. Cultures were exposed for 30, 60 and 120 minutes to the ELF-MF. The exposure did affect neither cell viability nor apoptosis. When the cultures were subsequently treated with the antibiotic staurosporine at concentration inducing a 50% increase of apoptosis, a reduction of staurosporine-induced early apoptotic cells was observed after exposure for 60 minutes ($p<0.05$), but not after 30 and 120 minutes. This exposure-time-dependent decrease was only observed at 400 μT and 1000 μT, but not with weaker and stronger magnetic fields (200 μT and 2000 μT). To explain these findings, reactive oxygen species (ROS) in the mitochondria was measured and was increased after 30 and 120 minutes of exposure ($p<0.05$), but not after 60 minutes. This suggests a specific mechanism for the removal of the ROS within this time slot. Indeed, the authors showed that the blocking of a pore in the mitochondrial membrane not only caused an increase of ROS after 60 minutes of exposure, but also protected from staurosporine-induced apoptosis. Opening of this pore, thus, causes an outflow of ROS and other molecules from the mitochondria influencing the cell response to the additional stressor staurosporine. By means of specific inhibitors, it was possible to show that the release of ROS into the cytoplasm leads to the activation of the Akt signaling pathway. This signaling pathway is known for supporting cell viability and counteracting apoptosis.
Nevertheless, it remains open whether the effect observed in human amniotic cell lines is common to various cell types, and whether it has a relevant impact on physiological processes.

2.1.9. Extremely low frequency magnetic fields and nanoparticles

Combined exposures with nanoparticles were studied by Jia et al. (2014). They treated rat pheochromocytoma PC12 cells with increasing concentrations of magnetic nanoparticles-SiO2 (MNPs), in presence or absence of a 50 Hz (400 μT) magnetic fields for 48 h. When cytotoxicity was evaluated, no effect was detected in culture exposed to MF alone compared to sham-exposed cultures. Treatments with MNPs resulted in a decrease in viability as a function of the MNPs concentration. Combined treatments induced a significant decrease in cell viability only in cultures treated with the highest MNPs concentration tested (100 μg/ml; $p<0.05$; 9 independent experiments). MF exposure or MNP-SiO2 treatment alone did not cause apoptosis in PC12 cells; instead, the proportion of apoptotic cells increased significantly under MF exposure and increasing doses of MNP-SiO2 ($p<0.05$). Therefore, combined treatments resulted in enhanced effects of MNPs.

2.1.10. Proteome

Kuzniar et al. (2017) carried out the proteome-wide semi-quantitative mass spectrometry analyses of human fibroblasts (VH10) and osteosarcoma (U2OS) cells, and of mouse embryonic stem (IB10) cells exposed for 15 hours (5 min on/10 min off cycles) to 50 Hz, 2 mT. By using more than one method for differential protein expression analysis, the numbers of significant protein hits was rather low. Moreover, the changes detected with one method were not confirmed by applying different assays. Therefore, the authors suggest that the possible identification of false positive candidates has to be

taken into account. In this study, similar results were obtained when cells were exposed to RF fields (see section 4.1.2). The results indicate that less than 1% of the quantitated human or mouse proteome is differentially regulated in response to these electromagnetic fields. Moreover, if there is an effect induced by electromagnetic fields exposure, it is smaller than the one induced by slight protocol variations.

2.1.11. Gene expression

Circadian rhythms are oscillations characterized by a period length of around 24 h. Some alterations of cell physiological processes might be mediated by modifications of biological clock machinery through variations of clock genes expression.

Manzella and co-workers (Manzella et al., 2015) investigated whether a 50 Hz ELF-MF at low magnetic flux density (0.1 mT) was capable of affecting circadian gene expression. In a first set of experiments, HuDe (human dermal fibroblasts) cells were exposed/sham-exposed for 1 h under starvation conditions (serum-free medium) and collected at regular intervals (1, 2, 3, 4, 8, 12, 16, 24, 28 , 32 , 36 , 40 and 48 hours from time zero). The ELF-MF exposure induced a significant circadian variation of clock gene expression with a peak after 8 h and 32–36 hours exposure ($p<0.05$ vs. sham). In further experiments, cells were cultured in a serum-free medium for 48 h and then stimulated with a serum-rich medium for 2 h (serum-shocked cells). Subsequently, cells were cultured in a serum-free medium and exposed for 1 h to ELF-MF. A significant variation of expression of clock genes examined was observed after serum shock in both sham-exposed and exposed cells compared to starved cells without an entrainment by serum shock. However, compared to sham-exposed cells, several genes were up-regulated by the exposure ($p<0.05$).

Two papers were published by Liu and co-workers, to evaluate Micro RNAs (miRNAs) regulation and control in mouse spermatocyte-derived GC-2 cells intermittently exposed to a 50 Hz ELF-MF for 72 h (5 min on/10 min off) at 1, 2 and 3 mT. MiRNAs are a class of small endogenous non-coding RNAs that predominantly negatively regulate gene expression and participate in the regulation of various cellular processes, including cell proliferation, cell cycle and apoptosis. Recently it has been suggested that miRNAs are also involved in the control of spermatogenesis and male fertility.

In the first study, no effects were detected at 1, 2 and 3 mT on cell growth, as assessed by evaluating cell morphology and viability. Moreover, apoptosis and cell cycle arrest was also unaffected by the exposure. When miRNAs expression was evaluated in samples exposed at 1 and 3 mT, the expression of 55 miRNAs markedly changed (fold change >1.5), as assessed by affymetrix microarray analysis. In particular, the most highly up- and down-regulated at 1 mT were miR-494-3p (+2.3) and miR-122-5p (-2.6), while the most highly up- and down-regulated at 3 mT were miR-494-3p (+3.3) and miR-3084-3p (-3.7). MiR-494-3p was the most highly up-regulated miRNA at 1 mT or 3 mT. Real time PCR quantification confirmed the differential expression. Each endpoint was measured in three independent experiments (Liu et al., 2015a). The authors suggested that, since the affected miRNAs modulate signaling pathways of circadian rhythms, cytokine-cytokine receptor interactions and the p53, these pathways can be epigenetically regulated by ELF-EMF, at least in GC-2 cells.

In a further study, the authors evaluate the effect of ELF-MF exposure on MiR-26b-5p, one of the most investigated miRNA, since it is involved in several regulation processes (Liu et al., 2016). MiR-26b-5p was differentially expressed at different field intensities: the expression was up-regulated ($p<0.05$) at 2 mT and down-regulated at 3 mT ($p<0.05$). However, 1 mT had no effect. DNA methylation, a key mechanism for miRNA deregulation, was also investigated and was not influenced by the exposure. In a further experiment, GC-2 cells were transfected for 6 h with a miR-26b-5p mimic and a mimic negative control and then exposed to a 50 Hz ELF-MF at a magnetic field intensity of 3 mT. Cell growth and apoptosis was unaffected. In contrast, when the cell cycle was examined the overexpression of endogenous miR-26b-5p significantly decreased the percentage of cells in G0/G1 phase ($p<0.05$) and slightly increased the percentage in phase S ($p<0.05$) compared to the control

group. To further characterize this phenomenon, the authors first identified CCND2, a crucial cell cycle regulatory gene, as a direct target of miR-26b-5p, and then evaluated the effect of ELF-MF exposure on its expression. The protein expression of CCND2 was consistent with the mRNA expression: CCND2 was under-expressed in samples exposed to 2 mT and over-expressed at 3mT. No effects were detected at 1 mT.

2.1.12. DNA methylation

Liu and co-workers, by employing the same cell type and the same exposure conditions, also investigated the effect of a 50 Hz ELF-MF on DNA methylation, a key mechanism in regulation of gene expression (Liu et al., 2015b). Following 72 h of exposure, the DNA methylation was lower than the sham-exposure group at 1 mT and higher than the sham-exposure group at 2 mT and 3 mT. Since DNA methylation is catalyzed by a class of enzymes named DNA methyltransferases (DNMTs), the expression profiles of several DNMTs were analyzed and was lower, higher or not varied with respect to sham controls, depending on the field intensity. The related protein expression varied accordingly.

2.1.13. Intracellular calcium

Wei et al. (2015) investigated if a 50 Hz electromagnetic field could affect intracellular calcium transients in cardiomyocytes isolated from neonatal Sprague-Dawley rats. Cells were exposed to rectangular-wave pulsed ELF-MF at four different frequencies of 15 Hz, 50 Hz, 75 Hz and 100 Hz and at a flux density of 2 mT. Normal calcium transients were measured for 60 s as the baseline. Then, the cardiomyocytes were exposed for 180 s with ELF-MF. Calcium transients were monitored for another 60 s after the field was turned off. The results of 7 experiments showed an increase in resting calcium and a decrease in Calcium transients amplitudes for all the frequencies investigated ($p<0.05$). It is known that perfusion of cardiomyocytes with a high concentration of caffeine (10 mM) inhibits sarcoplasmic reticulum Ca2+-ATPase (SERCA2a) and Ca2+ clearance from the cytoplasm is mainly through Na+/Ca2+ exchanger (NCX) in the plasma membrane. The half-decay time (T1/2) of caffeine-induced Ca2+ transients (C[Ca2+]i) could be used as an index of NCX function. For all the frequencies investigated, the exposure resulted in a significant reduction of calcium transients (5 independent experiments; $p<0.05$) and of calcium content in sarcoplasmic reticulum (6 independent experiments; $p<0.05$). On the whole, the results of this investigation suggest that ELF-MFs can alter Calcium signalling in cardiomyocytes.

2.1.14. Autophagy

Autophagy is a process necessary for cell homeostasis, in which cytosol and organelles are included within vesicles (autophagosomes) that deliver the contents for degradation and recycle the resulting macromolecules to optimize the usage of limited energy. Deficient autophagy can lead to diseases, such as neurodegenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis (ALS) and Parkinson's disease. Moreover, in cancer, autophagy acts both as a tumour suppressor and as a cancer cell survival.

Chen et al. (2014) evaluated the effect of 50 Hz MF (2 mT) in mouse embryonic fibroblasts exposed for 0.5, 2, 6, 12 and 24 hours. Two different methods were applied to evaluate autophagy: formation of autophagosomes, by transmission electron microscopy, and lipidation of LC3, a common marker of autophagic membranes. A significant increase in the autophagy was observed after 6 hours of exposure (4 independent experiments; $p<0.05$). Neither the signaling pathway mTOR – which plays a role in autophagy – nor apoptosis were activated by this exposure. Reactive oxygen species (ROS) formation is known to induce autophagy. In this study ROS were also measured and was increased after 2 and 6 hours but not after 12 and 24 hours of magnetic field exposure.

As suggested by the authors, further studies are necessary to identify the signaling pathways involved, and to clarify whether the absence of the observed effect after longer magnetic field exposure can be explained by a metabolic adaptation.

2.1.15. Intercellular communication

Normal cell growth depends on their ability to recognize and communicate with neighboring cells and gap junctional intercellular communication (GJIC) plays an essential role in regulating cell growth, differentiation, and proliferation.

In a study by Percherancier and co-workers (Percherancier et al., 2015), the effect of ELF-MF exposure on GJIC was investigated. Fluorescence recovery after photobleaching microscopy (FRAP) was used to visualize diffusion of a fluorescent dye between NIH3T3 fibroblasts through gap junctions. The effect of 24 h exposure to 50 Hz MF at 0.4 or 1 mT on GJIC function was assessed. Moreover, the potential synergism of MF with an inhibitor of GJIC, phorbol ester (TPA), was also investigated by observing FRAP when NIH3T3 cells were incubated with TPA for 1 h following 24 h exposure to MF. In contrast to other reports of ELF-MF effects on GJIC, the authors observed neither direct inhibition of GJIC nor synergism with TPA-induced inhibition. They speculated that the different results could be due to unknown differences in laboratory materials and procedures or unspecified genetic and physiological factors.

2.1.16. Summary and conclusions for cell studies

A large number of papers have been published in the period of interest on extremely low-frequency magnetic fields (ELF-MF) effects on cell cultures (Table 2.1.1). Although in several cases a difference was recorded with respect to sham-exposed samples, it is mainly related to the cell type investigated and is reversible, and therefore its biological relevance is unclear. It is interesting to note that, among the studies reporting effects, oxidative stress (and the parameters indirectly related to the redox state of the cells) is the most frequent endpoint affected by the exposure. Most of the studies dealing with combined exposures reported effects compared to treatments with the chemical or physical agents alone. Such effects were protective or damaging, depending on the experimental protocol adopted. In particular, it seems that the exposure to ELF-MF given before a damaging chemical or physical treatment is able to reduce the induced damage.

Table 2.1.1 – *In vitro* studies on exposure to ELF MF fields

Cell type	Endpoint	Exposure conditions ELF-MF	Effect	References
Embryonic neural mice stem cells	Differentiation	50 Hz, 1 mT 4 h/day for 1, 2 and 3 days	increased development of neurons when exposure was given during chemically-induced differentiation; increase of a specific calcium channel in the cell membrane; no effect on apoptosis.	Ma et al. (2016)
Human neuroblastoma cells (SH-SY5Y)	Proliferation, ROS, apoptosis, gene expression	50 Hz, 1 mT up to 3 days Co-exposure: neurotoxin MPP+	pre-exposure potentiate MPP+-induced ROS, apoptosis and p53 downstream gene expression. The effect was reduced by adding antioxidants	Benassi et al. (2015)
Primary rat cortical neurons	Viability, calcium homeostasis, neurite outgrowth and spontaneous neuronal activity	50 Hz, 1–1000 μT rms block pulses 7 days.	No effect on cell viability; depolarization- and glutamate-evoked increases in intracellular Ca++ concentration at 1 μT; slight inhibition at 1 mT; Neurite activity not affected; increased neurite length at 1000 μT	De Groot et al (2016)

Rat cerebella granule neurons (CGNs)	Current amplitudes (ion flux) upon administration of the neurotransmitter GABAA	50 Hz, 0.2 and 1 mT 30 to 120 min Co-exposure: neurotransmitter GABAA	Increased amplitude of GABAA currents after 60 min at 1 mT and after 120 min at 0.2 mT; no effect for shorter durations; Protein kinase C activated after 60 min at 1 mT.	Yang et al. 2015
Segments of sciatic nerve	Amplitude of evoked compound action potential (CAP)	0.16 Hz PMFs, 15 mT 30 min	enhanced amplitude of CAPs; treatments with antagonists of sodium channel reduced the effect if the exposure was given before but not after the chemical treatments; Chemically-modified action potential was reverted by exposure to PMFs	Ahmed and Wieraszko (2015).
Neutrophils from human blood	neutrophil extracellular traps production	irregular combination of four block waves at 320, 730, 880 and 2600 Hz, 300 µT from 1 up to 4 h Co-exposure: PMA	NET formation enhanced in PMA-activated neutrophils after 4 h exposure, but not in non-activated cells. synergistic effect on NET formation, when combined treatments with PMA and EMF were performed.	Golbach et al. (2015)
Human neuroblastoma cells (SH-SY5Y); rat C6 glioma cells	DNA damage; ROS formation	50 Hz, 10 or 30 µT 24 h Co-exposure: MQ	Increase in MN frequency at 30 µT in SH-SY5Y cells, with and without MQ; no effect in C6 cells; increase of cytosolic superoxide level and production of mitochondrial superoxide in C6 cells, but not in SH-SY5Y cells, more pronounced at 10 µT than at 30 µT. No effect of combined treatments.	Kesari et al. (2016)
Mouse splenic lymphocytes	expression of inflammatory factor genes and CD69 expression	50 Hz, 250 µT, 500 µT, 1 mT 6 h	No effect	Luo et al. (2016)
Human neuroblastoma cells (SH-SY5Y)	DNA damage	50 Hz, 100 µT 24 h Co-exposure: MQ at different concentrations	no effects on the cell cycle when the MF was given before 1h MQ; delay in cell cycle when it was measured after 3 h from the MF exposure, with or without MQ. Decreased MQ-induced DNA damage (MN formation) only in cell exposed for 24 h before 1 h MQ treatment. Decrease of DNA damage response-related protein p21 in cultures MF-exposed and treated for 1 h with MQ. No differences for 3 h MQ treatment	Luukkonen et al., 2017
Human lens epithelial cells (HLE)	DNA damage	50 Hz, 400 µT 2, 6, 12, 24 and 48 h	No effect in foci formation.	Zhu et al (2016)
Human neural cells (BE(2)C)	DNA methylation	50 Hz PMFs, 1 mT 24 and 48 h Co-exposure: hydrogen peroxyde	Increase in methylation level after 24 h PMFs exposure alone, but not after 48 h. Combined treatments gave a less methylation than hydrogen peroxide alone at 24 but not at 48 h.	Giorgi et al (2017)
Human keratinocytes (NCTC 2544)	Oxidative stress	50 Hz, 25 up to 200 µT 1, 2 or 4 h Co-exposure: o-Phe (ROS inducer) or Rot (ROS inhibitor9	Increased ROS formation at 50 and 100 µT for 1 h and 2h exposure. No effect for longer exposures. No effect on cell viability. 1 h with 50 µT and o-Phen reduced ROS production to control levels. variation of several antioxidant enzymes recorded after 1 h at 50 µT, that reverted to controls after 24 h of recovery	Calcabrini et al., (2016)

Primary cultured hippocampal neurons DIV7 and DIV 14	viability, apoptosis, genomic instability, autophagy and oxidative stress	50-Hz, 2-mT 30 min, 8 h, or 24 h (single exposure) or repeated 30 min or 8 h/day for 7 days	No effect of single exposures on viability; significant decrease of DIV 14 viable cells following repeated exposures. Repeated exposure induced no changes in ROS in DIV7 cells and increase in DIV 14. Higher level of Nox2 expression after repeated exposure for 8 h/day in both DIV7 and DIV14. No effect on DNA damage, apoptosis and autophagy	Zeng et al (2017)
Human neuroblastoma cells (SH-SY5Y)	Oxidative stress	75 Hz PEMF, 2 mT 30, 15 or 10min, for a total of 4 treatments over 7 days, or continuously for 72 h. Co-exposures: hydrogen peroxide	Decrease in mitochondrial activity in cells exposed for 72 h and intermittently exposed for 30 or 15 min, and in cells co-exposed for 30 min to hydrogen peroxide. No effects if hydrogen peroxide was given after PEMF. MnSOD activity was higher in all the PEMF-exposed samples, with or without co-exposures	Osera et al (2015)
Human neuroblastoma cells (SH-SY5Y)	Cell proliferation	50 Hz, 1 mT 5, 10 or 15 days	Increased glyceraldehyde 3-phosphate dehydrogenase activity and enhanced mitochondrial function	Falone et al (2016)
Human neuroblastoma cell line (NB69)	Cell proliferation	50 Hz, 100 µT 3h/day for 3 days 24, 42 or 63 h continuously for periods of 15 to 120 min	Proliferation increased after 24 h exposure but not for longer times and not mediated by activation of the JNK pathway	Martinez et al (2016)
Mouse embryo fibroblasts (Balb/c 3T3)	viability, cell cycle and apoptosis, transformation	50 Hz, 2.3 mT 2 hours per day, 5 days per week for 11 weeks	No effects in morphology, apoptosis and transformation Decrease in cell viability and deregulation of cell cycle-related proteins	An et al (2015)
MCF10A, MCF7, Jurkat, NIH3T3 cells	Cell proliferation	60 Hz, 0.1, 0.5, or 1.0 mT 4 h	Decrease in cell number, viability and cell cycle progression as a function of the exposure duration and of the cell type investigated	Lee et al (2015)
Human amniotic (FL) cell line	Apoptosis	50 Hz, 200, 400, 1000 or 2000 µT 30, 60 and 120 Co-exposure: staurosporine	No effect of ELF-MF alone. Reduction of staurosporine-induced apoptosis at 400 µT and 1000 µT after 60 min, but not after 30 and 120 min exposure. ROS increased after 30 and 120 min exposure but not after 60 min.	Feng et al (2016)
Human neuroblastoma cells (SH-SY5Y)	Viability, apoptosis	50 Hz, 400 µT 48 h Co-exposure: magnetic nanoparticles-SiO2	No effects of MF exposure alone. Decrease in cell viability ins samples co-exposed at the highest MNPs concentrations	Jia et al (2014)
Human fibroblasts (VH10) Human osteosarcoma (U2OS) cells Mouse embryonic stem (IB10) cells	Proteome analyses	50 Hz, 2 mT 15 h (5 min on/10 min off cycles)	Slight changes, not confirmed by applying different assays	Kuzniack et al (2016)
Human dermal fibroblasts (HuDe)	Circadian rhythms-related gene expression	50 Hz, 0.1 mT 1 h	Variation of clock gene expression as a function of the time after exposure	Manzella et al. (2015)

Mouse spermatocyte-derived GC-2 cells	Cell proliferation, apoptosis, miRNA-related	50 Hz,) 1, 2 and 3 mT 72 h (5 min on/10 min off cycles)	No effect on cell growth, cell cycle and viability. Up-regulation od miRNA-related circadian rhythms, cytokine-cytokine receptor interactions and the p53	Liu et al. (2015a)
Mouse spermatocyte-derived GC-2 cells	MiR-26b-5p regulation. DNA methylation	50 Hz,) 1, 2 and 3 mT 72 h (5 min on/10 min off cycles)	Up-regulation at 2 mT and down-regulation at 3 mT. No effect at 1 mT. Same results obtained in terms of related protein expression.	Liu er al. (2016)
Mouse spermatocyte-derived GC-2 cells	DNA methylation	50 Hz,) 1, 2 and 3 mT 72 h (5 min on/10 min off cycles)	DNA methylation lower at 1 mT and higher at 2 and 3 mT.	(Liu et al. 2015b)
Cardiomyocytes from neonatal Sprague-Dawley rats	intracellular calcium transients	15, 50, 75 and 100 Hz rectangular-wave pulsed 2 mT. 60 sec	Increase in resting calcium and a decrease in Calcium transients amplitudes	Wei et al (2016)
Mouse embryonic fibroblasts	Antophagy	50 Hz, 2 mT 0.5, 2, 6, 12 and 24 h	Increased autophagy after 6 h exposure. Increased ROS formation after 2 and 6 h but not after 12 and 24 h of MF exposure	Chen et al (2014)
NIH3T3 fibroblasts	gap junctional intercellular communication	50 Hz, 0.4 and 1 mT 24 h Co-exposure: TPA	No effect	Percherancier et al (2015)

Abbreviations: CD69: cluster of differentiation 69; DIVx: days of culturing *in vitro*; GABAA: gamma-aminobutyric acid A; JNK: c-Jun N-terminal kinases; MN: micronuclei; MNPs: magnetic nanoparticles; MnSOD: manganese superoxyde dismutase; MPP+: 1-methyl-4-phenylpyridinium; MQ: menadione; Nox2: Nicotinamide adenine dinucleotide phosphate oxidase 2; O-Phe: o-Phenanthroline; PMA: phorbol 12-myristate 13-acetate; ROS: Reactive oxygen species; Rot: Rotenone; TPA: 12-O-tetradecanoylphorbol-13-acetate

2.2. Animal studies

In continuation of previous years, again studies on brain, behaviour and physiology were reported. Similar to previous years, several small experiments using one exposure level only were identified. Those small studies consisted of n=6-10 rodents of one sex per sham control and a single ELF-MF exposure group. By contrast, two mega-experiments with several thousand rats addressing the endpoint cancer were presented by the Italian group of Soffritti and his co-workers.

2.2.1. Brain and behaviour

Akpinar et al. (2016) investigated mismatch negativity (MMN) and oxidative brain damage in developing male Wistar rats (n=10/group) exposed to 50 Hz electric fields (EF) (12 kV/m, 1h/d). Pregnant Wistar rats were (sham-)exposed during the entire pregnancy, pups were weaned for 22 days, and 10 male offspring each tested in the following groups: 1) Prenatal (22 d) and postnatal (90 d) sham-exposure, 2) prenatal EF- and postnatal sham-exposure, 3) Prenatal sham- and postnatal EF-exposure, and 4) pre- and postnatal EF exposure. After 3 months of (sham-) exposure, MMN was recorded by electrodes stereotaxically "positioned to the surface of the dura on the basis of online-recorded potentials to click stimuli". After MMN recordings, the rats were sacrificed (between 9 am and 2 pm) and the brain was removed for histological and biochemical analysis. The MMN amplitude was higher to deviant than to standard tones, and decreased in EF-exposed groups 2-4 compared to group 1 (sham-control). 4-Hydroxy-2-nonenal (4-HNE) levels [indicating lipid peroxidation] were increased in group 3 and decreased in groups 2 and 4. Protein carbonyl levels were decreased in group 4 only. In the hippocampus, auditory and frontal cortex, apoptotic cells, analyzed by the TUNEL assay, did not differ between the groups 1-4.
According to the authors, the MMN component of event-related potentials in brain "is regarded as a bioelectric correlate of a result of the mismatch between a sensory memory trace and an incoming

stimulus." The authors' speculation "EF decreased MMN amplitudes was possibly induced by lipid peroxidation" can not be judged with the presented 4-HNE data.

Madjid Ansari et al. (2016) exposed groups of 9 male adult NMRI mice to ELF-MF (50 Hz & 0.5 mT: 1) single (2 h), 2) single sham, 3) 2 weeks (2 h/d), 4) 2weeks sham exposure). After end of single ELF-MF or sham exposure, mice of groups 5) and 6) received intraperitoneally (ip) 30 mg/L NΩ-nitro-L-argingine methyl ester (L-NAME) as an anti-depressant and nonspecific NOS (Nitric Oxide Synthase) inhibitor. Similarly, groups 7) and 8) were given saline intraperitoneally (ip). Open-field locomotor activity was not affected in any of the groups. Immobility time in the Forced Swimming Test (FST) was reduced in the 2-weeks ELF-MF and in the single sham/saline treated mice. Considering the study design, the authors concluded that in contrast to a single 2 h exposure a 2 weeks, 2 h a day "long-term exposure could alter the depressive disorder in mice".

The effects of 9 and 30 days (2h /d) exposure to 60 Hz 1 mT magnetic field on social recognition and expression of estrogen receptors (ER) in the olfactory bulb of female Wistar rats was tested by Bernal-Mondragon et al. (2017)**.** 60 rats each were used for the consecutive exposures of 9 and 30 days. Intact and ovarectomized (OVX) females were subdivided into 2 x 6 groups of n=10: 1) sham, 2) EMF, 3) OVX + sham, 4) OVX + EMF, 5) OVX + E2 (25 µg/kg 17β-estradiol s.c.) + sham, 6) OVX + E2 + EMF. Locomotor activity was not impaired by ELF-MF exposure or hormonal status. In intact and OVX rats, social recognition was impaired after 9 days and 30 days of EMF exposure, but similar to sham exposure level after E2 replacement. 9 days of EMF exposure increased the expression of β-ER in intact females, but not in the others.
The authors' statement "longer exposure produced a decrease in intact but an increase in OVX and OVX+E2" does not reflect the presented data. Their conclusion "…findings suggest a significant role for β-estrogen receptors and a lack of effect for α-estrogen receptors on a social recognition task" could be corroborated by the inclusion of serum E2 measurements in a future study.

Celik et al. (2015) demonstrated in a concise study the ELF-MF effect on accumulation of manganese (Mn) in brain, liver and kidney of male Sprague-Dawley rats. Mn was chosen due to its importance for brain development and function. In humans, e.g., Mn deficiency causes seizures. Four months old rats received by oral gavage (p.o.) every second day for 45 days the respective Mn dose, using the following 8 groups (n=5/group): 1) cage-control, 2) ELF-MF, 3) 3.75 mg Mn, 4) 3.75 mg Mn + ELF-MF, 5) 15 mg Mn, 6) 15 mg Mn + ELF-MF, 7) 60 mg Mn, 8) 60 mg Mn + ELF-MF. Animals of the co-treatment groups were exposed to ELF-MF (50 Hz 1.5 mT) for the same period of 45 days (4 h/d, 5 d/wk). Twelve hours after the last exposure brain (cortex), liver and kidneys were collected and processed for chemical (ICP-OES) analysis. Compared to the non-ELF-groups, Mn concentrations increased in all 3 organs after co-exposure to ELF-MF, even in the absence of Mn treatment (group 1 vs. group 2).
A Mn dose dependency was not described but is, according to the presented data, obvious in brain and kidneys with dose-correlated increasing Mn concentrations. The authors' conclusion that increased Mn levels in the brain due to ELF-MF exposure may enhance behavioural and neurotoxicological effects (including Alzheimer's disease, Parkinson's disease and Huntington's disease) should be followed further and addressed in future studies.

Hu et al. (2016) investigated the effects of a 50 Hz 0.5 mT ELF-MF exposure for 3 months (20 h/d) in a transgenic Alzheimer disease (AD) mouse model. The transgenic mice (3xTg) bear an APP/PS1 mutation combined with a tau (P301L) mutation and develop cognitive deficits at an age of 6 months. Male 3xTg and non-Tg mice, 3 month-old, n=6-10 per group were allocated to 4 groups: 1) non-Tg +sham, 2) non-Tg +ELF-MF, 3) 3xTg +sham, 4) 3xTg +ELF-MF. Sham-exposed 3xTg mice showed impaired learning and memory (Morris water maze) and fear conditioning (unsignaled foot shock test), and increased levels of phosphorylated tau, Aβ aggregation, synaptic damages and apoptotic changes in brain tissue slices. In 3xTg +ELF-MF-exposed mice, all these changes were not detected and all parameters were in the 'normal' and similar range of non-Tg (sham- and 0.5 mT-exposed) mice.

Testing one flux density and a small group of a single but important AD mouse model only, the interpretation “protective effects of ELF-MF exposure..., ELF-MF can attenuate tau phosphorylation…, ELF-MF could act as a valid therapeutic strategy for ameliorating cognitive deficits…in AD” is the outcome of a pilot experiment which warrants further attention.

The Chinese group of Lai et al. (2016) sham-exposed 30 adult male Sprague-Dawley rats and exposed 30 more rats to ELF-MF (50 Hz 100 µT) for 24 weeks, 20 h/d. After termination of exposure, sub-groups of n=10 per main group were formed in order to reduce influences from testing time and the prior testing. 10 rats each were used for open field test (OFT), tail suspension test (TST) and Morris water maze (MWM), another 10 for the elevated plus maze (EPM) and forced swim test (FST), and the last 10 males for the fear conditioning test. During necropsy, all brains were isolated and weighed. 12 sections from each brain were prepared for histology and neuron staining. Body weight development, food and water intake were not affected by ELF-MF. No ELF-MF-effects on locomotor activity (OFT), on anxiety-like behavior (EPM test), on depression-like behavior (TST & FST), on spatial learning and memory (MWM test) and on fear learning and memory (fear conditioning test) were observed compared to sham control. Also brain weight, relative brain (to body) weight, brain morphology including neuron density were not -affected by ELF-MF exposure.
The presented data complement results of the same researchers who in 2015 did not detect effects of an identical 3-month exposure on clinical pathology including blood glucose and liver and kidney histology (see SSM report 2016-15).

2.2.2. Reproduction and Development

Krylov et al. (2016) exposed fish embryos (Rutilus rutilus) to 500 or 72.5 Hz ELF-MF (1.4 – 1.6 µT) for up to 144 h post fertilization. For co-exposures a) 23 °C elevated temperature, b) 0.01 mg/L trichlorfon or c) 0.01 mg/L copper sulfate pentahydrate (from blue vitriol) was used. After the exposure, the fish were raised in pond for 4 months. Data for early development collected over a 6-year period was studied. In summary, co-exposures resulted in increased embryo mortality, standard length and mass in underyearlings [fish less than a year old]. ELF-MF exposure mostly resulted in increasing total number of vertebrae and number of seismosensory system openings, additionally. The effects of exposure to ELF-MFs alone and co-exposure(s) to environmental stressors were intensively discussed but a clear conclusion cannot be drawn.

Udroiu et al. (2015) exposed groups of n=2 pregnant CD-1 mice and their offspring over a period of 30 days, 24 h/d to 50 Hz 65 µT ELF-MF. Group 1 served as control (27 pups), But it is not clear whether they were sham-exposed. Group 2 (20 pups) was ELF-MF-exposed. Group 3 (25 pups) was X-irradiated (1 Gy) on day 11.5 post-conception (pc), and group 4 (31 pups) was 1 Gy-radiated but also exposed to ELF-MF until weaning (30 days in total). 42 days after birth a subgroup, and 140 days after birth all remaining mice were sacrificed. Litter size and survival were not affected by any treatment. Micronucleus frequencies (MN) in peripheral blood were assessed at 1, 11, 21, 42 and 140 days of age. MN were similar between controls and ELF-MF-exposed mice, but similarly increased in 1 Gy solely and 1 Gy + ELF-MF-treated mice on days 1, 11, 42 and 140. Testis weight, postmeiotic 1C cells, and sperm count were decreased and sperm DNA was damaged at 1 Gy only, but not after co-exposure. The authors summarized, that “ELF-MF exposure had no teratogenic effect and did not affect survival, growth and development”, and “ELF-MF appeared to modulate the response of male germ cells to X-rays with an impact on proliferation / differentiation processes.”
Overall, the experiment could be questioned due to the basic statistical group size of n=2 dams per group.

2.2.3. Oxidative stress and/or Genotoxicity

Luo et al. (2016a) tested 6 groups of 12 male ICR mice for markers for oxidative stress after 28 days, 4 h/d of exposure to 1) sham, 2) 2 mT, 3) 4 mT, 4) 6 mT, 5) 8 mT, 6) 10 mT (50 Hz) ELF-MF. In

blood serum superoxide dismutase (SOD) and malondialdehyde (MDA) were measured daily. In the second part of their experiment, 5 groups of 12 male ICR mice were 7) untreated and sham-exposed, 8) received saline by oral gavage (po) + 8 mT ELF-MF, 9) 60 mg/kg lotus seedpod procyanidins (LSPC) po + 8 mT, 10) 90 mg/kg LSPC po + 8 mT, 11) 120 mg/kg LSPC po + 8mT. Daily oral gavage of saline or LSPC started 15 days before and lasted during the following 28 days (4 h/d) of ELF-MF exposure (50 Hz, 8 mT). Following 4 exposure-weeks all animals were decapitated, and blood, brain, thymus and spleen were collected. After 21 and 28 days of ELF-MF exposure serum SOD was exposure-dependently decreased and serum MDA increased; the values for 8 and 10 mT were similar. LSPC at 3 different doses revealed an exposure-dependent protective effect against oxidative stress damage induced by the 8 mT ELF-MF. LSPC significantly augmented SOD, CAT, GSH-Px, GR and GST in serum and cerebral homogenate. Histopathologically, 8 mT ELF-MF led to hyperemia and inflammatory cell infiltration in the cerebral cortex, to significantly decreased numbers of lymphocytes in the cortex of spleen and thymus, and to hyperplasia of spleen tissue. LSPC pre- and co-treatment reduced those alterations. Therefore, LSPC was shown to chemoprotectively act in an oxidative stress-preventing manner. The ELF-MFs were only used to initiate an exposure-dependent oxidative stress.

2.2.4. Cancer

Soffritti et al. (2016b) exposed Sprague-Dawley rats from day 12 post-conception (pc) until death, 19 h/d to sinusoidal 50 Hz MF. In experiment 1, groups of approximately 500 females and males each were exposed to 0, 2, 20, 100 or 1000 µT. For experiment 2, three further groups of each ca.100 female and male rats were similarly exposed to 0, 20, and 1000 µT, but received in addition 0.1 Gy of γ radiation at 6 weeks of age. 501 females and 500 males of experiment 1 served as non-exposed controls. The paper reported results of the co-exposure groups of experiment 2 only. Body weight and survival were unaffected. The incidence of adenocarcinomas of the mammary gland was significantly increased in 20 µT+0.1 Gy-exposed males and in 1000 µT+0.1 Gy-exposed females. The stated "significant dose-"(i.e. exposure-) "related increased incidence of mammary carcinoms in males ($p \leq 0.01$) and females ($p \leq 0.01$)" is not justified by the presented data. In males, malignant schwannomas of the heart were significantly increased in both co-exposed groups and hemolympho-reticular neoplasias (HLRN) in the 1000µT+0.1 Gy-exposed group.
Acknowledging the observation period over the entire rats' life span of up to three years, the tumor data of all organ systems should have been presented. But the complete tumor tabulation is missing. Selective reporting is really challenging the outcome of the study.

In a third experiment (Soffritti et al., 2016a) groups of 270 female and 250 male Sprague Dawley rats were lifelong exposed from day 12 pc onwards to 50 Hz 1 mT ELF-MF. Starting in week 6, group 2 (202 females and 200 males) received 50 mg/L of the carcinogen formaldehyde in their drinking water for 104 weeks, and group 3 (203 females and 200 males) was co-exposed (50 Hz 1mT ELF-MF lifelong, 50 mg/L formaldehyde for 104 weeks). The above-mentioned 501 females and 500 males of experiment 1 served as non-exposed controls. During the first year, consumption of drinking water with formaldehyde was decreased for males only. In both sexes no differences in body weight and survival were observed between the groups. No significant different incidences of benign tumors were reported, whereas in males only the incidence of malignant tumors was significantly increased in the co-exposed group 2 compared to the other groups. In males C-cell carcinomas of the thyroid and hemolymphoreticular neoplasias (HLRN) were significantly increased in the co-exposed group compared to the non-exposed controls. In females, no significant concurrent increases of specific and total malignant tumor incidences were observed.
Again, only selective tumour data are presented and limit the interpretation of the of the results.

2.2.5. Physiology

Hori et al. (2017) examined whether the electric field (EF)-dependent suppression of an immobilization-induced increase in GC plasma glucocorticoid (GC) levels that was previously reported by the same group in 2015, is reproducible by varying the voltage and distance between the electrodes (0.5 kV/50 mm, 1 kV/100 mm, 2 kV/200 mm). 50 Hz, 0.5, 1, or 2 kV was applied to the upper electrode and the lower electrode was grounded. During (sham-)–exposure, ten-week old male BALB/c mice were placed in cylindrical acrylic cages (200 mm in diameter, 50, 100, 200 mm height) between the electrodes. Groups of n=8 mice were exposed to the EF for 60 min, and tube-immobilized for 30 min in the second half of the 1 h: 1) No EF + no restraint, 2) No EF + restraint, 3) 0.5 kV/ 50 mm + restraint, 4) 1 kV/100 mm + restraint, 5) 2 kV/200 mm + restraint. Further groups of n=6 ten-week old mice were similarly exposed to detect the influence of direct contact with the electrode: 6) No EF + no restraint, 7) No EF + restraint, 8) 1 kV/100 mm, mouse contacted to the lower electrode, 9) 1 kV/100 mm, 0.1 mm polypropylene (PP) sheet between mouse and the lower electrode + restraint, 10) 1 kV/100 mm, 1 mm PP sheet + restraint, 11) 1 kV/100 mm, 5 mm PP sheet + restraint. Directly after the respective EF- or sham-treatment, blood plasma was obtained and frozen stored until GC analysis. Stress (restraint)-induced GC levels were significantly decreased in 1 kV/100 mm EF-exposed mice, but not at 0.5 kV/50 mm or 2 kV/200 mm. The authors conclude that "the suppressive effect of the 1 kV/100 mm EF was canceled when a PP sheet was placed between animal and lower electrode". No significant correlation was observed but there was a trend towards lower GC levels and sheet thickness.
In principle, the study confirmed that EF may inhibit a stress-induced rise of GC levels, but it strongly depends on the above described configurations of the EF exposure system.

Harakawa et al. (2017) reported another complex follow-up experiment to Hori et al. (2015) (described in the previous SSM report (SSM, 2016)). Again plasma glucocorticoid (GC) levels as an indicator for stress response were determined in 50 Hz electric field (EF)-exposed male BALB/c mice. In addition, red and white blood cell counts (RBC, WBC), hemoglobin and hematocrit levels were analyzed. Groups of n=8 eight-week-old mice were exposed to 10 kV/m for 60 min, and tube-immobilized for 30 min between minute 30 to 60. The second 60 min served as recovery phase without any treatment. A control group and an immobilization-alone group delivered basic (stress) data. Blood samples were taken every 10 min during the first hour and every 20 min during the second hour. Despite some inconsistencies of the experimental description [e.g., text vs. figures, blood sampling every 10 vs. 60 min, 6 vs. 7 subgroups for blood collection], the following results were obtained: 1) An increasing circadian rhythm-dependent plasma GC level between 9:00 and 15:00, 2) GC levels were highest after 30 min immobilsation stress and therafter decreasing, 3) GC was lower in the stress-EF co-treated group compared to the immobilization-alone group, 4) increase of RBC, hemoglobin, hematocrit after immobilisation stress but not after EF exposure, 5) WBC unaffected. Overall, the short 50 Hz 10 kV/m EF exposure reduced the time-dependent increase in plasma GC in immobilisation-stressed mice.

Li et al. (2016) induced a diabetic nephropathy (DN) in male 300 g Sprague Dawley rats by an ip injection of 55 mg/kg streptozotocin (STZ). An open-circuit voltage waveform with a repetitive burst frequency at 15 Hz (burstwidth, 5 ms; burst wait, 60 ms; pulse width, 0.2 ms; pulse wait, 0.02 ms; pulse rise and fall time: 0.3, 2.0 µs) was generated by a pulsed signal apparatus. Such a 15 Hz ELF pulsed 1.6 mT MF was applied to 8 non-diabetic (control) and 8 diabetic DN rats (DN +ELFpMF) for 6 weeks, 6 d/wk, 8 h/d. A third group of 8 diabetic rats (DN) was sham-exposed. Body weight of DN and DN +ELFpMF groups were significantly lower and blood glucose levels significantly higher than in controls, but not different between sham and exposed rats. Histopathologically, ELFpMF partially restored the normal morphology of glomeruli in diabetic rats. ELFpMF significantly decreased the renal expression of the endothelial growth factor (VEGF)-A but increased the renal expression of the connective tissue growth factor (CTGF). The applied ELFpMF with its specific type of waveform has been used by the research group for prevention and treatment of bone disorders, cardiovascular and neurological diseases.

The two-sided effects (expression of VEGF-A decreased and of CTGF increased) after ELFpMF exposure require a further mechanistic study.

Luo et al. (2017) exposed 5-weeks old male Sprague-Dawley rats (n=16/group) for 4 weeks (2 h/d) to 50 Hz MF of 0 (sham), 20, 100 and 500 µT. Except of increased creatinine and slightly decreased cholesterol levels in the 500 µT group, the chosen MFs had no significant effects on body weight, relative organ weights, and blood biochemical parameters related to heart, liver and kidney function. The slight but statistically significant increase in creatinine and decrease in cholesterol (TC) are judged as biologically non-relevant by the researchers.

Zhou et al. (2016) exposed 64 male 8-week-old Sprague-Dawley rats to a 50 Hz 100 µT ELF-MF for 24 weeks and 20 h/d. Another 64 rats were sham-exposed. Blood pressure (bp) measurements every 4 weeks did not show differences in systolic, diastolic and mean bp and pulse rate between the two groups. Also echocardiography, cardiac catheterization, electrocardiography (ECG) and finally histopathology of the heart, performed after 24 weeks, did not result in significant differences in haemodynamics, ECG, cardiac morphology including histomorphology and genes involved in cardiac hypertrophy. The presented data did not demonstrate any effects on the cardiovascular system of a 50 Hz 100 µT ELF-MF for 24 weeks.
Unfortunately, this in other details well-described study is lacking precise time-points after the respective last exposure before obtaining all the data for bp, echocardiography and ECG.

2.2.6. Immunology

Using again an ELF-MF signal mimicking fields from so-called "dirty" power nets (see Bouwens et al. (2012), discussed in the 8th SSM report (SSM, 2013)), the Dutch/South Africa team of de Kleijn et al. (2016) investigated immunomodulation and stress hormone levels in male BALB/c mice (n=20/group) exposed for 1 week and 15 weeks (each 1h/d, 4h/d, or 24 h/d). The applied ELF-MF signal contained frequencies of 20-50 000 Hz and a flux density of 10 µT. Leukocytes were dose-dependently (1, 4, 24 h/d) increased after 1-week exposures, but not after 15 weeks. Those leukocytes mainly represented neutrophils and $CD4^+$ lymphocytes. Compared to sham-exposed controls, after 1 week plasma ACTH (adrenocorticotropic hormone) and its precursor POMC (proopimelanocortin) were significantly lower, POMC in a dose-dependent manner.
Since in none of the parameters analysed consistent results were demonstrated, the authors' conclusion "Changes in stress hormone release may explain changes in circulating leukocyte numbers and composition" cannot be supported.

Luo et al. (2016b) exposed in a small experiment ten 6-week-old male Kunming mice to 50 Hz 0.5 mT ELF-MF for 60 days (5 d/week, 8h/d). A further 10 males served as sham control. A significant body weight decrease on days 20 and 30 was described and discussed - but the corresponding figure in the paper showed an increase. Spleen weight, histopathology and cytokine levels of IFN-γ, T-bet, IL-2, IL-4 and GATA-3 of spleen mRNAS were not (statistically) different from controls. For the in vitro experimental part (Section 2.1.4) lymphocytes were isolated from the spleen of an additional 10 male mice and the cells were exposed for 6 h to 0, 0.25, 0.5 or 1 mT in an incubator (37 °C, 5% CO_2). The cytokine levels of IFN-γ, T-bet, IL-2, IL-4 and GATA-3 as well as T-cell activation (proven by the expression of CD69) were not changed by the different MFs.

2.2.7. Other endpoints

Samiee and Samiee (2017) exposed groups of 10 freshwater carp Cyprinus carpio 12-15 cm long, 25-30 g, < 6 months old, to 50 Hz ELF-MF of 0.1, 1, 3, 5 and 7 mT once for 0.5 and 1 hour. Two weeks after exposure the fish were decapitated, the brains processed for preparing standard hematoxylin-eosin (H&E) stained sections and microscopically evaluated. No changes were observed at field

strengths of 0.1 and 1 mT, after exposures of 0.5 or 1h. A single exposure of ≥ 3 mT resulted in alterations as gliosis, edema, necrosis and loss of brain tissue. According to the authors, these lesions increased in a time- and intensity-dependent manner.
Unfortunately, a tabulation of the brain lesions is missing. Therefore it is difficult to assess the brain lesions and to follow the stated dependencies.

Shahbazi-Gahrouei et al. (2016) exposed groups of each 6 male Wistar rats for 15 days to ELF-MF (10 Hz, 690-720 µT). Group 1 was exposed 1 h/d, group 2 for 3 h/d, groups 3 and 4 were similarly sham-exposed. After termination of exposure, a microdialysis probe was surgically implanted into the raphe nuclei and continously (2 µL/min) perfused with artificial cerebro-spinal fluid. In total 6 dialysate samples were collected every 20 min. Post-mortem histology confirmed the correct position of the probes. The major (urinary) metabolite of serotonin and neurotransmitter 5-HIAA (5-hydroxindolacetic acid) was not significantly affected after exposure for 1 h/d but significantly lowered after 3 h/d of ELF-MF exposure.
These data are seen by the author as "an initial step towards helping cure depression with … ELF-MF". Future studies may add weight to these pilot data.

Wyszkowska et al. (2016) exposed adult desert locusts (4-9 days post-moult, both sexes) to 50 Hz ELF-MF of 3 different flux densities (1, 4, 7 mT) for 24 hours. At least 5-6 locusts were exposed together (gregarious species!). If necessary (and corresponding to the respective heat of the coils for the MF-exposed groups), temperature-matched controls were used. Following exposure, 36 locusts per group were subjected to a walking behaviour test using an open tunnel. After 4 mT and 7 mT exposures, the number of complete trials were less than in controls, i.e. walking was reduced. Results from a 1 mT-exposed group were not reported or evaluated. A special muscle force test of ETi (the hind leg extensor tibia muscle) with n=6-12 locusts/group/sex resulted in a significant decrease in 7 mT-exposed locusts only. Intracellular recordings from FETi (fast extensor tibiae motor) neurons after 7 mT exposure demonstrated an increased spike latency and duration (n=8 controls vs. 11 exposed to 7 mT only). Accordingly, 7 mT increased Hsp70 (heat shock protein), isolated from metathoracic ganglia (containing the somata of FETi) of male locusts.
The authors' strong conclusion "that ELF MF exposure has the capacity to cause dramatic effects from behaviour to physiology and protein expression…" cannot be fully supported by the above, incompletely described results (missing 1 mT data, mentioning the sex for e.g. the parameter "walking behaviour" etc).

2.2.8. Summary and conclusions on ELF animal studies

Similar to the previous Council report, various studies used one exposure level only and normally in the 1mT range at 50 or 60 Hz. Behavioural and cognitive disturbances were reported again. In addition, a preventive effect of 0.5 mT exposure to ELF magnetic fields on alterations comparable to Alzheimer disease (AD) was demonstrated in an AD mouse model. Testing different exposure levels (2 – 10 mT), oxidative stress increased in a way dependent on the magnetic field strength. Two studies confirmed that a single exposure of 10 kV/m, lasting 30-60 minutes, may inhibit a stress-induced rise of glucocorticoid (GC) levels in mice, but it strongly depends on the configuration of the electric field exposure system. Other studies (chapters 2.2.6, 2.2.7) using < 1 mT ELF magnetic field exposures gave conflicting results without a clear picture on the reported effects, if any.

The two large Italian co-carcinogenicity studies reported on single tumour types only, including hemolymphoreticular neoplasias (HLRN). This limited and selective evaluation of tumour incidences clearly decreases the significance of the studies. In addition, HLRN of adults are not relevant for childhood leukaemia, i.e. during this reporting period, again, none of the animal studies directly addressed childhood leukaemia which is still of relevance in view of the results of epidemiological studies.

Finally, study designs with 2 to 3 groups of 6 or less animals per group and using one sex only are often not well justified. To test one MF exposure level only is often meaningless. A typical conclusion "further research is needed" does not give useful information. Entitling these small studies as "pilot studies" should be a minimum.

Table 2.2.1 Animal studies on exposure to ELF magnetic fields

Endpoint	Reference	Exposure ELF - MF	Duration	Effect
Rodents studies (mostly)				
Brain and behaviour	Akpinar et al. (2016)	50Hz 12kV/m EF	1h/d, 22+90d (pregnancy+90d after birth)	EF decreased MMN amplitude and did not induce apoptosis in brain cells
	Ansari et al. (2016)	50Hz, 0.5mT	2h/d, 2d & 14d, 2d + 30mg/L ip L-NAME	Immobility time in FST reduced after 2wk, "Pro-depressant like effect" after 2h exposure
	Bernal-Mondragón et al. (2016)	60Hz, 1mT	2h/d, 9 and 30d	1mT impaired social recognition, but not in E2 substituted OVX rats. No effect on locomotor activity. Results on ER expression inconclusive.
	Celik et al. (2015)	50Hz, 1.5 mT + 0, 3.75, 15, 60mg Mn/kg bw every 2nd day	4h/d, 5d/wk, 45d	1.5 mT increased Mn in brain, liver, kidneys. Relevance for brain develepment and function?
	Hu et al. (2016)	50Hz, 0.5mT	20h/d, 3mo	0.5mT prevented learning, memory & fear deficits and AD-specific changes in brain slices in a AD (3xTg) mouse model.
	Lai et al. (2016)	50 Hz, 0.1mT	20h/d, 24 wk	No induction of anxiety- or depression-like behaviors. No influence on learning. Brain morphology not affected.
Oxidative stress	Luo, Chen et al. (2016)	50 Hz, 2,4,6,8,10mT	4h/d, 28d	SOD↓ & MDA↑ MFstrength-dependently
		50Hz, 8mT + 0, 60, 90, 120 mg LSPC/kg bw	4h/d, 28d + po daily (d-15 till d28)	Inhibition of oxidative stress shown by SOD, CAT, GSH-Px, GR & GST activities and histopathology of cerebrum, spleen & thymus
Reproduction & Development	Bekhite et al. (2016) (see ch. 1.2.1)	1, 10mT SMF; 50 Hz, 1, 10mT ELF-MF	20d gestation period, 8h/d	Malformation(s), VEGF decrease at both 10mT (SMF & ELF-MF) exposures
	Udroui et al. (2015)	50Hz, 65µT	24h/d, 30d (d11.5pc -);	n=2 dams/gr only! No teratogenicity, no genotoxicity. Testis weight, sperm count &

		50Hz, 65µT + 1Gy	24h/d, 30d +1Gy on d11.5pc	cells decreased, spermDNA was "damaged" due to 1 Gy only (but not after co-exposure!)
Cancer	Soffritti et al. (2016a)	50Hz, 0, 20, 1000 µT + 0.1 Gy	19h/d, d12 pc -- (up to 3 years) + once at 6 wks	Co-exposed rats: Mammary carcinomas; males only: malignant schwannomas (heart) and HLRN
	Soffritti et al. (1996b)	50Hz, 0, 1000 µT + 50mg/L FA in drinking water	19h/d, d12 pc -- (up to 3 years) + 6-104 wks	Co-exposed males only: Increase in malignant tumors, in C-cell carnimoas (thyroid) and HLRN
Physiology	Hori et al. (2017)	50 Hz EF, 05kV/50mm, 1kV/100mm, 2kV/200mm	1h	10kV/m inhibits restraint stress induced GC level-increase in blood plasma (confirming Hori et al., 2015). Exposure set-up important.
	Harakawa et al. (2017)	50Hz 10kV/m EF	single 1h	GC highest after 30min restraint stress & lowered by EF. RBC↑, HB↑, HCT↑ after stress but not affected by EF. WBC completely not affected.
	Li et al. (2016)	15Hz, 1.6mT, pulsed	8h/d, 6d/wk, 6wk	STZ diabetic SD rats: no effect on hyperglycemia; restoration of glomeruli morphology; partial renal VEGF-A decreased, CTGF increased
	Luo et al. (2017)	50Hz 0, 20, 100µT, 0.5mT	2h/d, 4 wk	No influence on body weight, rel. organ weights; slight creatinine increase and TC decrease at 0.5mT
	Zhou et al. (2016)	50Hz 100µT	20h/d, 24wk	No effects on cardiovascular system (bp, ECG, heart morphology)
Immunology	deKleijn et al. (2016)	20-50000Hz, 10µT	1,4,24h/d; 1wk, 15wk	1wk only: Leukocytes (neutrophils, CD8+ lymphocytes) increased dose-dep., ACTH & POMC
	Luo, Jia et al. (2016)	50Hz, 0.5 mT	8h/d, 5d/wk, 60d	No change in spleen weight, histology and cytokine expression
Others	Shahbazi-Gahrouei et al. (2016)	10Hz, 690-720µT	1h/d and 3h/d, 15d	5-HIAA levels in cerebrospinal fluid decreaed after 3/d (but not after 1h/d)
Studies in non-mammalians				
Developmental effects in fish (Rutilus rutilus embryos)	Krylov et al. (2016)	500Hz, 72.5Hz; 1.4-1.6µT +temp↑ or +0.01 mg/L	0-144h post fertilization	Co-exposures -> Embryo mortality↑, standard length↓,

		trichlorfon or +0.01blue vitriol		changes in total vertebrae & number of seismosensory openings
	Samiee & Samiee (2017)	50 Hz, 0.1, 1, 3, 5, 7mT	0.5, and 1 h 2 wk recovery	Brain lesions at ≥ 3mT, intensity- and time-dependently increasing
Behaviour & physiology in desert locusts	Wyszkowska et al. (2016)	50Hz, 1, 4, 7mT	24h	Walking↓ (4, 7mT). 7mT: Musle force↓, spike latency↑ and duration↑ in FETi neurons, hsp↑ in corresponding ganglia

Abbreviations: ↑=increase(d); ↓=decrease(d); 5-HIAA: 5-hydroxindolacetic acid; ACTH: adrenocorticotropic hormone; AD: Alzheimer disease; bp: blood pressure; CAT: catalase; CTGF: connective tissue growth factor; E2: 17β-estradiol; ECG: electrocardiography; ELF-MF: extremely low frequency magnetic field; EF: electric field; ER: estrogen receptor; FETi: fast extensor tibiae motor; FST: Forced Swimming Test; GC: glucocorticoid (level); GR: glutathione reductase; GSH-Px: glutathione peroxidase; GST: glutathione-S-transferase; HB= hemoglobin, HCT: hematocrit; HLRN: hemolymphoreticular neoplasias; Hsp: heat shock protein; iv: intravenously; L-NAME: NΩ-nitro-L-argingine methyl ester; LSPC: lotus seedpod procyanidins; MDA: malondialdehyde; MMN: mismatch negativity; Mn: manganese; OVX: ovarectomized; RBC: red blood cell count; ROS: Reactive oxygen species; SMF: static magnetic field; pc: post conception; po: per os (oral gavage); POMC: proopimelanocortin, SOD: superoxide dismutase; STZ: streptozotocin; VEGF: vascular endothelial growth factor; WBC: white blood cell count.

2.3. Human studies

During this reporting period just one study was published which investigated effects of ELF magnetic fields on short-term memory (Navarro et al., 2016), which is reported here. A study which investigated effects of ELF pulse electromagnetic fields on electrocardiographic output parameters (Fang et al., 2016), was not considered here due to methodological weaknesses (single-blind parallel-group design). Another study, which investigated effects of pulsed electromagnetic fields, delivered by a commercial device, on peripheral blood circulation in a randomized controlled trial (RCT, in patients with diabetes and healthy controls) (Sun et al., 2016b) was also not considered in this context since medical applications are beyond the scope of this report.

2.3.1. Cognitive performance

Navarro et al. (2016) investigated effects of a magnetic stimulation (2 kHz and approximately 0.1 μT) applied by four coils attached to a cap bilaterally and symmetrically close to the temporal-parietal area on Sternberg's working memory task. Exposure was delivered double-blind during the approximately 11 min of the test duration. All tests were conducted between noon and 1 p.m. A sample of 65 male subjects was divided into 31 non-exposed and 34 exposed subjects (non-exposed: age 23.6 ± 2.3 years; exposed: 22.8 ± 2.5 years). The authors state that exposure had a significant effect on reaction time. However, the results indicate that size of the target set, as well as reaction times for targets/non-targets show much more pronounced differences in reaction time than exposure effects for a given combination of size set and target/non-target. Another limitation of the study is the parallel-group design.

2.3.2. Conclusions on human studies

Given the limitations mentioned above, the Navarro et al (2016) study does not substantially contribute to the knowledge about effects on cognitive performance from exposure of ELF magnetic fields.

2.4. Epidemiological studies

In the previous Council reports (SSM, 2015, SSM, 2016) it was concluded that little progress had been made to resolve whether the consistently observed association between ELF magnetic fields (ELF-MF) exposure and childhood leukaemia in epidemiology was causal or not. Newer studies were small and did not alter the current interpretation of this subject. Another open question is related to occupational ELF-MF exposure and/or electric shocks as a risk factor for amyotrophic lateral sclerosis (ALS) and Alzheimer diseases (AD). Although associations are often reported, there is no consistent pattern that suggests either ELF-MF or electric shock as the cause. It was also noted that little research was conducted on other outcomes in relation to ELF-MF exposure.

2.4.1. Childhood cancer

In China, Su et al. (2016) performed a meta-analysis by pooling 12 studies on associations of parental occupational exposure to ELF-MF with childhood leukaemia risk. The overall results showed that neither maternal nor paternal occupational exposure was associated with childhood leukaemia risk. This result is in line with the current knowledge of health effects from exposure to ELF below the recommended limit values.

Crespi et al. (2016) reported a relatively large case-control study on childhood leukaemia in children living close to high voltage power lines. All childhood leukaemia as well as central nervous system (CNS) tumour cases aged less than 16 years that had occurred in California, US, between 1988 and 2008 were included. Cancer cases were identified from the state-wide cancer registry. Cases were matched to the Birth Registry and for each case a randomly selected control was chosen from the birth registry, matched on date of birth by +/- 6 months. An open source geocoder was used to assign coordinates to addresses and a geographic information system was used to determine distance to the nearest power line (>60 kV). All in all, 5 788 leukaemia cases and 3 308 CNS cancer cases were included. Children living within 50 m from a power line had an OR of 1.4 (95% CI 0.7-2.7). ORs increased very slightly for younger children (<5 years of age) and for more recent years of analysis (OR of 1.7 (95% CI 0.8-3.7) and 1.9 (95% CI 0.6-5.4), respectively. ORs decreased somewhat with decreasing accuracy of the exact location of the place of residence, indicating exposure misclassification. CNS tumours had an OR of 1.2 (95% CI 0.4-3.4) for children living within 50 m of a power line.
A strength of the study is that it was completely registry-based, which means that selection bias or recall bias could not have affected the study results. The main limitation is the use of distance as exposure metrics, the strength of the magnetic field is not necessarily proportional with the voltage of the power lines. Interestingly, the observation by Bunch et al. (2014) and by Pedersen et al. (2015) of increased risks only in earlier, but not in later periods could not be confirmed by Crespi et al. Even though the study was not indicative of strong or significantly elevated risks of leukaemia, all in all this study also did not contradict previous findings of a slightly increased risk of childhood leukaemia in children living in close proximity to overhead power lines.

Bunch et al. (2016) presented additional analyses of risk of childhood cancer for a previously published study (Bunch et al., 2015). Risks were evaluated by distance categories of 0-199 m, 200-599 m, 600-999 m and compared to children living 1km or further from the overhead lines or underground cables. Risks were also presented by decades, by type of diagnosis (acute myeloid vs. lymphoid leukaemia), by age groups, and by region. As in previous publications, most prominent results were findings on an existing risk in earlier decades (1962-1989) disappearing in later periods (1990-2008). In the new paper they conclude that this risk decrease is linked to calendar year of birth or of cancer occurrence rather than the age of the power lines concerned. The reasons for this risk change over time remain unclear.

In Denmark, Pedersen et al. (2015) published a case-control study on residential exposure to ELF and risk of leukaemia, CNS tumours and malignant lymphoma in children during the period 1968 to 2003.

This study extends the period of a previous study with the same approach and material for the period 1968-1986 (Olsen et al., 1993). 3 277 children diagnosed with the actual diseases before the age of 15 during the period 1968 to 2003 were identified in the Danish Cancer registry. 9 129 controls were randomly selected from the Danish childhood population. Cases and controls were matched by sex and year of birth. The residential magnetic field exposure for all participants were calculated, and grouped into three exposure categories < 0.1 μT (reference), 0.1-0.39 μT and ≥ 0.4 μT. Only 11 (0.3%) cases and 19 (0.2%) controls were in the highest exposure category. For the extended period, 1987-2003, the ORs of leukaemia, CNS tumours and malignant lymphoma were 0.80 (95% CI 0.16-4.12), 0.75 (95% CI 0.16-3.53) and 1.67 (95% CI 0.17-16.02), respectively in the highest exposure group compared to the lowest, adjusted for age and sex. For the total period, 1968 to 2003, the RR estimates for leukaemia was 1.67 (95% CI 0.51-5.46).
These estimates are markedly lower than those from the first period, 1968-1986. Analyses of potential confounders such as residential radon, traffic related air pollution, maternal age etc., available for the period 1968-1991, did not affect the risk estimates in the corresponding subset of the data. The wide confidence intervals indicate high statistical uncertainty of all the risk estimates. This is a register-based case-control study, and common limitations as recall- and selection bias is not likely to occur in this study. Thus, the large differences in risk estimates between the first and last period is difficult to explain, but the fact that just few cases were exposed might have influenced the results and thus chance is a likely explanation. Interestingly, the strongest change in relative risks appears to originate from a change in the proportion of exposed controls, rather than cases, over time. In the time period 1968-1986, 0.1% of controls were exposed to levels ≥ 0.4 μT, for 1987-2003 this percentage increases to 0.4%. In the same time, the percentage of exposed cases remained similar (0.4 and 0.3%, respectively). The same temporal exposure pattern in controls was observed in the paper by Bunch et al (2015), where also a strong decrease in relative risks over time was reported.

2.4.2. Adult cancer

A meta-analysis on ELF-MF and risk of cancer in general, was performed by Zhang et al. (2016b)**.** 42 case-control studies were included in the analysis; the authors evaluated breast cancer, brain tumours and leukaemia, and addressed residential as well as occupational, electric blanket and in-house exposures, presumably from electric device use. Risk estimates were presented across all evaluated cancer types and across different exposure assessment methods, but it is unclear how different risk estimates from the individual studies were summarised. Cohort studies were excluded from the study base, but it is unclear why that was done. Heterogeneity between the studies was likely present across studies but was neither presented, nor discussed and evaluated.
This meta-analysis is not helpful in understanding whether the exposure to ELF-MF is related to presence or absence of risks of different types of cancer.

In Canada, Grundy et al. (2016) conducted a case-control study on the association between occupational ELF-MF exposure and breast cancer in men. During the period 1994-1998, 115 cases in the age group 20-74 years were recruited from the Canadian National Enhanced Cancer Surveillance System (NECSS) and 570 controls were selected from the full NECSS-control group (general population controls). Controls were frequency-matched to the case group by age and sex. There is no information regarding participation rate for the breast cancer cases, but an overall participation rate of 68% was reported for the NECSS-project as a whole. All participants completed a questionnaire where they provided information regarding their age, ethnicity, marital status and household income. In addition, lifestyle factors, occupational and residential histories were specified. Occupational exposure to ELF was assessed by expert reviews, considering information from the literature, personal communications and data collected from an earlier study on occupations, and assigned to participants blinded for case or control status. ELF exposure for each occupation was grouped into three categories: < 0.3 μT, 0.3-0.6 μT and ≥ 0.6 μT on average. Evaluated exposure metrics were average exposure, cumulative exposure (average multiplied with years on the job and % of full time status), duration of exposure, age at first exposure and time since last and first exposure. Associations between exposure and breast cancer were evaluated using unconditional logistic regression adjusted for

potential risk factors as body mass index, age and physical activity. Breast cancer risk of persons with occupations involving exposure to ELF-MF of at least 0.6 μT was non-significantly increased by a factor of 1.8 (95% CI: 0.82-3.95). In addition, a tendency was found for an association between breast cancer risk and the total time worked in an occupation with increased exposure (≥0.3 μT, p=0.06). For persons who had worked in such an occupation for 30 years or longer, risk was increased by the factor 2.77 (95% CI: 0.98-7.82). Other exposure features such as age during first exposure or cumulative magnetic field exposure did not show consistent or significant associations.
Breast cancer in men is rare and this is one of the largest studies on this topic. Still, the number of breast cancer cases is relatively small and the statistical power thus limited. The strength of this study is the long duration of exposure and the systematic expert judgement of exposure. To date, there is no established link between ELF-MF exposure and breast cancer in men. In order to make more statistically precise statements regarding a potential risk, it will be necessary to perform a meta-analysis or pooled analysis with other studies related to breast cancer in men.

2.4.3. Neurodegenerative diseases

A systematic review by (Gunnarsson and Bodin, 2017) on occupational exposures to different agents including ELF-MF concluded that there was no increased risk of Parkinsonism or Parkinson's disease in workers exposed to ELF-MF. This result is in line with previous systematic reviews (Huss et al., 2015a, Vergara et al., 2013).

Koeman et al. (2017) conducted a case–cohort analysis within the prospective Netherlands Cohort Study to investigate the association between amyotrophic lateral sclerosis (ALS) and occupational exposure to solvents, pesticides, metals, ELF-MF and electrical shocks. Out of the full cohort of ca. 120 000 individuals enrolled in 1986, a sub-cohort was created with all 76 men and 60 women who died due to ALS and a random sample yielding a study population of 2 092 men and 2 074 women for analysis. The follow-up period was 17.3 years. Information on occupational history and potential confounders were collected at baseline through a self-administered questionnaire and exposures were assigned to occupational titles (ISCO codes) by means of job exposure matrices (JEMs). In men a significant trend (p=0.02) between ALS mortality and occupational ELF-MF exposure was observed with a 2.19 (95% CI: 1.02 to 4.73) fold increased risk for men ever holding a job with high exposure versus background. No association was seen for electrical shocks. Only a few women were exposed and thus corresponding risk analyses were largely uninformative. The study suggests that ELF-MF exposure rather than electric shocks is related to ALS.
The prospective cohort design is a strength of the study. Number of included deaths for this rare disease is relatively high compared to other cohort studies. Comprehensive data on potential confounders were available and use of JEM for exposure assessment prevents from systematic exposure misclassification. Nevertheless, random misclassification is expected to have occurred and no information about occupation exposure was available after enrolment in the cohort. Mortality instead of incidence data is a limitation but given the high mortality rate for ALS, this is not expected to result in substantial bias.

2.4.4. Reproduction

Lewis et al. (2017) performed a systematic review of studies evaluating maternal ELF-MF exposure and infertility and adverse pregnancy outcomes. Thirteen studies were summarised, of which some reported effects but others didn't. No overall conclusions as to epidemiological evidence were drawn. Suggestions for improvements for future studies included addressing measurement error (of outcomes and exposures) and residual confounding.

A small cohort study by Eskelinen et al. (2016) evaluated maternal exposure to magnetic fields and time to pregnancy and foetal growth. A group of 373 mothers who gave birth between 1990 and 1994 at Kuopio University hospital in Finland were followed up for time to pregnancy and the authors

evaluated if their children were small for gestational age (SGA). ELF-MF exposure was measured by means of spot measurements in the homes before and during the pregnancy of the women. Time to pregnancy and risk for SGA babies was not statistically different among exposed or unexposed women.
The power in this study was very low due to the small study base and the low prevalence of exposure. For example, among women whose bedroom spot measurements exceeded 0.3 microtesla, only 2 exposed cases occurred. The study was therefore too small to add to the evidence base of a potential association between residential ELF-MF fields and the evaluated reproductive health outcomes.

2.4.5. Other outcomes

In a small cross-sectional study from Teheran, Iran, investigating memory loss among students, four primary schools were selected, of which two were located 30 and 50 m from a 63 kV substation (Ghadamgahi et al., 2016). The other two schools were at a distance of 610 and 1 390 m from the same station. Magnetic fields were measured in classrooms, halls and courtyards. 50 measurements per school were taken, but it was not described how these points were selected, when and for how long the measurements were done. Magnetic field exposures in classrooms were similar across schools, did not correlate with distance to the substation, and varied between 0.16 to 0.25 μT. The two schools close to the substation were nevertheless defined as "exposed" and the other two schools were defined as "controls". 102 boys aged 10-12 from the "exposed" school filled in an intelligence-testing questionnaire (Wechsler Scale), as did 74 boys of the same age from the "control" school. It remained unclear what the response rate was. Sociodemographic variables were not significantly different between the schools, but in all five Wechsler scale scores, "unexposed" children scored higher (better) compared to their "exposed" counterparts.
This is an insufficiently described study where it is unclear with which measurement strategy exposure was assessed and what the observed values mean for average exposures of the respective students. It also remains unclear how students were recruited and if selection bias could have introduced such a strong effect on memory in children. It is a typical example that study populations recruited from a few clusters may differ for many reasons, and such studies are vulnerable to confounding.

de Vocht and Olsen (2016) systematically reviewed studies that had addressed high-frequency voltage transients ("dirty electricity", DE) and health. The authors highlight that few efforts exist to translate DE, usually measured at electricity outlets, to a person's exposure. Previous studies evaluating health effects from high-frequency voltage transients were primarily based on case reports or ecological studies, not suitable to provide an informative answer regarding any potential health effects. The authors suggest to properly define the metric in questions, evaluate personal exposure, develop a hypothesis on a biological mechanism of how high-frequency voltage transients could interact with the body, and finally, to perform informative epidemiological studies. They conclude that previously used 50 Graham/Stetzer units as "safe" limits are arbitrary.

2.4.6. Conclusions on ELF epidemiological studies

Of recent studies on residential exposure to ELF-MF exposure and childhood leukaemia, two found a change of risk estimates over time, with decreasing risks in more recent decades, but this finding is not consistent across epidemiological studies. Altogether, while it remains an open question as to what caused the decrease of observed relative risks, these studies do not alter the current interpretation of an observed association of residential exposure to ELF-MF and childhood leukaemia yet absence of a causal explanation. Research on other outcomes is scarce and does not indicate new insights for health risk assessment.

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.

There were no cell, animal, human or epidemiological studies identified in the IF region of the electromagnetic field spectrum during the period covered by this report.

4. Radiofrequency (RF) fields

4.1. Cell studies

In this section 11 papers, dealing with the effect of radiofrequency fields (RF) alone, and in combination with chemical or physical agents, have been described.

4.1.1. Proteome

Kuzniar et al. (2017) carried out proteome-wide semi-quantitative mass spectrometry analyses of human fibroblasts (VH10) and osteosarcoma (U2OS) cells, and of mouse embryonic stem (IB10) cells exposed for 24 h to 2100 MHz, UMTS (E = 45 V/m RMS) or 5.8 GHz, WiFi (E = 9.5 V/m RMS). By using more than one method for differential protein expression analysis, the numbers of significant protein hits was rather low. Moreover, the changes detected with one method were not confirmed by applying different assays. Therefore, the authors suggest that the possible identification of false positive candidates has to be taken into account. In this study, similar results were obtained when cells were exposed to ELF fields (see section 2.1.9). The results indicate that less than 1% of the quantitated human or mouse proteome is differentially regulated in response to these EMFs. Moreover, if there is an effect induced by EMF exposures, it is smaller than technical variations.

4.1.2. Human Thyroid

The effects of RF exposure on primary human thyroid cells were investigated by Silva et al. (2016). Cell cultures were exposed to 900 MHz at SAR of 0.082 W/kg for 3 and 16 hours and at 895 MHz at 0.17 W/kg for 65 h. Following the exposure, cells were grown for different additional times, according to the biological endpoint to be investigated and then processed to evaluate several parameters associated with carcinogenesis, such as cell proliferation, DNA ploidy, reactive oxygen species (ROS) production, heat shock protein 70 (HSP70) and tumour-suppressor p53 protein (p53) expression. The results from 3 to 5 independent experiments did not show a significant difference between exposed and sham-exposed samples, in any of the experimental conditions tested.

4.1.3. Cytotoxicity

In a study conducted by Wang and co-workers, the potential cytotoxicity of RF exposure was assayed in bone marrow MSCs (BM-MSCs) cells isolated from C57BL/6 mice bone (Wang et al., 2015a). Cell cultures were exposed to pulsed 2.856 GHz (4 W/kg SAR). The microwave pulses were delivered at 50 pulses per second (pps), with a pulse width of 500 ns and the exposure was 6 min long. No effects on apoptosis, cell cycle and cell proliferation were detected by comparing exposed and sham-exposed samples, while in cultures treated with gamma rays as positive controls, all the investigated parameters was affected, as expected. To evaluate the effect of RF exposure on differentiation to osteoblasts, adipogenic, and chondrogenic cells, MSCs were treated with appropriate induction media immediately after RF exposure. Also in this case, no differences were detected between exposed and sham-exposed samples. Furthermore, the relative osteogenic proteins, osteocalcin (OCN) and osteopontin (OPN) were detected using qPCR. Compared with sham-exposed samples, OCN and OPN mRNA levels were significantly decreased by RF ($n = 3$, $p < 0.01$), indicating that the induced mRNA expression levels of OPN and OCN were both significantly reduced, suggesting an effect of RF at transcriptional level.

4.1.4. Mitochondrial DNA

Several parameters related to the stability of mitochondrial DNA (mtDNA) were examined by Sun et al. (2017) in human-derived promyelocytic leukaemia (HL-60) cells. Cultures were exposed for 4

h/day for five consecutive days to 900 MHz, continuous wave, at 120 μW/cm^2 power intensity corresponding to a calculated average SAR of 2.5 × 10^{-4} W/kg. Following the exposure, cells were collected after 30 min, 4 h or 24 h. The damage to mtDNA mediated through reactive oxygen species (ROS) formation, the effect on 8-hydroxy-2-dexoyguanosine (8-OHdG, a biomarker for oxidative damage), and on the mitochondrial synthesis of adenosine triphosphate (ATP) were measured. The results of three independent experiments indicated that ROS formation was increased at 30 min and 4 h ($p < 0.05$), but not at 24 h after RF exposure, while 8-OHdG levels were decreased for all the exposure durations investigated ($p<0.05$). Moreover, the mitochondrial transcription factor A, mtDNA polymerase gamma, mtDNA transcripts and mtDNA copy number was significantly decreased in exposed cells compared to sham exposed ones ($p<0.05$). In addition, a significant decrease in ATP levels was also detected in RF-exposed cells ($p<0.05$). Treatment of the cells with melatonin, a well-known free radical scavenger, for 4 h before RF exposure was able to attenuate mitochondrial dysfunction as well as mtDNA damage. Overall, the results from this investigation suggest that RF exposure affects ROS production leading to mitochondrial dysfunctions. The results refer to a cancer cell line.
It should be interesting to confirm these findings on healthy cells under several exposure conditions in terms of frequency, modulation and SAR values.

4.1.5. DNA damage

Several studies were devoted to investigating the induction of genotoxic effects induced by RF exposure, given alone or in combination with other stressors.

Al-Serori et al. (2017) exposed two human derived glioma cell lines U87 and U251 to 1959 MHz, UMTS signal, for 16 hours at SAR of 0.25. 0.50 and 1W/kg. Moreover, to evaluate cooperative effects, exposures were also carried out in the presence of mitomycin-C (MMC), a well-known DNA damage inducer. During and before exposure, the cells were either cultivated under optimal conditions (with culture medium supplemented with serum) or in serum free medium. The induction of DNA damage was evaluated by applying the MN assay. Moreover, on the same slides, other indicators of genotoxicity were recorded, such as nuclear buds (reflecting gene amplification), nucleoplasmatic bridges (derived by dicentric chromosomes), apoptosis, necrosis and alterations of cell proliferation. No effects were detected for all the parameters investigated, for all the conditions tested. The only endpoint which was statistically significantly affected by RF exposure in one of the cell lines (in U251) was apoptosis. An increased number of apoptotic cells was detected at 1 W/kg SAR, regardless if the cells were grown with or without serum. It should be stressed that U251 cells are defective in tumour protein p53, acting as a tumour suppressor and described as "the guardian of the genome" because of its role in conserving stability by preventing genome mutation. Moreover, it is not clear how many experiments for each conditions have been carried out (it seems just two).

Sannino et al. (2017) investigated the effect of 1950 MHz, UMTS, given alone or in combination with MMC in the induction of genotoxic effects in V79 cells, a Chinese hamster lung fibroblast cell line. In a first set of experiments, cells were exposed for 20 h at four SAR values: 0.15, 0.3, 0.6, and 1.25 W/kg. A statistically significant increase in MN frequency was found in cultures exposed to 0.15 and 0.3 W/kg ($p<0.05$) compared to sham-exposed ones, while SAR values of 0.6 and 1.25 W/kg did not exert any effect (four independent experiments each). Moreover, to evaluate the ability of RF to exert protective effects with respect to a chemical mutagen, cell cultures were also pre-exposed for 20 h at 0.3 or 1.25 W/kg, and then treated with MMC. A significant reduction in the frequency of MN was detected in cultures pre-exposed to 1.25 W/kg compared to cultures treated with MMC alone ($p<0.05$), indicating induction of adaptive response. Such a decrease was not induced by pre-exposure at 0.3 W/kg SAR. The authors concluded that their results provide certain evidence that RF exposure is capable of inducing both adverse and beneficial effects in V79 cells, depending on the exposure conditions adopted.

Similar results were reported by Sun and co-workers (Sun et al., 2016a). They exposed mouse embryonic fibroblasts (MEFs) with proficient or deficient protein kinase ataxia-telangiectasia-mutated (ATM; Atm+/+ and Atm−/−, respectively). This enzyme regulates the cellular response to genotoxic stress. To evaluate the possible effects of RF exposure on DNA, the effect of the exposure was evaluated by applying alkaline and neutral comet assays to detect single-strand breaks (SSBs) or double-strand breaks (DSBs), respectively. Moreover, the activation of the corresponding DNA damage repair and the effect on cell behaviour were also examined. Cell cultures were exposed for 1 h at 1800 MHz, 4 W/kg SAR. The results of three independent experiments indicated that in both Atm+/+ and Atm−/− MEFs a significant increase of SSBs was induced (alkaline comet assay; $p<0.01$). When the exposure duration was longer (up to 36 h), no changes were detected in the 12- or 24-h-exposed groups, and the levels of SSBs were even lower than the background level after 36 h of exposure ($p<0.01$). The results from the neutral comet assay indicated that RF exposure induces transient DNA DSBs in Atm−/− MEFs ($p<0.05$) but not Atm+/+ MEFs. Further experiments indicated that the DSB repair pathway was activated in both cell types after long exposure times. However, exposure up to 36 h had no significant influence on the cell cycle or cell viability. A similar effect was observed for treatments with low doses of 4-nitroquinoline 1-oxide (4NQO) and hydrogen peroxide, indicating that even a well-recognized genotoxic substance could induce the same phenomenon observed following RF exposure, when its concentration is sufficiently low.
On the whole, the results of this investigation indicate that RF exposure is able to activate the DNA-repair mechanisms, inducing a hormesis-like effect. The results are in agreement with those reported by other authors on the ability of RF in inducing adaptive response in cells exposed and then treated with chemical or physical stressors. The long-term biological consequences of these phenomena and their health impact are not known and deserve further investigation.

The induction of effects on DNA integrity and cellular behaviour was systematically evaluated by Su et al. (2017) in different neurogenic cells. Human glioblastoma (U251 and A172) and neuroblastoma (SH-SY5Y) cells were intermittently (5 min on/10 min off) exposed to 1800MHz GSM at an average SAR of 4.0 W/kg for 1, 6, or 24 hours. The frequency of ɣH2AX foci, an early marker of DNA double strand breaks, was assessed in five independent experiments. In addition, cell cycle progression, proliferation and viability were also examined. No effects were detected for all the endpoint investigated when exposed cultures were compared to their sham-controls (three to four independent experiments for each endpoint investigated). Furthermore, prolonged incubation of these cells for up to 48 h after exposure did not significantly affect cellular behaviour.

Another research group exposed a mouse neuroblastoma (Neuro-2a) cell line for 24 h to 900 MHz GSM signal at SAR values of 0.5, 1 and 2 W/kg to evaluate DNA damage by means of the alkaline comet assay (Wang et al., 2015b). Cells treated with methyl methane sulfonate (MMS) served as positive control. The results of five independent experiments showed no differences in exposed cultures compared to sham-treatments, while a significant increase was detected in positive controls. On the contrary, when the alkaline comet assay, modified by using lesion-specific endonucleases, such as formamido-pyrimidine-DNA glycosylase (FPG) was applied, an increase in the comet parameters was recorded ($p<0.05$) in cultures exposed at 2 W/kg compared to sham controls, indicating an oxidative DNA damage. Such an increase was not induced at lower SAR values. Moreover, when cells were treated to inhibit 8-oxoguanine glycosylase-1 (OGG1), an enzyme that protects from DNA oxidation damage, the FPG-modified comet assay showed significant oxidative damage at SARs of both 1 and 2 W/kg. Positive controls worked properly.

4.1.6. Neurodegenerative diseases

In two studies the involvement of RF exposure in altering parameters related to neurodegenerative diseases was investigated.

Alzheimer's disease involves the formation of plaques of amyloid beta (Aβ) that induce cellular damage including oxidative DNA damage. Lee et al. (2016) investigated the effect of combined

radiofrequency field exposure on amyloid-beta–induced cytotoxicity in HT22 mouse hippocampal neurones. Cells were exposed to multiple signals (837 MHz, CDMA at 2 W/kg plus 1950 MHz, W-CDMA at 2 W/kg) for 2 h. Treatment with Aβ alone suppressed HT22 cell proliferation in a concentration-dependent manner, decreased the G1 fraction and increased the subG1 fraction of the cell cycle progression, increased apoptosis, increased reactive oxygen species (ROS) generation, and stimulated the ataxia telangiectasia and Rad3-related protein/checkpoint kinase 1 DNA single-strand breakage pathway, and enhanced beta-site amyloid precursor protein expression. RF exposure did not significantly affect any of the Aβ-induced endpoints.
Unfortunately, in this interesting paper the number of independent experiments is not reported.

The possibility that RF exposure alters activity and gene expression of acetylcholinesterase (AChE), an enzyme involved in learning, memory and several neurodegenerative disorders, was investigated byValbonesi et al. (2016). Rat pheocromocytoma (PC12) cells were exposed for 24 h (5 min on/10 min off cycles) to 1800 MHz, GSM, 2 W/kg SAR. The enzymatic activity was increased in exposed cells compared to sham controls ($p<0.05$, 6 independent experiments), while no differences were detected in AChE protein expression and mRNA levels, suggesting that the RF-induced enhancement in enzyme activity is not due to an increase in gene expression. The authors suggest that one of the possible explanations of their findings is a RF-induced conformational change in protein structure, leading to changes in its enzymatic activity.

4.1.7. Summary and conclusions on cell studies

In line with the findings from the previous reports, several *in vitro* studies reported no effect of radiofrequency exposure, although in some cases parameters related to oxidative stress were affected. Moreover, the cell type plays an important role in eliciting the effect, if any. In two studies a protective effect was detected against treatments with chemical or physical damaging agents. As for the other frequency ranges, a large number of studies has been excluded from the evaluation, due to the poor quality, mainly related to absent or inadequate dosimetry and to the lack of sham-exposed controls.

Table 4.1.1 – *In vitro* studies on exposure to RF fields

Cell type	Endpoint	Exposure conditions RF	Effect	References
Human fibroblasts (VH10); osteosarcoma (U2OS) cells; mouse embryonic stem (IB10)	Protein expression	2100 MHz, UMTS (E = 45 V/m RMS) 5.8 GHz, WiFi (E = 9.5 V/m RMS). 24 h	Slight changes not confirmed by applying different assays.	Kuzniar al (2016)
Primary human thyroid cells	proliferation, DNA ploidy, ROS,HSP70, p53 expression	900 MHz, 0.082 W/kg 3 and 16 h 895 MHz 0.17 W/kg 65 h	No effect	Silva et al (2016)
Primary mouse bone marrow (BM-MSCs) cells	Apoptosis, cell cycle, cell proliferation and differentiation	2.856 GHz pulsed 4 W/kg 6 min	No effect on apoptosis, cell cycle progression and cell proliferation. Significant reduction in mRNA expression levels of OPN and OCN	Wang C et al (2015)
Human-derived promyelocytic leukemia (HL-60) cells	Oxidative stress, mtDNA	900 MHz, CW 10^{-4} W/kg 4h/day for 5 days	Increased ROS formation after 30 min and 4 h exposure; Decreased 8-oHdG levels Decreased mtDNA damage-related parameters Decreases ATP levels Effects attenuated by treatments with Mel 4 h before RF exposure	Sun et al (2017)

Human derived glioma cell lines U87 and U251	genotoxicity	1950 MHz, UMTS 0.25. 0.50 and 1 W/kg 16 h Co-exposure: MMC	No increase in MN frequency following exposure and co-exposures. Apoptosis induced in U251 cells by RF alone	Al-Serori et al (2017)
Chinese hamster lung fibroblasts (V79)	genotoxicity	1950 MHz, UMTS 0.15, 0.3, 0.6 and 1.25 W/kg 20 h Co-exposure: MMC	Increased MN frequency by RF alone at 0.15 and 0.3 W/kg. Reduction of MMC-induced MN in cultures pre-exposed at 1.25 W/kg	Sannino et al (2017)
Embryonic fibroblasts Atm+/+ and Atm-/-	DNA damage and repair	1800 MHz 4 W7Kg 1, 12, 24 and 36 h	Increased SSB following 1h RF exposure; no effects for longer exposure times. Transient DSB repaired for longer exposure times. No effects on cell cycle progression	Sun et al (2016)
Human glioblastoma (U251 and A172) and neuroblastoma (SH-SY5Y) cells	Genotoxicity, cell cycle, proliferation, viability	1800 MHz, GSM 4W/kg 1, 6 and 24 h	No effect	Su et al (2016)
Mouse neuroblastoma (Neuro-2a) cells	Oxidative DNA damage	900 MHz, GSM 0.5, 1, 2 W/kg 24h	No effect with comet assay. SB increased at 2 W/kg with FPG-modified comet assay. No effect at 0.5 and 1 W/kg. SB increased at 1 and 2 W/kg when OGG1 was inhibited.	Wang X et al (2015)
HT22 mouse hippocampal neurons	Cell cycle, proliferation, apoptosis, ROS	837 MHz, CDMA at 2 W/kg plus 1950 MHz, W-CDMA at 2 W/kg 2 h Co-exposure: amyloid beta	No effect of RF exposure, alone and in combination with amyloid beta	Lee et al (2016)
Rat pheocromocytoma (PC12) cells	AChE activity and gene expression	1800 MHz, GSM 2 W/kg 24 h (5 min on/10 min off cycles)	Increased enzymatic activity. No effect on protein expression and mRNA levels,	Valbonesi et al (2016)

Abbreviations: 8-oHdG: 8-hydroxy-2-dexoyguanosine; AChE: acetylcholinesterase; ATP: adenosine triphosphate; CDMA: code division multiple access; CW: continuous wave; DSB: double strend breaks; FPG: formamido-pyrimidine-DNA glycosylase; GSM: Global System for Mobile Communication; HSP: heath shock proteins; Mel: melatonin; MMC: Mitomycin-C; mtDNA: mitochondrial DNA; OCN: Osteocalcin; OGG1: 8-oxoguanine glycosylase-1; OPN: Osteopontin; ROS: Reactive oxygen species; SSB: single strend breaks; UMTS: universal mobile telecommunications system; W-CDMA: Wideband Code Division Multiple Access.

4.2. Animal studies

A large number of studies using a variety of endpoints investigated the effect of different types of radiofrequency electromagnetic field exposure in experimental animals. Unless otherwise noted, exposed groups were always compared to a sham-exposed group.

4.2.1. Gene expression

McNamee et al. (2016) exposed male C57BL/6 mice (5 per group) for 4 h per day during 5 days to a 1.9 GHz field, either pulse-modulated at 50 Hz or continuous wave. The brain SAR was calculated to be 0.763 ± 0.023 or 0.104 ± 0.002 W/kg for the CW field and 0.827 ± 0.040 or 0.086 ± 0.002 W/kg for the pulsed field. After the last exposure the brain was removed, total RNA isolated from different parts of the brain and differential gene expression assessed. No differences compared to sham controls were observed.

Kim et al. (2016) exposed male C57BL/6 mice in groups of five to 835 MHz for 5 h per day during 4 or 12 weeks at a whole-body SAR of 4.0 W/kg. After the last exposure the brains were removed and the hypothalamus and striatum isolated. Total RNA was extracted and differential gene expression assessed. Several autophagy-related genes were (semi)quantatively assayed with PCR. Some of these were up-regulated in the striatum, with a higher expression in the longest exposed group. In the hypothalamus, several genes were down-regulated at 4 weeks and not at 12 weeks, with the exception of one gene that was also down-regulated at 12 weeks. Electron microscopy revealed more autophagic vacuoles in both brain sections of exposed animals compared to sham-exposed controls, which were more pronounced at 12 weeks than at 4 weeks.

Kim et al. (2017b) exposed male C57BL/6 mice (5 per group) to 835 MHz for 5 h per day during 4 weeks at a whole-body SAR of 4.0 W/kg. After the last exposure the animals were sacrificed and the cerebral cortex and brainstem removed. In the cortex, increased levels of genes and proteins related to autophagy, as well as accumulation of autophagosomes and autolysosomes were observed. In the brainstem, apoptosis pathways were up-regulated.

Kim et al. (2017a) exposed male C57BL/6 mice (6 per group) to 835 MHz for 5 h per day during 12 weeks at a whole-body SAR of 4.0 W/kg. After the last exposure the animals were sacrificed and the cerebral cortex was removed. They observed increased induction of autophagy genes and production of proteins and accumulation of autolysosomes in neuronal cell bodies. However, a proapoptotic factor was down-regulated. Damage to the myelin sheaths was observed and the mice were found to display hyperactivity-like behavior.
Autophagy is considered to be a protective response to stress. The applied whole-body SAR of 4 W/kg in these three studies is a thermal burden to the mice, so the effect of heat stress cannot be excluded and therefore it is difficult to conclude that the RF exposure per se caused the autophagy. The temperature of the animals was not monitored, however.

Ohtani et al. (2016) exposed male Sprague-Dawley rats (4 per group) to a 2.14 GHz RF field at whole-body SARs of 4 and 0.4 W/kg for 6 h once, or for 3 or 6 h per day during 3 days. With the highest SAR the core body temperature increased by 1.0-1.5 °C, while with the lower SAR and sham exposure no changes in temperature were observed. The expression of heat shock protein genes in brain tissue was increased after exposure at 4 W/kg, but not different from that in sham controls after 0.4 W/kg.

Woelders et al. (2017) exposed fertilized Leghorn chicken eggs (20-104 per group) for 22 days to 1800 MHz GSM, 1880 MHz DECT, 2100 MHz UMTS or 5.6 GHz WLAN signals. The field strength was 3.0 V/m for GSM, DECT and UMTS and 3.4 V/m for WLAN. The respective SARs were 0.038, 0.041, 0.045 and 0.038 mW/kg. No effects were observed on survival or on weight of and gene expression in the entire embryo and heart, liver, spleen, bursa of Fabricius and yolk.

Manta et al. (2016) exposed female Drosophila fruit flies in groups of three for 30 min to a 1800 MHz signal from a mobile phone. The electric field strength was 10 V/m and SAR was calculated at 0.15 W/kg. In developing oocytes, increased oxidative stress was observed immediately after exposure and apoptosis 4 hours later. Two hours after exposure, 168 genes in the oocytes of the exposed animals were expressed differently from those in the sham controls; these genes were associated with different biological processes, such as basic metabolism and stress response and apoptotic death.
The external E field was used for this calculation, but in view of the very small dimensions of the flies this is probably not different from the internal E field, which is the correct parameter to use.

4.2.2. Cell proliferation and death

Xu et al. (2017) exposed 7- or 21-days-old Kumming mouse pups (6 males and 6 females per group) to 1800 MHz at a brain SAR of 1.16 W/kg, for 8 h per day during 3 consecutive days. 24 h after the last exposure the brains were removed and cell death and stem cell proliferation in the dentate gyrus of

the hippocampus assessed. Exposure did not influence cell death, but in the 7-day-old mice stem cell proliferation was higher in the exposed group than in the sham-exposed controls, while there was no such difference in the 21-day-old animals.

4.2.3. Blood-brain barrier

Sirav and Seyhan (2016) exposed male and female Wistar (8-9 per group) rats to 900 or 1800 MHz GSM-like fields for 20 min. The electric field strength was 4.96 ± 0.01 V/m for 900 MHz and 4.70 ± 0.02 V/m for 1800 MHz. Exposure was given directly after injection of the dye Evans blue, under anesthesia. Uptake of this dye in brain tissue is an indication of breakdown of the blood-brain barrier. In males they observed a higher dye concentration in brain tissue after exposure to both frequencies, with the largest increase occurring after 1800 MHz. In females there was an increase in the 900 MHz group only. The dye concentration in the brains of the female sham-exposed controls was higher than in the males.
The authors calculated an average – presumably whole-body – SAR of 0.02 W/kg, but incorrectly assumed that the internal electric field is equal to the external electric field, so this SAR cannot be used.

4.2.4. Behaviour, memory

Barthélémy et al. (2016) exposed male Sprague-Dawley rats in groups of 14-20 to a 900 MHz GSM signal for 15 min at a brain SAR of 1.5 or 6 W/kg or for 45 min at a SAR of 6 W/kg. After the last exposure, several memory and behavioural tests were performed and the levels of proteins indicating brain damage were assessed in six different areas of the brain. After 15 min exposure at a SAR of 1.5 W/kg an increased level of glial fibrillary acidic protein (GFAP), a marker of brain tissue injury, was observed in the entire homogenate of the striatum, but a reduced level in the cytosolic fraction. Cytosolic GFAP was increased in the hippocampus and olfactory bulb after exposure for 15 min at a SAR of 6 W/kg. No changes in the levels of the other investigated proteins were observed. Behaviour and memory were not changed, except for long-term memory, which was reduced after exposure for 15 min at a SAR of 6 W/kg.

From the same group, Petitdant et al. (2016) exposed juvenile male Sprague-Dawley rats (8 per group) starting at 32 days after birth to 900 MHz RF fields for 45 min per day, 5 days per week, for 4 weeks. The average SAR in the brain was 1.5 or 6 W/kg. In addition, inflammation of brain tissue was induced, under the hypothesis that this would increase sensitivity to the exposure. A number of behavioral tests was performed and GFAP was assessed. No differences were observed in any of the endpoints between exposed and inflammation-induced animals and sham-exposed controls, which indicate a lack of effect of exposure up to 6 W/kg on these markers of brain function in young animals.

In a third study from these researchers, Bouji et al. (2016) exposed young (4–6 months) and old (22–24 months) male Wistar rats (6-8 per group) to 900 MHz for 45 min per day during 1 month. The SAR in the brain was 6 W/kg. The difference in learning capabilities and behaviour between the young and old rats was not modified by the EMF exposure. However, an age-independent decrease in anxiety-related behaviour was observed. No effect of exposure was found on IL-1β, IL-6 or GFAP levels in the brain in either age group.

Son et al. (2016) exposed female 5xFAD mice transgenic for the expression of several Alzheimer-related proteins in groups of 8 to a 1950 MHz RF field for 2 h per day, 5 days per week during 3 months at a whole-body SAR of 5 W/kg. After the last exposure, several memory and behavioural tests were performed and the levels of the Alzheimer proteins in the brain and blood were assessed. No effects of the exposure were observed for any of these endpoints despite the fact that the exposure probably resulted in an increase in body temperature.

Wang et al. (2017) exposed female C57/LB mice (group size 7-21) to an 1800 MHz RF field for 30 min with resulting whole-body SARs of 1.98, 2.2, 2.42, 2.86 and 3.3 W/kg. The mice exposed to all but the lowest SAR level took more time to explore a new object (i.e. object recognition was stimulated), and this effect lasted up to 8 days after the exposure. The brains of animals exposed to a SAR of 3.3 W/kg were further investigated. Increased dendritic spine density and length of hippocampal and prefrontal cortical neurons were observed, as well as altered resting membrane potential and action potential frequency and reduction of the action potential half-width, threshold, and onset delay in pyramidal neurons.

4.2.5. Oxidative stress

Hidisoglu et al. (2016) exposed male Wistar rats (14 per group) to 2100 MHz fields for 2 h per day during 1 or 10 weeks. They report a brain SAR value of 0.57–0.95 W/kg, but this was erroneously calculated from the external electric field, which was measured at 27–35 V/m around the head. They observed a decreased latency in visually evoked potentials after 1 week and an increased latency after 10 weeks. Antioxidants were increased after 1 week and decreased after 10 weeks.

Sahin et al. (2016) exposed female Wistar rats (6 or 9 per group) to a UMTS-like signal at a whole-body SAR of 0.4 W/kg for 6 h per day, 5 days per week for either 2 or 8 weeks. After the last exposure they extracted DNA from the brain and assessed 8-hydroxy-2'deoxyguanosine (indicative for oxidative DNA damage) and malondialdehyde (indicating lipid peroxidation). Oxidative DNA damage was increased after 10 days of exposure, but decreased after 40 days exposure. Lipid peroxidation was unchanged after 10 days, but decreased after 40 days.

López-Furelos et al. (2016) exposed male Sprague-Dawley rats in groups of 10 to either 900 MHz, 2450 MHz or 900+2450 MHz fields for 1 or 2 hours at two exposure levels and assessed heat shock proteins and caspase-3 levels (indicating apoptosis) in the left and right hemispheres of the cerebrum and cerebellum. Since the animals were laterally exposed from the left side, the exposure of the hemispheres differed. The SAR in the cerebrum varied from 0.026–0.055 W/kg for the low exposure level and 0.050–0.111 W/kg for the high level and in the cerebellum the SARs varied from 0.025–0.090 and 0.050–0.183 W/kg, respectively. No significant differences between exposed and sham-exposed groups were observed for any of the three endpoints in the cerebrum. In the cerebellum, however, HSP-90 and HSP-70 levels in the left hemisphere of the animals exposed to either 900 or 2450 MHz at the highest exposure level were higher than in the corresponding sham- or combined-exposed animals. No differences were observed in the right hemispheres and at the lower exposure level. The only differences in caspase-3 level were observed in the group exposed to 2450 MHz at the highest exposure level: the caspase-3 level in the left hemisphere was higher than in the right one and also higher than in the left hemisphere of the sham-exposed animals.

Ahmed et al. (2017) exposed male Wistar rats (4-6 per group) to a 900 MHz GSM-type signal for 1 h per day, for up to 4 months, at a power density of 0.2 W/m^2. Immediately after the last exposure, or one month later with the 4-month exposure, they determined the levels of various oxidative stress parameters (malondialdehyde, nitric oxide, glutathione, glutathione reductase, superoxide dismutase, and catalase) in the hippocampus and striatum. Variations were observed, but without a clear pattern. Sometimes the levels in the exposed animals were increased relative to that in the controls, sometimes they were decreased and often there was no difference.
There was a large variation over time for all parameters in the control groups which casts doubt on the stability of the procedures used to assess the oxidative stress parameters. Consequently these data are difficult to interpret. The indicated power density was stated to result in a presumably whole-body SAR of 1.245 W/kg, but the method of assessment is not provided, so the SAR cannot be used.

Kerimoğlu et al. (2016b) exposed male Sprague-Dawley rats to a 900 MHz field at a whole-body SAR of 0.0067 W/kg for 1 h per day for 19 days during adolescence (day 22–60). Compared to the sham-exposed group, they observed a decrease in the total number of pyramidal neurons in the cornu

ammonis of the hippocampus. Moreover they also observed an increase in malondialdehyde and glutathione and a decrease in catalase in the brain, indicating increased oxidative stress levels.

In the same animals also damage to the spinal cord was investigated (Kerimoğlu et al., 2016a). In exposed animals they observed increased histopathological damage in the lumbar spinal cord, but this was not quantified. They did find significantly increased apoptosis in both glia cells and neurons. Malondialdehyde levels were increased and superoxide dismutase and glutathione levels decreased in the exposed compared the sham exposed animals, indicating increased oxidative stress.

Akdag et al. (2016) exposed male Wistar rats (8 per group) to a 2.4 GHz Wi-Fi signal at a whole-body SAR of 0.14 mW/kg. The exposure was continuous, 24 h per day for 12 months. After the exposure period, DNA damage in several organs was assessed. No differences in DNA damage were observed in brain, kidney, liver and skin. Only in the testis more DNA damage was present in the exposed animals.
The maximum SAR was stated to be 7.13 mW/kg, but it is not indicated where this was found.

Tuncal et al. (2016) exposed groups of six female Wistar rats for 6 h per day, 5 days per week, for 10 or 40 days to a 2100 MHz GSM phone-type signal. The whole-body SAR was 0.4 W/kg. Two days after the last exposure the thyroid glands were removed for analysis of oxidative stress parameters. In the group exposed for 10 days, superoxide dismutase and glutathione peroxidase were not different from controls, while catalase and xantine oxidase were increased. In the 40-day exposed group, only catalase was increased, while all other parameters were not different between exposed and control groups.
It is not clear whether the control groups were sham-exposed.

Chauhan et al. (2017) exposed male Wistar rats (4 per group) for 2 h per day during 35 days to a 2.45 GHz RF field at a whole-body SAR of 0.14 W/kg. They observed histological changes in brain, liver, testis, kidney and spleen. An increased level of lipid peroxidase was observed in liver, brain and spleen.
It is not reported whether they also measured lipid peroxidase in kidney and testis.

Sokolovic et al. (2015) exposed male Wistar rats in groups of 21 to a 900 MHz field for 4 h per day during 20, 40 or 60 days. The whole-body SAR of the free-roaming animals was estimated at 0.043–0.135 W/kg. The animals were injected with saline or melatonin early in the morning and exposed later. Malondialdehyde in testicular tissue was increased after all exposure durations, while co-treatment with melatonin resulted in lower levels. For protein carbonyl, the levels were increased only after 40 and 60 days and there was no influence of melatonin. Catalase levels were decreased at all exposure durations, and again no effect of melatonin administration was observed. Xanthine oxidase was increased after 40 and 60 days exposure, with a reducing effect of melatonin. Alkaline DNAse was increased after all exposure durations with no effect of melatonin. Acid DNAse activity was increased after 40 and 60 days exposure; melatonin reduced the level both in controls and exposed animals to the same extent.

4.2.6. Fertility

Türedi et al. (2016) exposed pregnant Sprague-Dawley rats to a 900 MHz field for 1 h per day on days 13–21 of the pregnancy at a whole-body SAR of 0.01 W/kg. Female pups were sacrificed at an age of 34 days and their ovaries investigated. In the exposed animals, primordial and tertiary follicle numbers were reduced and the number of atretic follicles and the apoptotic index levels were increased. Histopathological examination showed severe damage to the follicles.

Odaci et al. (2016) exposed pregnant Sprague-Dawley rats to a 900 MHz field for 1 h per day on days 13–21 of the pregnancy at a whole-body SAR of 0.024 W/kg. Male pups (9 per group) were sacrificed

at an age of 60 days. The diameter and epithelial thickness of the seminiferous tubules and the sperm motility and vitality were decreased in the prenatally exposed animals. Apoptosis and plasma DNA oxidation were increased, while there were no effects observed on malondialdehyde in the testis tissue and in serum, and on the total sperm count.

Pandey et al. (2017) exposed Swiss mice (n=15 per group) to 904 MHz RF fields for 4 or 8 h per day during 35 days. The whole-body SAR in the free-roaming mice ranged from 0.0054–0.0516 W/kg. Directly after the last exposure or after an additional 35 days without exposure, the animals were sacrificed and the testes removed. Various indices showed damage to the testes and reduction of sperm production after exposure, as well as DNA damage and changes in mitochondrial membrane potential. All these were generally more severe after the longer exposure and showed recovery to various extents after the 35 days resting period.

4.2.7. Growth and development

Kuybulu et al. (2016) exposed pregnant Wistar rats throughout pregnancy and their male offspring from an age of 18 days until 12 weeks. A second group of pregnant rats received sham exposure during pregnancy and real exposure of the male offspring. A third group received sham exposures only. The exposures were to a 2.45 MHz field for 1 h per day, at a whole-body SAR of 0.1 W/kg. In the pre- and postnatally exposed group (n=8) malondialdehyde and total oxidant status were increased, while superoxide dismutase and total antioxidant status were decreased; in the group that was only postnatally exposed (n=8) no differences were observed with the sham-exposed group (n=8). N-acetyl-beta-D-glucosaminidase (NAG) activity in urine, an indicator of renal tubular dysfunction, was increased in both exposed groups.
The exposure was given by an antenna located near the head, so the distribution of the field over de body is very inhomogeneous; the exact exposure of the kidney, the organ under investigation, is not provided, so the experiments are difficult to interpret.

Shirai et al. (2017) exposed female Sprague-Dawley rats to multiple-frequency RF fields for 20 h per day during 8 weeks, starting at the 7th day of pregnancy until 21 days after birth. The fields were two mobile phone 800 MHz bands, two mobile phone 2 GHz bands, and four Wi-Fi/wireless LAN bands (2.4, 2.5, and 5.2 GHz). The mean whole-body SAR was 0.43 or 0.09 W/kg for the pregnant females, 0.38 or 0.08 W/kg for the pups until weaning and 0.39 and 0.08 W/kg for the offspring after weaning. All frequencies contributed equally to the exposure. The offspring was allowed to mate and produce an F2 generation. No differences between exposed and sham-exposed animals (groups of 8) were observed on a number of developmental and fertility parameters for both the dams of the F1 and for the F2 offspring.

Chen et al. (2016) exposed female KM mice to a 935 MHz RF field for 2 or 4 h per day during 3 days, at power densities of 1.5, 5.7, 14.0 W/m^2. The day after the last exposure the animals were sacrificed and oocytes collected. These were *in vitro* fertilized. Development of the embryos (48-135 per group) was decreased after the exposure to the two highest power densities, with a stronger effect with the higher level.

Nisbet et al. (2016) exposed male Wistar rats in groups of 11 to 900 or 1800 MHz RF fields for 2 h per day during 90 days. SAR values are not provided, but in the study that the authors refer to for this (Nisbet et al., 2012), the values decrease with age from 3.0 mW/kg at 10 days to 1.2 mW/kg at 70 days for 900 MHz and from 0.053 to 0.011 mW/kg for 1800 MHz. The age in the current experiment is from 2–90 days, however. The weight and length of the exposed animals increased more and faster than in the sham-exposed controls, with no difference between the two types of exposure. Calcium, growth hormone, estradiol and testosterone levels in the EMF groups were higher, but again without differences between the exposure groups. The growth plate in the femur in the 1800 MHz group was thinner than in the 900 MHz and sham control group.

It is remarkable that the effect observed is not dependent on the exposure level, since the widely different SAR levels for the two frequencies result in similar growth stimulating effects, and that only in the 1800 MHz group an effect on the growth plate was observed. Additional studies would be needed to interpret the importance of these findings.

4.2.8. Immunology

Mina et al. (2016) exposed male Aegean wall lizards (five per group) to the signal from a DECT base station (1880–1900 MHz, electric field strength 3.2 ± 5% V/m) 24 h per day for 4 or 8 weeks. Inflammatory responses (caused by the innate immune system) in the exposed animals were significantly reduced compared to the sham-exposed animals. No effects were observed on T-cell responses, indicating no effect on acquired immune responses.

4.2.9 Summary radiofrequency exposure animals

As in previous years, a variety of endpoints has been investigated in relation to radiofrequency field exposure of experimental animals. A substantial number of studies focused on effects in the brain. Several studies observed changes in gene expression in brain tissue, but in these cases the exposure was a whole-body SAR of 4 W/kg, which means that thermal effects cannot be excluded. A study on the blood-brain barrier showed contrasting results in males and females and is therefore difficult to interpret. Studies on behaviour and memory were also not consistent. One French study showed changes in parameters indicating increased damage in brain tissue, and a reduction in long term memory, but only after 15 min and not after 45 min exposure. Two other studies from the same researchers with exposures up to 4 weeks did not observe any such effects in young or old animals. In another study whole-body SARs up ranging for 2.2 to 3.3 W/kg resulted in stimulation of object recognition.

Studies investigating oxidative stress usually found increased levels in brain and other tissues, even after whole-body SARs as low as 0.0067 W/kg. In studies investigating different exposure durations, the oxidative stress levels were reduced after longer exposures. In several studies pregnant animals were exposed and effects in the offspring investigated. Negative effects were observed on the female and male reproductive systems employing low exposure levels (whole-body SARs of less than 0.05 W/kg). Variable results were obtained with regards to developmental endpoints.

All these studies were done on rodents, but there were also three studies on non-mammalian species. In chicken embryos no effect was observed on survival and gene expression of exposures throughout development, but the exposure levels were very low, around 0.04 mW/kg. In fruit flies a 30-min exposure resulted in differential expression of 168 genes in oocytes, including genes associated with metabolism, (oxidative) stress and apoptosis. In a lizard, finally, long-term exposures resulted in reduction in innate immune reactions, but no effect on acquired immune responses.

Table 4.2.1. Animal studies on exposure to RF fields

Endpoint	Authors	Exposure	Exposure	Effect
Rodents studies				
Gene expression	McNamee et al. (McNamee et al., 2016)	1.9 GHz, CW or 50 Hz pulsed 4 h/day, 5 days	Brain SAR 0.763 ± 0.023, 0.104 ± 0.002 W/kg (CW) 0.827 ± 0.040, 0.086 ± 0.002 W/kg (pulsed)	No effect on gene expression in brain.

	Kim et al. (Kim et al., 2016)	835 MHz 5 h/day, 4 or 12 weeks	WBA SAR 4.0 W/kg	Some autophagy-related genes up- or downregulated in striatum and hypothalamus. Autophagy observed.
	Kim et al. (Kim et al., 2017b)	835 MHz 5 h/day, 4 weeks	WBA SAR 4.0 W/kg	Upregulation of autophagy-related genes in cortex and brainstem. Autophagy observed in cortex.
	Kim et al. (Kim et al., 2017a)	835 MHz 5 h/day, 12 weeks	WBA SAR 4.0 W/kg	Upregulation of autophagy-related genes in cortical neurons. Myelin damage and hyperactivity observed.
	Ohtani et al. (Ohtani et al., 2016)	2.14 GHz 6 h once; 3 or 6 h/day, 3 days	WBA SAR 0.4, 4 W/kg	Heat shock protein genes in brain upregulated after 4 W/kg.
Cell proliferation and death	Xu et al. (Xu et al., 2017)	1800 MHz 8 h/day, 3 days	Brain SAR 1.16 W/kg	No effect on cell death. In 7-d-old mice higher stem cell proliferation, not in 21-d-old mice.
Blood-brain barrier	Sirav and Seyhan (Sirav and Seyhan, 2016)	900, 1800 MHz GSM 20 min	E field 4.96 ± 0.01 V/m (900 MHz), 4.70 ± 0.02 V/m (1800 MHz)	Males: BBB breakdown, more at 1800 MHz; females: only at 900 MHz.
Behaviour, memory	Barthélémy et al. (Barthélémy et al., 2016)	900 MHz GSM 15 min (1.5, 6 W/kg) 45 min (6 W/kg)	Brain SAR 1.5 or 6 W/kg	Increased GFAP in striatum (15 min @ 1.5 W/kg), hippocampus, olfactory bulb (15 min @ 6 W/kg). Reduced longterm memory (15 min @ 6 W/kg).
	Petitdant et al. (Petitdant et al., 2016)	900 MHz 45 min/day, 5 days/week, 4 weeks starting 32 days after birth	Brain SAR 1.5 or 6 W/kg	No effect on behavior, GFAP.
	Bouji et al. (Bouji et al., 2016)	900 MHz 45 min/day, 1 month 4–6 months vs. 22–24 months old rats	Brain SAR 6 W/kg	No effect learning; age-dependent increase anxiety-related behavior. No effect brain IL-1β, IL-6, GFAP.

	Son et al. (Son et al., 2016)	1950 MHz, 2 h/day, 5 days/week, 3 months	WBA SAR 5 W/kg	No effect on memory, Alzheimer proteins in brain and blood.
	Wang et al. (Wang et al., 2017)	1800 MHz 30 min	WBA SAR 1.98, 2.2, 2.42, 2.86 or 3.3 W/kg	Stimulation of object recognition with highest 4 SARs. Alterations in neurons after 3.3 W/kg (other SARs not investigated).
Oxidative stress	Hisidoglu et al. (Hidisoglu et al., 2016)	2100 MHz 2 h/day, 1 or 10 weeks	Brain E field 27–35 V/m	Antioxidants in brain increased after 1 week, decreased after 10 weeks. Decreased latency visually evoked potentials after 1 week, increased after 10 weeks.
	Sahin et al. (Sahin et al., 2016)	2100 MHz UMTS 6 h/day, 5 days/week, 2 or 8 weeks	WBA SAR 0.4 W/kg	Oxidative DNA damage increased after 10 days, decreased after 40 days. Lipid peroxidation unchanged after 10 days, decreased after 40 days.
	López-Furelos et al. (López-Furelos et al., 2016)	900, 2450, 900+2450 MHz 1 or 2 h Exposure from left side	Cerebrum: SAR 0.026–0.055, 0.050–0.111 W/kg Cerebellum: SAR 0.025–0.090, 0.050–0.183 W/kg	Cerebrum: no effect heat shock proteins, caspase-3. Cerebellum: increased HSP left hemisphere with 900 or 2450 MHz at highest level; increased caspase-3 left hemisphere with 2450 MHz at highest level.
	Ahmed et al. (Ahmed et al., 2017)	900 MHz GSM 1 h/day, 4 months	PD 0.2 W/m^2	Variable effect on oxidative stress parameters up to 4 months, but large variation in controls (instable procedures).
	Kerimoğlu et al. (Kerimoğlu et al., 2016b)	900 MHz 1 h/day, 19 days	WBA SAR 0.0067 W/kg	Increased oxidative stress in brain. Decreased pyramidal neurons in hippocampus.

	Kerimoğlu et al. (Kerimoğlu et al., 2016a)	900 MHz 1 h/day, 19 days	WBA SAR 0.0067 W/kg	Increased oxidative stress, apoptosis in spinal cord.
	Akdag et al. (Akdag et al., 2016)	2.4 GHz 24h/day, 12 months	WBA SAR 0.14 W/kg	Increased DNA damage in kidney, not in brain, liver and skin.
	Tuncal et al. (Tuncal et al., 2016)	2100 MHz GSM 6 h/day, 5 days/week, 10 or 40 days	WBA SAR 0.4 W/kg	Increased oxidative stress in thyroid, more at 10 days.
	Chauhan et al. (Chauhan et al., 2017)	2.45 GHz 2 h/day, 35 days	WBA SAR 0.14 W/kg	Increased oxidative stress in liver, brain, spleen; histological changes in liver, brain. spleen, testis, kidney.
	Sokolovic et al. (Sokolovic et al., 2015)	900 MHz 4 h/day, 20, 40 or 60 days	WBA SAR 0.043–0.135 W/kg	Increased oxidative stress, at different exposure times for different parameters, with sometimes reducing effect of melatonin.
Fertility	Türedi et al. (Türedi et al., 2016)	900 MHz 1 h/day, days 13-21 of pregnancy	WBA SAR 0.01 W/kg	Females at age 34 days: reduced number and damaged follicles.
	Odacı et al. (Odaci et al., 2016)	900 MHz 1 h/day, days 13-21 of pregnancy	WBA SAR 0.024 W/kg	Males at age 60 days: reduced epithelial thickness of seminiferous tubules, sperm motility and vitality. Increased apoptosis, DNA damage in testes..
	Pandey et al. (Pandey et al., 2017)	904 MHz 4 or 8 h/day, 35 days	WBA SAR 0.0054–0.0516 W/kg	Damage to testes, reduction of sperm production ,DNA damage, changes in mitochondrial membrane potential. Some recovery after 35 days.
Development	Kuybulu et al. (Kuybulu et al., 2016)	2.45 MHz 1 h/day, throughout pregnancy and/or at age 18 day – 12 weeks (males)	WBA SAR 0.1 W/kg	Increased oxidative stress in kidney when exposed pre- and postnatally, no effect when exposed postnatally. Tubular dysfunction increased after both treatments.

	Shirai et al. (Shirai et al., 2017)	Multiple frequencies (mobile phone: 800 MHz, 2 GHz, WiFi: 2.4, 2.5, 5.2 GHz) 20 h/day, 8 weeks (7th day of pregnancy – 21 day after birth)	WBA SAR 0.09 or 0.43 W/kg (pregnant females); 0.08 or 0.39 W/kg (pups)	No effects in F2 generation for various developmental and fertility parameters.
	Chen et al. (Chen et al., 2016)	935 MHz 2 or 4 h/day, 3 days	PD 1.5, 5.7 or 14.0 W/m^2	Development of in vitro fertilized embryos decreased with two highest power levels.
	Nisbet et al. (Nisbet et al., 2016)	900 or 1800 MHz 2 h/day, 90 days	WBA SAR 900 MHz: 3.0 (10 days) – 1.2 (70 days) mW/kg 1800 MHz: 0.053 (10 days) – 0.011 (70 days) mW/kg	Higher weight and length. Calcium, growth hormone, estradiol, testosterone increased. No difference frequencies. Thinner femur growth plate with 1800 MHz.
Non-mammalian animals				
Gene expression Chicken	Woelders et al. (Woelders et al., 2017)	1800 MHz GSM, 1880 MHz DECT, 2100 MHz UMTS, 5.6 GHz WLAN 22 days	SAR 0.038 (GSM), 0.041 (DECT), 0.045 (UMTS), 0.038 (WLAN) mW/kg	No effect on embryo survival, weight and gene expression.
Fruit fly	Manta et al. (Manta et al., 2016)	1800 MHz 30 min	SAR 0.15 W/kg	168 genes in oocytes expressed different from controls, associated with e.g. metabolism, stress, apoptosis.
Immunology Lizard	Mina et al. (Mina et al., 2016)	1880–1900 MHz 24 h/day, 4 or 8 weeks	E field 3.2 ± 5% V/m	Reduced innate immune reactions, no effect acquired immune responses.

Abbreviations: BBB: blood-brain barrier; CW: continuous wave; DECT: digital enhanced cordless telecommunication; GFAP: glial fibrillary acidic protein; GSM: global system for mobile communication; HSP: heat shock protein; IL: interleukin; PD: power density; SAR: specific absorption rate; UMTS: universal mobile telecommunication standard; WBA: whole-body average; WLAN: wireless local area network.

4.3. Human studies

During this reporting period human provocation studies were published addressing various outcome parameters: resting state waking EEG (Zentai et al. 2015b, Yang et al 2016, Burgess et al. 2016)(Roggeveen et al., 2015b, Roggeveen et al., 2015a), inter-hemispheric coherence (Yang et al. 2016), interhemispheric functional connectivity (Lv et al., 2015) evoked potentials (Roggeveen et al., 2015a, Singh, 2015)(Burgess et al. 2016,), sleep EEG (Danker-Hopfe et al 2016), vigilance (Zentai et al. 2015b), cognitive performance (Burgess et al 2016), physiological parameters (heart rate

variability: Burgess et al 2016) and symptoms (Burgess et al 2016). For various reasons four of the eight studies were not considered here.

4.3.1. Waking EEG

In a study with a well characterized exposure, which is described in detail in a separate publication (Zentai et al., 2015a, Zentai et al., 2015b) investigated possible effects of a Wi-Fi exposure (2,452 MHz, peak power: 100 mW; and duty cycle of 66.19%) on the spontaneous EEG activity and on psychomotor vigilance in healthy human volunteers. The endpoints were investigated in different provocation experiments with different samples. Real and sham exposures were applied in a double-blind counterbalanced design in two sessions with a minimum 1-week interval between sessions. This interval, however, does not allow controlling for changes in the EEG with the menstrual cycle in females. Within individuals, daytime of assessment was kept constant. Between subjects, time of day varied from 8 am to 6 pm.

In the first experiment (Zentai et al., 2015b) effects of a 60 min 2.4 GHz Wi-Fi exposure (peak SAR10g: 99.2 mW/kg) on the spectral power of the spontaneous waking EEG activity was assessed in 25 subjects (15 females and 10 males; mean age = 23.3 years; SEM = 0.6 years). EEG was recorded from three midline electrodes (Fz, Cz, Pz, reference nose) with eyes open while the subjects watched a silent documentary. The choice of reference is unusual, but possible to use in EEG studies. Furthermore, spontaneous EEG is usually recorded from an occipital location in a condition without visual stimulation. To identify and reject artefacts horizontal and vertical eyes movements were monitored with two electrodes, however only an amplitude criterion was used to eliminate artefacts. There is also no information on the control of interference exposure system and recording device. Analysis is based on three 10 min EEG recordings: 10 min preceding exposure, 10 min immediately after the end of exposure and 10 min in the middle of a 60 min exposure. A three-way repeated measures analysis of variance (rANOVA) of the EEG spectral power with exposure, block, and electrode as factors performed separately for each of six EEG frequency bands revealed no significant exposure effect.

In a study with 25 young right-handed healthy male volunteers (mean ± SD: 30.2 ± 2.7 years) Yang et al. (2017) investigated possible long-term evolution (LTE, 2.61 GHz) exposure ($pSAR_{10g}$: 1.34 W/kg; $pSAT_{1g}$: 1.96 W/kg) effects on the resting state EEG and interhemispheric coherence. Exposure was realized by a well characterized exposure system. Subjects were exposed in a double-blind counterbalanced design in two different sessions separated by one week. Each session lasted 50 minutes divided into five 10 min slots. In one of the two sessions subjects were exposed to LTE in the middle three time slots, time slot 1 was a pre-exposure condition, timeslot five a post-exposure condition. EEG was recorded with eyes closed and with 19 electrodes placed according to the 10-20 system and referenced to the left ear lobe. EEGLAB toolbox was used to remove artefacts. EEG power spectra were calculated for four frequency bands. Information from 19 electrodes was grouped into 10 brain regions. The authors used a watermelon recording to control interferences from the FR signals on the EEG. For each frequency band a repeated analysis of variance (rANOVA) design was used to investigate time slot and exposure effects. Within subject tests revealed a significant reduction in alpha (left frontal region) and beta band (right frontal and right temporal region) during and post exposure (as compared to the pre-exposure time slot). With regard to inter-hemispheric coherence, significant within-subject reductions were observed for the alpha (left-right frontal) and beta band (left-right temporal) coherence.

Two experiments with different samples have been performed to investigate effects of a TETRA exposure on the electroencephalogram (EEG) and other outcome parameters (Burgess et al., 2016). Experiment 1 was performed with 164 police officers (140 males and 24 females; mean ± SD: 39 ± 7.3 years, range 22-62 years) of whom 107 reported health symptoms due to TETRA exposure. The experimental TETRA signal (390-400 MHz) was calibrated to give a peak SAR_{10g} = 1.3 W/kg for head exposure (no corresponding information for the chest exposure). Since head exposure interfered

visibly with the EEG signal recorded from 29 electrodes the experiment could not be conducted double-blind. Artefact-adjustment reduced the sample to n=156 for EEG power analysis and to n=151 and to n=146 for analysis of event related potentials, which were investigated with regard to two cognitive tasks: the Attentional Blink Task (ABT) and the Sustained Attention to Response Task (SART). The authors observed a significant effect of TETRA on the resting EEG (specifically at low frequencies: delta, < 4 Hz and an enhancement under verum exposure in the beta frequency range). These effects were only seen for the eyes closed condition with the radio positioned against the chest, but not when the radio was positioned against the head. With head exposure no effect on event-related potentials have been observed. However, with chest exposure significant effects on SART related ERPs have been observed, which were "most prominent at right frontal sites (Fp2, Fz, F4, FC6) when ERP was more negative to TETRA, and at posterior sites (P4, PO1, PO2, O2 and Oz) where the direction of the effect was reversed" (Burgess et al 2016, p. 464). Chest exposure had no effect on the ABT-related ERP. Neither head nor chest exposure resulted in significant differences in performance between TETRA and sham exposure. Experiment 2 was performed with 57 volunteers (20 males and 37 females; mean ± SD: 34 ± 13.5 years, range: 18.64 years). The experimental TETRA signal (381 MHz) was calibrated to give a peak SAR_{10g} of 1.35 W/kg for head exposure and a peak SAR_{10g} of 1.0 W/kg for body exposure. Since the exposure system again interfered with the EEG signal this experiment could also not be conducted double-blind. Resting state EEG was recorded from 21 electrodes in an eyes open and an eyes closed condition, respectively. Furthermore ERPs from the SART were also investigated in this sample. The EEG effects, which have been observed in experiment 1 could not be replicated in experiment 2, neither for the eyes open nor for the eyes closed condition. For the SART ERP, no significant exposure effects were observed.
The authors state that these results could also be observed when subjects with EEG interference were excluded. In summary the results with regard to the EEG are inconsistent between the two experiments performed in this study. From the supplementary material it is obvious that the sham and real exposure conditions were applied on the same day, so carry-over effects cannot be ruled out. And finally the technical problems (interference) are a limitation of this study.

4.3.2. Cognitive performance

In the second experiment (Zentai et al., 2015a) (see 4.3.1) investigated effects of Wi-Fi exposure on six outcome parameters of a computerized psychomotor vigilance test (PVT). The sample consisted of 19 subjects (10 females and 9 males; mean age = 21.0 years; SEM = 0.4 years). The PVT was performed in four blocks of 15 min each. The first three blocks were under exposure with a pause after the first block. The fourth block started 20 min after the end of exposure. Effects were analysed by three-way repeated analyses of variance. For none of the performance parameters a significant exposure effect was observed.

Besides other parameters (see 4.3.1) (Burgess et al., 2016) also investigated possible effects of RF-EMF exposure on performance parameters in the Attentional Blink Task (ABT) and the Sustained Attention to Response Task (SART). They did not find any statistically significant differences between TETRA and sham exposure.

4.3.3. Symptoms

Additionally to the spontaneous waking EEG and cognitive performance Zentai et al. (2015a) investigated possible effects of the Wi-Fi exposure on subjectively perceived fatigue. A two-way rANOVA with exposure and block as factors did not reveal a significant exposure effect.

In the second experiment of the Burgess et al. (2016) study (see 4.3.1) effects of TETRA exposure on symptoms were not observed.

4.3.4. Other physiological outcomes

In the Burgess et al. (2016) study besides EEG electrocardiogram (ECG) was recorded to investigate possible effects of TETRA exposure on heart rate variability. All HRV indices were affected by exposure. However there is no information, whether the authors controlled possible interference of the ECG recording device and exposure.

4.3.5. Sleep macrostructure

In a study with 30 healthy young male volunteers (mean ± SD: 25.3 ± 2.6 years, range 18-30 years), Danker-Hopfe et al. (2016) investigated, at an individual level, whether EF-EMF exposure had an effect on the macrostructure of sleep. After an adaptation night each subject was exposed in a random, counterbalanced cross-over design to three exposure conditions (GSM 900, UMTS, both with a peak spatial SAR10g of 2W/kg). Each exposure condition was applied three times. Time intervals between the nine study nights was 2 weeks; nights were scheduled if possible at the same day of the week. Exposure was delivered by a head worn antenna, which was specifically designed for the study. To avoid interference between the exposure and the recording system EEG was recorded with specifically constructed electrodes from 19 scalp locations. Sleep was analysed according to the international standard of the American Academy of Sleep Medicine. For each subject nine individual differences between sham and verum exposure (separately for GSM and UMTS) were calculated and the mean of the distribution was tested for a significant deviation from 0. Results showed that RF-EMF effects could be observed in 90% of the subjects and that each of the considered eight sleep variables was affected in at least four individuals. The results, however, were not consistent with regard to the direction of observed deviations from the sham condition between individuals nor did deviations within an individual point in the same direction (improvement of deterioration of sleep). The only exception was stage R sleep. 10 and 9 out of 30 subjects showed an increase of REM sleep under UMTS and GSM exposure, respectively.
The authors speculate that the observed increase in REM sleep, which is not indicative of a disturbed sleep, might be due a thermal mechanism. However, the observation needs replication.

4.3.6. Conclusion on human studies

With regard to the spontaneous waking EEG the results are inconsistent. While one study found no effects, the other two did. With regard to the alpha frequency range, which is often discussed to be increased under radiofrequency electromagnetic field exposure, one study found a decrease in the alpha frequency range, while the other one found more effects in the delta and beta ranges. Cognitive performance and symptoms were not affected in the studies published in this reporting period, which confirms previous findings. Results on heart rate variability are not informative due to methodological reasons. Finally there is a study indicating that macro-structure of sleep, especially REM sleep, is affected when analysed at an individual level. This, however, needs confirmation.

4.4. Epidemiological studies

In the previous Council reports (SSM, 2015, SSM, 2016) it was concluded that no, or at most small, indications were found for a brain tumour risk up to approximately 15 years of mobile phone use. Studies on symptoms in relation to exposure from fixed-site transmitters were pointing to an absence of association. Several studies reported associations of self-reported mobile phone use and symptoms in 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 was also a noted increase of low quality studies.

4.4.1. Childhood cancer

Sato et al. (2017) compared mobile phone ownership among 82 children aged 6 to 18 years diagnosed with a brain tumour between 2006 and 2010 with mobile phone ownership in the general population using three different surveys. Ownership prevalence among the patients did not differ from the estimates of any of the surveys.
If there were a risk from using mobile phones one would expect to see higher prevalence rates among patients than the general population. This was not the case. This small ecological study is not vulnerable to recall bias. However, there are several limitations. It was not demonstrated that cases were selected from the same source population and that information was retrieved at the same time point as in the surveys, which were conducted at different time points. Mobile phone ownership in this age group has increased strongly in the last decade and this introduces uncertainty. Furthermore, participation rate was low, in the surveys as well in the case selection and thus selection bias may have occurred. Also, amount of mobile phone use was not considered in the analysis.

4.4.2. Adult cancer

In India, Prasad et al. (2017) performed a systematic review of mobile phone use and risk of brain tumours, aimed to investigate whether methodological quality of studies and source of funding could explain heterogeneity of individual studies' results. The overall results for mobile phone use showed an OR of 1.03 (95% CI 0.92-1.14), and use for 10 years or more showed an OR of 1.33 (95% CI 1.07-1.66). Funding source was not associated with risk estimates, but study quality was.

A similar review was performed by Bortkiewicz et al. (2017) with similar risk estimates, both for general and long-term use. These results are in line with previous results. The elevated risk estimates for long-term use has been discussed for several years, and there is broad agreement that the elevated risk estimates mirror the methodological challenges for this kind of mobile phone studies.

Use of mobile phones is very common nowadays and thus, if it were a risk for brain tumour, one would expect to observe an increase in the incidence during the last decade. To evaluate such a link, de Vocht (2016), plus corrigendum, (de Vocht, 2017), analysed the incidence of selected brain cancer subtypes in England between 1985 and 2014 using a Bayesian structural time series approach. Annual case numbers of the following subtypes were considered: unspecified malignant neoplasm of brain, glioblastoma multiforme, malignant neoplasms of the temporal lobe and malignant neoplasms of the parietal lobe, obtained from the Office of National Statistics (ONS). The effect of mobile phone use on the changes in brain cancer incidence was inferred from differences between recorded and modelled number of cases for each year. The modelled number of cases included incidence of all cancers, annual population estimates, median age of the population, prevalence of cigarette smokers, urbanization rate and a quality measure for the cancer coding. Temporal changes in unspecified malignant neoplasm of brain and glioblastoma multiforme incidence were not related to the increase in mobile phone subscriptions. Malignant neoplasms of the parietal lobe were negatively correlated with time trends of mobile phone subscriptions. For malignant neoplasms of the temporal lobe, time series indicated a risk increase of 1.35 (95% CI: 1.09-1.59) with a 10-year latency but not with 15 years latency. The temporal lobe is mostly exposed when using wireless phones. The observed risk increase would result in an additional 188 cancer cases in England each year.
The strongest concern for this type of analyses is changes in the coding praxis over time. It would thus have been important to show the results for all subtypes of tumours to evaluate potential shifts in diagnoses between subtypes. It is unclear why de Vocht considered only unspecified diagnoses. Most likely, these diagnostic groups are mostly affected by changes in coding practice over time. For instance, with the introduction of improved diagnostic techniques in the last 20 years, coding of location information may have changed over time. This would affect the analyses. It seems implausible that an increased risk is restricted to a latency period of 10 year but not seen with a15-year latency. This may indicate bias from secular time trends. For example, median age does not well represent population growth in older age groups with the highest risk for developing a brain tumour.

Lack of individual exposure data is another limitation of this approach. In general, the study would have been more informative if results had been shown for all subtypes of brain tumour to enable systematic evaluation of the time trend patterns with respect to the exposure of various brain areas.

In Australia, Chapman et al. (2016) conducted an ecological study to investigate the association between mobile phone coverage and brain cancer incidence. During 1987 to 2014 the percentage of the population with mobile phone accounts increased from 0% to 94%. Brain cancer incidence data for the age groups 20-39 years, 40-59 years, 60-69 years, 70-84 years and 20-84 years for the period 1982 to 2012 was collected from the Australian Institute of Health and Welfare. Observed incidence rates were compared with modelled incidence rates assuming a relative risk of 1.5 for regular use and 2.5 for heavy use with a 10 year latency period between exposure and diagnosis. In all age groups, there was no indication that increase in mobile phone use was followed by a corresponding increase in brain tumour incidence.
As other time series studies, the analyses are not affected by recall- and selection bias but lack individual exposure data and could, in principle, be biased by secular time trends such as improvement in diagnostics. Some indication for this was observed in the study for the very old age group but this occurred before the increase in mobile phone use. No increase in brain tumours in the other age groups indicates that is unlikely that use of mobile phone use increases risks, unless this risk has been compensated by some other factor. However, no plausible explanation for such a factor exists.

In Japan, Sato et al. (2016) conducted an incidence study to analyse the incidence rate of malignant tumours in the central nervous system in relation to mobile telephone use among people in the age group 10-39 years during the period 1993-2010. They used joinpoint regression analysis to detect possible changes in time trends indicative for a risk due to the increasing mobile phone use of the population. Incidence data was extracted from regional cancer registries in Japan and annual percent change (APC) during the period 1993 to 2010 for the age groups 10-19 years, 20-29 years and 30-39 years were calculated. In addition, expected incidence rates during the period by sex and 10-year age-groups assuming relative risk of 1.4-12.0 among mobile phone users were calculated. The relative risk of 1.4 was chosen because that was the risk estimate from the participants with longest cumulative exposure in the Interphone study, which was > 1640 hours. The results for the joinpoint analyses of APC for all age groups showed an increasing trend during the period 1993-2010 without any indications of stronger increase in more recent years due to more prevalent mobile phone use. The authors conclude that the steady increase in incidence observed over the last 20 years cannot be explained by heavy mobile phone use and may be rather due to improved diagnosis.
This study shares the same strengths and limitations as previously discussed incidence time trends studies. The population size is relatively small and thus annual incidence rates are highly variable. Thus, the power to detect joinpoints in this short time series of 18 years is relatively low.

Another ecological time trend study addressing the incidence study of thyroid cancer in Sweden and the Nordic countries during 1970-2013 was published by Carlberg et al. (2016). The Swedish data was obtained from the Swedish cancer registry, the Nordic incidence data was obtained from the NORDCAN database. The main finding in this study was an increasing incidence of thyroid cancer, both in Sweden and the Nordic countries together. In the Swedish data, incidence in women decreased between 1979 and 2001 and subsequently increased (+5.3% (95%CI +3.9% - +6.8%) per year). In men, a joinpoint with stronger increase after 2005 was observed (+7.6% (95%CI +3.3%,-+12.0%) per year). In the NORDCAN data, a joinpoint with stronger increase was found in 2006 for both, men (+6.8 % (95%CI +3.7 - +10.1 %) per year) and women (+6.2 % (95%CI +3.9 - +8.4 %) per year). The authors discuss several possible explanations for this increase, such as better diagnostic procedures, exposure to ionizing radiation, environmental pollution, RF-EMF exposure, but most focus on RF-EMF exposure from mobile phones.
This is an interesting approach to this field since recall and selection bias, which can affect case-control studies, is prevented. However, the lack of individual exposure data is a limitation. For this type of analysis it cannot be excluded that temporal trends in the incidence data are introduced by other secular time trends. It is well known that diagnosis of thyroid cancer depends highly on the

screening rate in a population. Increase in incidence in recent years was observed in many countries and is most often attributed to an increased detection. The authors of this paper do not provide any quantitative data to support their notion that better diagnostic imaging cannot solely account for the increase.

In Sweden, Hallberg (Hallberg, 2016b, Hallberg, 2016a) performed two small studies evaluating FM radio transmitters and malignant melanoma, breast cancer and total cancer incidence, and reported an association between FM radio density and especially melanoma incidence.
Due to unclear methods (unclear selection of areas in Sweden, unclear selection of European countries), undefined source of transmitter data, undefined source and undefined underlying types of cancer data, lack of individual exposure estimates, the study is not informative as to an association of FM radio transmitters and the types of cancer in question.

In South-Korea, Yoon et al. (2015) conducted a case-control study based on the Interphone protocol, aimed at investigating the association between mobile phone use and risk of glioma. The results from the Interphone study which included original data from 13 countries using the same protocol were published in 2010 (Interphone 2010). In total, 285 (32%) glioma cases and 285 (27%) controls in the age group 15-69 years were selected from nine hospitals in 2002- 2007 and individually matched according to the protocol. Information related to mobile phone use was obtained by means of a questionnaire which included type of mobile phone, lifetime year of use, cumulative use and daily use. For regular users, an OR of 1.17 (95% CI 0.63-2.14) was observed. This study found no significant relationship between glioma and mobile phone use for any of the exposure categories.
Compared to the whole Interphone study, this is a small sample size, providing little new insights. Confidence intervals are wide and exposure misclassification, recall- and selection bias may have biased the results.

In an attempt to improve the method of accurate glioma localization when investigating a possible association between brain tumours and use of mobile phones, Grell et al. (2016) performed a study based on data from the Interphone study. Information of data collection and countries participating in the Interphone study has been covered in earlier SSM reports (2009:36, 2010:44). For 1 530 glioma localizations performed by radiologists, 792 were defined as regular users by use of self-reported information on preferred side of the head on which the mobile phone was used. Based on this information on cases, a case-only approach with use of a 3-dimensional point process model was developed to make a grid map of the human head and brain consisting of 1-cm cubes. Then, neuro-radiologists estimated the tumour contours in the actual cube. The observed glioma localization was statistically closer to the ear on the side of the head where the mobile phone was reported to have been mostly held. This result was not related to amount of mobile phone use.
This result is in concert with previous Interphone-publications where recall bias is an alternative explanation for the observed lateral association. It is commendable that an attempt is made to develop new methods to improve the accuracy of tumour localisations. Nevertheless, a study design with use of self-reported data makes it still challenging to draw conclusions regarding the association between brain tumours and use of mobile phones.

4.4.3. Reproduction

To investigate the association between electromagnetic field exposure and abortion, Abad et al. (2016) recruited 475 women from Teheran aged 18-35 years who were pregnant and up to gestational age of 12 complete weeks. For 413 of these women an RF EMF measurement in the frequency range 88-2500 MHz at the front door of their home was collected and an in-person interview was completed. Reproductive information was obtained from medical files in the hospitals where they had delivery. Spontaneous abortion rate in the study collective was 12.3%. After adjusting for various sociodemographic factors and family conflict no association was seen between RF-EMF exposure and spontaneous abortion (OR=1.12, 95% CI: 0.83-1.52).

The paper leaves open several questions: Front-door RF-EMF exposures were surprisingly high, with on average 16 μW/cm^2 (about 7.7 V/m) and it remains unclear from the presented numbers which source contributed most to these exposure levels. In addition, repeated measurements (3, one in each trimester) were conducted, but the authors just report that measurements were similar and only one measurement was used in the analysis, but they did not report how similar results were and which result they used. Univariate as well as adjusted analyses did not support an association of abortion risk with EMF exposure levels. It remains unclear what the authors' conclusion of an association between EMF exposure and abortion is based on. In principle, the conduct of exposure measurements is a strength, but measurements at the front door are subject to considerable exposure misclassification. Furthermore, exposure from use of wireless communication devices was not quantified which is more relevant than environmental RF-EMF. It is not reported why analyses were not adjusted for maternal smoking although corresponding information was available.

Yildirim et al. (2015) reported a survey on mobile phone use and effect on sperm, performed during 2013-2014 in men attending the andrology department of the Turgut Özal University Medical School, Turkey. Semen samples were collected from 1 082 men, and after exclusion of some underlying conditions (e.g. diabetes, hypertension, and history of genetic disease) 1 031 persons were included in the analysis. By means of a questionnaire, participants provided information regarding usual daily mobile phone use, where they usually carried their mobile phone, and their usual internet usage duration, if wireless. The analysis was not adjusted for any potential confounder, although this information was collected. There was no difference in sperm count, total motile sperm count, progressive motile sperm count or morphology across mobile phone usage categories. Total motile and progressive motile sperm count was decreased in persons with higher wireless internet usage (0.5-2 hours or >2 hours compared to < 0.5 hours per day). Morphology was decreased in men who usually carried their mobile phone in their jacket pocket. Total sperm count was not statistically significantly different across the exposure groups.
It remains unclear why the authors evaluate mobile phone use as having a potential effect on sperm, given that phone calls are usually done with the phone raised to the head. Usage of headphones was apparently not inquired. Carriage of the mobile phone in pocket as such, be it in a jacket, trouser or other pocket, would also not be expected to greatly contribute to the exposure of the testis. It is unclear if the categorization into wireless internet users into <0.5 hours per day, 0.5-2 hours, or >2 hours per day, is sufficient to group people into low, medium or highly exposure of their testes. Given that there were differences across groups in terms of age and smoking behaviour, and that this was not considered in the analysis, the results are uninformative in terms of a potential causal RF-EMF effect on semen quality.

In a similar study, Zilberlicht et al. (2015) included 80 men who underwent a semen analysis in the Carmel Medical Centre, Haifa, Israel, between 2011 and 2012. Again, mobile phone usage duration per day was inquired (grouped into up to 1 hour per day and > 1 hour per day), as was talking during charging the phone and keeping the mobile phone within 50 cm from the groin when not in use. The authors analysed total sperm concentration, progressive motility and abnormal forms. In this study, no association emerged of any of the exposure categories and progressive motility. In contrast, an association was found for risk of having abnormal sperm concentration, which was associated with talking while charging.
All in all, the study improves on previous studies in that it evaluates several potential confounders and also takes them into account in a regression analysis if the corresponding factors are associated with the outcomes in univariate analyses. However, as discussed in the previous study, it is unclear why duration of mobile phone calls is used as the primary exposure variable, given the distance to the testis during calling and associated low exposures. That different outcomes were affected in the Zilberlicht study compared to the results reported by Yildirim et al. may indicate chance findings of the respective studies.

Zhang et al. (2016a) performed a cohort study on cell phone use and semen quality in college students in Chongqing, China. During 2013, 2014 and 2015, N=794, 666 and 568, students were included into

the study, respectively. The response rate was not reported. The authors investigated the association between daily cell phone use (talking, and having the cell phone on), as well as daily duration of cellular networks in 2013, and monthly data traffic in GB in 2014 and in 2015. Regarding semen quality, volume, sperm concentration, total sperm count and progressive motility were evaluated. Analyses were adjusted for age, duration of abstinence, BMI, smoking and alcohol consumption, cola, coffee, fried food consumption and a few others. Daily duration of having the phone switched on was not related to any of the outcomes. Daily duration of talking on the phone and data traffic was associated with total sperm count and volume in adjusted models (borderline significant for duration of talking and volume, p=0.056), but not with concentration or progressive motility.
All in all, this is one of the better studies on mobile phone use and sperm quality in that the authors at least attempted to take several potential confounding factors into account, including age and smoking. But again, the exposure assessment focuses on call duration and does not consider the contribution of the exposure to the testis received by the own mobile phone during talking compared to other RF-EMF sources, including for example cordless landline phones or using the mobile phone for browsing in front of the belly. Interestingly, amount of physical activity was not considered as a relevant confounder, although more moderate-vigorous amount of physical activity has been shown to be related to sperm concentration as well as to sperm counts, but not to motility (Gaskins et al., 2015). If talking on the phone as well as duration of use of cellular networks (or data transfer), were proxies for lack of physical activity, then this could potentially serve as an explanation for the observed associations.

A cross-sectional analysis embedded in the longitudinal "Environment and Reproductive Health Study" (EARTH) examining the potential association between self-reported mobile phone use and semen quality was performed in USA by Lewis et al. (2017). During the period 2004-2015, 384 men were enrolled in the study, recruiting couples seeking infertility treatment. Data of 153 men (40%) with 350 semen samples could be included in this study. Information about mobile phone use in the three months prior to enrolment was collected by means of a nurse-administered questionnaire, with information collected regarding duration of use, use of handsfree and whether the telephone was carried in pants pocket, belt or elsewhere. The duration of use was divided into three categories; no use, <2 hours/day, and >2 h/day. For semen, volume, total sperm count, concentration, total motility, total motile sperm count and morphology were measured. In mixed linear models, relationships were adjusted for age, race, abstinence time and body mass index. Eight of 66 evaluated estimates were statistically significant, but results showed no consistent pattern for the exposure groups, indicating no relationship between use of mobile phone and semen quality. Storing the phone in the trouser pockets was related to total motile count, as was use with an earpiece, but not in an exposure-response manner. In this study, some basic confounders were considered, which rarely was the case in previous semen quality studies. Further, exposure assessment did also consider whether a phone was stored in a pant pocket in addition to mobile phone use.
However, given the low participation rate and recruitment from fertility clinics, selection bias is of concern. The sample size is small and also the number of heavy mobile phone users using handsfree (N=14 with >2 hours and using an earpiece). In conclusion, the power to observe an effect is relatively low in this study.

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

A recent meta-analysis evaluated whether radiofrequency fields emitted by mobile phone base stations affect well-being in adults (Klaps et al., 2016). Based on 17 included studies the author concluded that effects of mobile phone base stations on adult well-being seem to be unlikely. However, indications for nocebo effects were found.

A Dutch study of 2 361 children evaluated if exposure to RF-EMF was associated with reported quality of sleep (Huss et al., 2015b). At the age of 5 years, school and residential exposure to RF-EMF from base stations was assessed with a geospatial model (NISMap). Indoor sources (cordless phone/Wi-Fi) and mobile or cordless phone use was obtained from parental reports. At the age of 7

years, sleep quality was reported by the parents with the Child Sleep Habits Questionnaire (CSHQ). Cut-offs at the median and 90th percentile of modelled RF-EMF exposure from base station were used to categorise low, medium or high exposure levels. Median mobile and cordless phone use was 2 and 3 minutes per day. In multivariable models adjusted for child's age, sex and indicators of parental socio-economic position, no association was observed for sleep onset delay, night wakenings, parasomnias and daytime sleepiness with residential exposure to RF-EMF from base stations. Sleep duration, however, correlated positively with base station exposure (p=0.05). Use of mobile phones was associated with less favourable sleep duration, night wakenings and parasomnias, but cordless phone use was not related to any of the sleeping scores. A similar pattern was seen for bedtime resistance, sleep anxiety, sleep disordered breathing, symptoms which were à priori considered not to be affected by RF-EMF (negative control outcomes). For that reason and given the inconsistency in terms of EMF-exposure the authors concluded that the study does not support a link between RF-EMF exposure and sleep quality, but potentially other factors that are related to mobile phone usage may negatively affect the sleep of children.
The large sample size and the use of negative control outcomes are strengths of this paper. A comprehensive exposure assessment was conducted but the time gap of 2 years between exposure and outcome assessment may represent a limitation if exposures strongly change over this time frame. As discussed by the authors, it is well conceivable that amount of mobile phone use of children represents other lifestyle factors which are related to sleep quality of small children.

A prospective cohort study with 439 adolescents attending 7th to 9th grade in Central Switzerland (Schoeni et al., 2016) aimed at investigating whether non-specific symptom prevalence or development of symptoms within one year was associated with exposure from fixed site transmitters (broadcasting and mobile phone base station). Exposure from fixed site transmitters at home and school was calculated using a geospatial propagation model. Five different symptoms (headache, tiredness, exhaustibility, lack of concentration, lack of energy) and a well-being scale consisting of various symptoms were assessed with a questionnaire filled in by the adolescents at school in 2012/2013. The survey was repeated approximately 12 months later and 425 adolescents agreed to participate again (97%). Mean (median; 75th percentile) modelled RF-EMF exposure was 0.08 V/m (0.05, 0.07 V/m). In multivariable cross-sectional and longitudinal models adjusted for relevant confounders (age, sex, nationality, school level, physical activity, alcohol and education of parents), no indications were found that environmental RF-EMF from fixed site transmitter affects health-related quality of life.

In the same study, potential associations of these six outcomes with wireless device use and resulting RF-EMF exposure was also investigated (Schoeni et al., 2017)**.** Data on the use of wireless communication devices (calls, text, and data transmission) were collected from all study participants using questionnaires, and 53% of the participants consented to provide their operator recorded mobile phone use data. In addition, the above mentioned propagation modelling, and personal measurements from a subsample were considered in a dose calculation model (Roser et al., 2015) in order to assess the cumulative absorbed EMF exposure of the brain and the whole body in the period between the two examinations. Sending text messages and playing computer games caused virtually no RF-EMF exposure and these exposures were thus included in the analyses as negative exposure control variables for RF-EMF. The data was analysed in a cross-sectional model (data of both questionnaires was pooled) and in a cohort model (to investigate whether occurrence of the symptom was related to cumulative wireless device use or cumulative RF-EMF dose). All analyses were adjusted for relevant confounders. In both analyses, cross-sectional and cohort, various symptoms tended to be mostly associated with usage measures that are only marginally related to RF-EMF exposure such as data traffic and texting (4-5 symptoms each). Outcomes were generally less strongly (1-2 symptoms only) or not associated with mobile phone call duration and RF-EMF exposure measures. The authors conclude that such a result pattern does not support a causal association between RF-EMF exposure and symptoms. Rather it suggests that other aspects of extensive media use by adolescents are related to symptoms.
This is the first longitudinal study with adolescents on symptoms and RF-EMF from fixed site transmitters or wireless device use. A strength of the study is the high proportion of participants that

participated in the follow-up tests. Exposure assessment was done in a comprehensive way including brain and whole body exposure modelling. However, the sample size is relatively small.

A retrospective cohort study conducted in the Netherlands with 1 069 adults explored whether exposure to RF-EMF from mobile phone base stations was correlated with prevalence of non-specific symptoms (Baliatsas et al., 2016)**.** Based on interviews with 5 933 adults in 2010/2011 (see (Baliatsas et al., 2015), discussed in (SSM, 2016)), all individuals with symptom data available from electronic health records of general practices that did not move residence since 2004 were included in the present survey. A total of 27 non-specific symptoms that are often mentioned in relation to EMF were selected. Residential exposure to RF-EMF emitted from mobile phone base stations was modelled for 2010/2011. Spearman correlation coefficients for measured and modelled exposure were between 0.21 for GSM900 and 0.45 for GSM1800. For 2004, the exposure was extrapolated based on the ratio of the number of antennas at both points in time within a 500 m distance of houses. The number of antennas increased by 30 % between 2004 and 2010/2011. Average exposure in the study population was 0.12 V/m in the year 2010/2011 and 0.11 V/m in the year 2004. Cross-sectional analysis of the whole study sample did not reveal associations of any of the symptoms with exposure to RF-EMF from mobile phone base stations. A total of 55 out of the 1 069 individuals stated that they were sensitive to mobile phone radiation. This group reported more symptoms in 2010/2011 compared to 2004, and for several symptoms, a correlation with modelled exposure at the place of residence was seen.
A strength of the study is the use of health records from practitioners. Objective exposure assessment by modelling prevents from systematic errors. But the exposure model is simple and does not account for relevant factors of the base stations and the environment, which led to the moderate correlations between modelled and measured exposures. In addition, exposure from wireless device use was not considered in this study. The differences in exposure between the two points in time are relatively small. A weakness of this analysis is that it was retrospective, i.e. that the statement regarding hypersensitivity to RF-EMF from mobile phone base stations was made in 2010/2011. It thus remains unclear whether newly emerged symptoms were attributed to RF-EMF from mobile phone base stations simply because such base stations were present at the residential location, or whether indeed a causal link exists. The statistical analyses only accounted for age, sex, and ownership of a house. Other confounders could therefore bias the result. Furthermore, a longitudinal analysis would have been desirable.

Cho et al. (2016) analysed the associations between mobile phone use and non-specific symptoms in 532 adults from the Korean Genome and Epidemiology Study, a general-population prospective cohort study. Information about exposure, covariables and outcomes (Headache Impact Test-6 (HIT-6), Psychosocial Well-being Index-Short Form, Beck Depression Inventory, Korean-Instrumental Activities of Daily Living, Perceived Stress Scale (PSS), Pittsburgh Sleep Quality Index, and 12-item Short Form Health Survey) were obtained by interview. Fifty-six percent of the participants were female. Mean age of study participants was 57 years and the median daily average number of phone calls was five with a median duration of 1.5 minutes. After adjusting for age, alcohol consumption, smoking, and body mass index, mobile phone use in females was associated with headache and with the Perceived Stress Scale. In males, only headache was associated with mobile phone use. Headache score HIT-6 increased by 0.07 (95% CI: 0.02, 0.13) in females and by 0.10 (95% CI: 0.04, 0.17) in males per increase in daily minute call time. Association with call frequency was not statistically significant.

Two years later the same 532 participants underwent a follow-up investigation (Cho et al., 2017). Compared with two years before, the average duration per call and HIT-6 score decreased significantly. However, subjects whose call duration was ≥ 5 minutes in both, the baseline and follow-up surveys, had no statistically significant reduction in HIT-6 scores. In women, change in duration of mobile phone use was significantly correlated with changes in the HIT-6 score (r=0.125) and changes in mobile phone call frequency was associated with the Korean Instrumental Activities of Daily Living (r=0.184). In men, none of the changes in mobile phone use variables was correlated with any of the outcomes. No confounders were considered in these correlation analyses.

The 100% participation rate in the follow-up is a strength of this study. Little information is given, however, about the selection of study participants for enrolment and thus the representativeness of the samples cannot be judged. Exposure data is self-reported and thus subject to bias. Lack of adjustment for confounding is another limitation of the study. Results of the change analyses might represent regression to the mean but this was not discussed by the authors.

A cross-sectional study assessing the relationship between several health problems and use of mobile phones was performed in Tamil Nadu, Southern India (Stalin et al., 2016). During 10 data collection days, as many people as possible were interviewed, by randomly selecting a street and then trying to interview every person living there. All in all, 2 121 persons participated of a total of 16 000 inhabitants, but the response rate was not reported. Blood pressure was measured and symptoms were asked during the house-to-house survey. Logistic regression was used to evaluate risk of hypertension and 11 symptoms in mobile phone users compared to non-users. It remains unclear if that list was pre-selected or if only statistically significant associations were reported. Regression models adjusted for age, sex and socio-economic status indicated increased risks for all symptoms, but significantly reduced risk of hypertension in mobile phone users.
Overall, this study reports more symptoms in mobile phone users compared to non-users. However, the type of interviews may have triggered reporting bias. They also considered only very basic adjustment for confounders, which sometimes resulted in large changes compared to crude risk estimates. This indicates that residual confounding is very likely in this study. No exposure-response relationships were evaluated. The authors did not discuss (or attempt to disentangle) mobile phone usage from EMF exposure. For nearly all analysed outcomes, causality is unclear – e.g. it could well be that people who are more ill are more likely to get a mobile phone in order to be able to communicate to others when necessary. There is no underlying mechanism that could explain the reduced risk of hypertension in mobile phone users. In summary, the study is not informative regarding an association of RF-EMF exposure with symptoms.

A survey on EHS among Dutch GPs, occupational physicians and occupational hygienists was published by Slottje et al. (2017). In each professional's group, about a third reported ever having been consulted by at least one EHS person. Fewer GPs (18%) than occupational physicians (22%) or occupational hygienists (37%) judged the association between EMF exposure and reported symptoms to be plausible. The survey showed that EHS can also represent a problem on the work floor. Because most of the professionals felt insufficiently informed about EMF and health, the authors conclude that targeted information campaigns could assist them in their evidence-based dealing with subjects who attribute symptoms to EMF.

van Moorselaar et al. (2017) tested a new approach for EHS individuals. They conducted repeated individualized provocation testing of EHS individuals at their home to overcome limitations of previous research in this population group. In total, 42 persons with a mean age of 55 years participated in the study. They reported sensing either radiofrequency or extremely low frequency fields within minutes of exposure. Participants were visited at home and first unblinded exposure sessions were conducted to select exposure settings that the participant responded to. After the unblinded session, 10 double blind tests were conducted using either an RF or ELF mobile custom-made exposure unit, using the exact exposure settings that participants had reported to sense in the unblinded session. Participants had to identify presence or absence of EMF exposure. The results were communicated to the study participants immediately after the double blind testing. Thirty-eight participants wanted RF testing with an electric field that ranged between 0.2 and 6 V/m (median: 0.44 V/m). Four participants preferred an ELF-MF test at levels between 0.15 and 6.6 µT. None of the participants was able to identify when they were being exposed better than chance in the double-blind testing. Four months after the testing self-reported level of EHS was unchanged, but certainty to react to EMF within minutes was somewhat decreased. Further, number of symptoms and severity score of the symptoms was significantly lower than at baseline. This may indicate that a subgroup of persons profit from a personalized EMF testing procedure.
A strength of this study is the verification of an individualized testing signal together with the study

participant. This could be achieved by a mobile testing system which was able to generate a wide range of EMF signals. Since there was no true control group (just an internal comparison of immediate testing compared to delayed testing), the study provides no proof as to whether the observed symptom reduction within four months was the consequence of study participation or not. Nevertheless, this is a very innovative approach to help EHS individuals who report to react to EMF exposure within a short time. It would thus be useful to collect more experience how helpful such an individualized testing is in the long run and for which subgroup of EHS individuals it is beneficial.

Since the previous SSM report, two studies addressed the physiological state of EHS individuals (Andrianome et al., 2016, Belpomme et al., 2015)**.** These studies did not consider EMF exposure of their study participants and thus cannot make any conclusions about a causal link between EHS and EMF exposure. In principle, such studies are not considered in this report. However, to date, no parameter has been found that can be used for characterising or diagnosing electromagnetic hypersensitivity (EHS). Thus the question whether the physiological parameters of EHS individuals differ from the general population is relevant for the management of EHS patients. For this reason the two studies are summarized here as well.

In order to evaluate potential diagnostic criteria or biomarkers, 1 216 patients suffering from EHS and/or multiple chemical sensitivity (MCS) were examined in a study launched in 2009 (Belpomme et al., 2015)**.** Following a standardised approach, the patients were thoroughly examined in a systematic manner, and treated depending on the result. The initial clinical examination of each patient comprised a detailed anamnesis, a physical examination, medical imaging of the brain by MRI and/or CT, carotid echodoppler, measurement of a pulsometric index of the brain by computerized ultrasonic cerebral tomosphygmography (UCTS), and the analysis of a series of biomarkers by commercially available tests. Patients were included in the study if their symptoms could not be attributed to another disease, and if they did not suffer from chronic diseases such as diabetes, cancer, and/or neurodegenerative or psychiatric diseases. 727 of the 839 cases that had been analysed so far fulfilled these inclusion criteria. The results of the biomarker tests were compared with the reference values provided by the test manufacturers. Depending on the test, between 6% and 55% were outside of the specified normal range. The authors thus conclude that EHS and MCS can be objectively characterised with simple tests. Furthermore, they suspect that both, EHS and MCS, show a similar pathologic mechanism because the proportion of people outside normal range was similar in both groups.
Based on the presented data, the conclusions of the authors cannot be supported. The main limitation of the study is the lack of a control group, and the lack of a detailed discussion of the sensitivity, specificity, referencing and reproducibility of the applied tests. In addition, the consistently decreased melatonin levels are problematic, since determining melatonin levels is very difficult, as it strongly reacts on outside influences such as light, lifestyle habits, diet and medication. In this case, as well as for all other biomarkers with a diurnal secretion profile, a single measurement is not informative and rather a 24-h profile is required, ideally over several days. The procedure for measuring the pulsometric index is not established, and only the result of a single case has been graphically presented. Persons included in this study represent a symptomatic subgroup of the population and would therefore be expected to differ in a range of biomarkers from a “normal” population. This means that the diagnostic procedures and criteria as applied in this study are not specific for a diagnosis of EHS or MCS and the informative value of this method cannot be evaluated. The way in which data are presented in this publication does not contribute to a better understanding of EHS and MCS.

In a French study (Andrianome et al., 2016)**,** self-reported sleep quality as well as melatonin levels in saliva and urine of 30 EHS individuals was compared with 25 non-EHS individuals matched for gender, age and body mass index. The 30 EHS individuals were recruited from a previous survey on the topic. The 24-hour melatonin concentration was determined based on urine collected separately during night and day, and the profile over the day based on 12 saliva samples collected at several time points. The subjective sleep quality in the EHS group was significantly lower than in the control group. Melatonin concentration in urine and saliva did not differ between the two groups, neither

during night-time nor during daytime.
A strength of this study is the inclusion of a control group. Only the comparison with a control group allows the identification of potential differences between EHS and non-EHS individuals. The sample size was relatively small, and, as expected, melatonin concentrations varied considerably between individuals and across the day. Therefore, only rather large differences would have been possible to reveal a statistically significant effect in this study. Potential confounders such as light exposure, sleeping times or chronotype were not taken into account, and the recruitment of the control group is not described.

4.4.5. Other outcomes

In the above mentioned prospective cohort study with 439 adolescents from Central Switzerland was further investigated whether memory performance (Schoeni et al., 2015), concentration capacity and behavioural problems (Roser et al., 2016) are affected by the cumulative EMF exposure within one year. Cognitive tests were conducted at baseline and follow-up using a standardized, computerized cognitive testing system. Behavioural problems were assessed with the Strength and Difficulties Questionnaire (SDQ) independently by the adolescents and their parents. The statistical analyses were adjusted for a range of confounders. The authors reported that performance in a figural memory test decreased with increasing EMF dose. However, there was no apparent association regarding the number of sent text messages, or the time spent playing computer games. In general, verbal memory performance was not associated with RF-EMF exposure, but the results were depending on laterality: the subgroup of about 20% of study participants who also used their mobile phone on the left side of the head showed a tendency for decreased verbal memory performance. This is an interesting finding because verbal memory involves mainly the left brain hemisphere. In general, findings were consistent and similar regarding questionnaire and operator recorded data. The overall pattern of results suggests that EMF exposure, rather than other aspects of mobile phone use, affect the memory capacity of adolescents (Schoeni et al., 2015)**.**
However, this pattern was different for concentration capacity and behavioural problems, where lack of consistent exposure-response patterns in the longitudinal analyses suggests that behavioural problems and concentration capacity are not affected by the use of wireless communication devices nor by RF-EMF exposure (Roser et al., 2016)**.** Likely explanations for the observed cross-sectional findings are thus information bias and reverse causality. This is the first longitudinal study with adolescents that includes brain exposure calculations and objectively recorded mobile phone use data. A further strength of the study is the high proportion of participants that participated in the follow-up tests, and the consideration of objective data on mobile phone use. Most of the previous studies relied on self-reported exposure data of the study participants. Such estimations are unreliable. However, the sample size is relatively small.

In a subsample of 123 boys aged 9 to 11 years belonging to the Environment and Childhood cohort from Granada (Spain) the association between RF-EMF (100 kHz to 6 GHz) spot measurements in the immediate surroundings of the dwelling (2 m from children's houses) and neurocognitive and behavioural functions were investigated (Calvente et al., 2016)**.** Median RF-EMF exposure was 0.33 V/m. In multivariate linear and logistic regression models, adjusting for potential confounders (smoking during pregnancy, maternal education, urbanity and internet/Wi-Fi), most of the cognitive and behavioural parameters were not associated with RF-EMF. However, children living in areas above median RF-EMF had lower scores for verbal expression/comprehension and higher scores for internalizing and total problems, and obsessive-compulsive and post-traumatic stress disorders, in comparison to those living in areas with lower exposure.
The strengths of the study include the application of a standardized test battery and objective exposure assessment. However, it is unclear whether spot measurements performed outside of homes (presumably on ground floor level") has any correlation with personal exposure levels, especially in urban environments. In addition, the analysis did not take into account indoor sources such as WLAN and cordless phones. The sample size was small and the cross-sectional design is vulnerable to selection bias and residual confounding. Some findings might be due to chance since 72 statistical

models were conducted. The environmental exposure levels observed outdoors were relatively low and thus exposure to the brain in these study participants is likely to be dominated by their mobile and cordless phone use, which was not accounted for. The most likely alternative explanation for the few observed associations except chance is residual confounding: study participants living in areas with higher outdoor RF-EMF exposure may be more deprived.

In an Australian study of 619 fourth-grade students (8-11 years) from 37 schools around Melbourne and Wollongong, Australia, the association between wireless phone use and cognitive functions was investigated (Redmayne et al., 2016)**.** Parents filled in a questionnaire on the number of mobile and cordless phone calls of their children. Study participants completed a short questionnaire, a computerised cognitive test battery, and the Stroop colour-word test. The median number of calls/week was 2.5 for mobile and 2.0 for cordless phone. After adjusting for age, gender, language other than English, handedness, and socioeconomic status, five out of 78 comparisons were statistically significant and the authors concluded that there was little evidence that cognitive function was consistently associated with wireless phone use.
The number of calls was low in this study. There was a striking disagreement of reports of mobile phone usage and ownership between parents and children, agreement was only 64%, which means that considerable exposure misclassification may have occurred. Strikingly many children, whose parents reported that they not use a mobile phone, reported themselves that they were doing so. This may have included exposure misclassification. According to a power analysis the study sample was sufficient. However, participation rate was not reported and there was no discussion as to whether relevant selection bias could have occurred.

In a Saudi Arabian study the link between RF electromagnetic fields from mobile phone base stations and glycated hemoglobin (HbA1c) as well as prevalence of type 2 diabetes mellitus was investigated (Meo et al., 2015)**.** They recruited 96 male students from school 1, with age range 12–16 years, and 63 male students with age range 12–17 years from school 2. RF-EMF was measured inside both schools and was 0.18 V/m in school 1 and 0.08 V/m in school 2. The mean HbA1c for the school 1 students was significantly higher (5.44 ± 0.22) than the mean HbA1c for the school 2 students.
It is not described how study participants within schools were selected and for how long the RF-EMF measurements have been conducted. No confounders have been considered in the analysis. In this low exposure range the own mobile phone use would be very relevant for exposure, but was not considered in the analysis. Given all these limitations the study is not informative.

In an attempt to overcome limitations such as reverse causation and recall bias from an earlier cross-sectional analysis of a cohort in Denmark (Divan et al., 2012), a prospective cohort analysis of mobile phone use and emotional and behavioural difficulties in children was performed by Sudan et al. (2016). Data from the Danish Birth Cohort study collected during the period 1996 to 2002 is described in more detail in SSM reports from 2009 and 2013 (SSM, 2009:36, SSM 2013:19) In short, information regarding maternal mobile phone use before birth and mobile phone use of her child at the age of 7 was collected. In addition, the mothers completed a Strengths and Difficulties Questionnaire when their child was 7 years. The subgroup of children with normal total emotional and behavioural difficulties scores at age 7 were followed to the age of 11 where a new collection of the Strengths and Difficulties Questionnaire was carried out. Among the 51 000 children in the cohort with normal total emotional and behavioural difficulties scores at age 7, 55% were exposed to mobile phones. Of them 21% had been prenatally exposed only, 16% used mobile phones at 7 years only and 19% were exposed both before birth and at age 7 years. Among children exposed before birth and at age 7 years the OR to develop emotional and behavioural difficulties at the age of 11 was 1.36 (95% CI 1.14-1.63) after adjustments for gender of child, mothers age at birth, parents' history of psychiatric, cognitive and behavioural problems as a child etc. For combined analyses of exposure both before birth and at 7 years, an OR of 1.58 (95% CI 1.34-1.86) was observed. These findings show a relatively consistent link between use of mobile phones and risk of emotional and behavioural difficulties.
The large sample size and the longitudinal approach are strengths of this paper but retrospective assessment of mobile phone use during pregnancy seven year later is likely to introduce considerable

exposure misclassification. This study gives no answer whether the observed associations are the consequences of direct effects from RF exposure or indirect effects from behavioural differences between users and non-users of mobile phones.

In China, Xu et al. (2016) evaluated female occupational groups in the shoe industry with high or low RF-EMF levels and compared their health status to workers from nearby supermarkets (as the unexposed group). Overall, 529 women were included, of which 71 worked in "high" exposure factories, 109 in "low" exposure factories and 349 in supermarkets ("unexposed"). Women aged 18-40 years were included and the age distribution between the worker groups was similar. Exposure frequencies were between 25 and 30 MHz and originated from plastic welding machines used in shoe production. In front of the welding machines and approximately at exposure locations, mean exposure levels in "high" exposed factories were between 87 V/m (abdomen exposure) and 369 V/m (chest exposure). The corresponding values in "low" exposure factories were 51 and 118 V/m and below 1 V/m in supermarkets. Group differences were analysed with Chi-square tests not taking into account any potential confounders. Of 20 evaluated symptoms, 11 were statistically significantly different between the worker groups, and 7 indicated exposure-response associations. In particular, menstrual disorders were different among exposure groups and ranged from 12% in unexposed, 27% in low exposed and 34% in high exposed women. When taking working duration into account, statistically significant trends were observed for 11 of the 20 symptoms. In addition, in a subgroup of 30 workers per exposure group, hormone levels of six hormones were evaluated, of which progesterone (P4) was significantly lower in the exposed women. This might be associated with the observed higher frequency of menstrual disorders.
A weakness of this study is the lack of control for confounding. For instance, other exposures are likely to occur in the shoe industry. It is thus not clear if health effects are associated with EMF exposures or possibly with other exposures from plastic welding or any other group differences regarding health behaviour. The exposure levels are very high and, it would have been interesting to learn what the individual exposure to the measured RF-EMF levels is. The ICNIRP-defined occupational reference levels of 61 V/m for the range between 10 and 400MHz are exceeded and dosimetric evaluations needed to be done to see whether basic restrictions are exceeded as well. Independent of the weakness of the study, the findings merit follow-up.

In Brazil, Siqueira et al. (2016) published a survey to evaluate whether mobile phone exposure was associated with differences in parotid secrete inflammatory cytokine levels. Saliva samples from both parotid glands were collected from 83 volunteers (students) from a university campus. Each participant completed a questionnaire including information regarding use of mobile phones, including predominantly used side of the head. Inflammatory cytokine levels in saliva samples from the exposed side (ipsilateral side) were compared with the levels from the contralateral side (not exposed). According to non-parametric Wilcoxon tests, no differences in salivary flow, salivary levels of IL-6 and TNF-α between contralateral and ipsilateral side were observed. However, statistically significantly increased levels of total protein and IL-1β and decreased levels of IL-10 were observed from the ipsilateral gland, and these remained statistically significant also after correction for multiple testing. In addition, subjects who reported use of more than 10 years had higher levels of IL-10 on the ipsilateral side.
Using the own person as the control subject is an appealing approach since it prevents many potential confounding factors. It is unclear if there are factors that could predispose persons to a specific side. However, such a predisposition would also have to be related to the measured biomarkers assessed in the study as well as to the usual side of use of mobile phones (or at least the reporting of this side). Since participants were not aware of their analysis results, self-reported information regarding which side was the predominant one used for mobile phone calls is unlikely to be subject to recall bias as discussed for case-control studies in brain tumour patients. In light of this, one cannot exclude the possibility that the differences between ipsi- and contralateral samples might be a consequence of use of mobile phones. The authors discuss heating as the most likely explanation due to the established link of RF-EMF exposure with heating, and the investigated parameters. Whether these results represent a real association or a chance finding needs to be clarified in further studies. The biological relevance remains unclear.

Bhagat et al. (2016) compared in 40 healthy medical students pure-tone audiometry, speech audiometry, impedance audiometry, and brainstem evoked response audiometry (BERA) of the ear predominantly used for mobile phone calls (31 right side and 9 left side users, ipsilateral) with the non-phone (contralateral) ear. In addition, separate analyses were done for two groups of 20 students using their phone either ≤60 min or >60 min per day. No statistically significant differences were found for any of the outcomes with respect to mobile phone use. None of the subjects reported any subjective symptoms, such as headache, tinnitus, or sensations of burning or warmth behind, around, or on the ear primarily used for calling.
This within-subject comparison of outcomes is not affected by confounding factors. However, reverse causality is of concern. If students would have hearing problems with one of their ear, they would most likely switch mobile phone to the other ear. If so, one would even see apparent protective effects of mobile phone use on the auditory system. This was not the case, however.

In the Netherlands, Guxens et al. (2016) conducted a cross-sectional study to assess the association between residential EMF-RF exposure and children`s cognitive function. During the period 2003-2004, 8 266 pregnant women were enrolled in the Amsterdam Born Children and their Development study, where their children`s cognitive function was assessed at 5-6 years of age. To assess the exposure from different RF-EMF sources, mothers of 2 354 children at the age of 7 from this study, completed a questionnaire with information of cordless phone base stations, Wi-Fi in the child`s home and frequency of the child`s use of mobile- and cordless phones at the time point of the cognitive function test. In addition, exposure from base stations was estimated for each home using a 3 D geospatial radio wave propagation model. Exposure to RF-EMF was categorised as no exposure at home, cordless phones base stations or Wi-Fi, and both cordless base stations and Wi-Fi. Use of mobile phone and cordless phone was categorised as none, <1, 1-2 and 3 ≥ calls per week respectively, and no use vs. use. In the analysis adjustments were made for several socio-economic- and lifestyle factors. Various RF-EMF sources were associated with both improvements and impairments of cognitive functions in an inconsistent manner.
The strength of this study is the relatively large sample size with possibilities to adjust for several potential confounding variables and the standardized cognitive testing. The cross-sectional design with no historic information regarding exposure is a limitation. In addition, the low contrast in exposure levels from the RF-EMF sources in this study opens up for the possibility for chance findings and residual confounding. In summary, the lack of consistent associations makes it difficult to conclude regarding causality. All in all, the findings do not support the hypothesis that RF-EMF exposure has a negative effect on cognition in children.

4.4.6. Conclusions on epidemiological studies

Whether mobile phone use causes brain tumours or not was mainly addressed by means of time trends study in the last two years. Results were not entirely consistent but rather point towards a lack of association. Whereas these time series studies do not suffer from recall and selection bias, which is of concern for case-control studies, they are vulnerable to secular time trends. Changes in coding praxis or improved diagnostic tools and thus better detection rate may produce a seemingly increase or a decrease in the incidence of brain tumours or specific subtypes. The few indications of changing incidence are thus rather attributed to such methodological limitations than real changes in risk.

Several studies observed decreased semen quality of mobile phone users. Mobile phone radiation produces heating, and heating can affect sperm quality. However, at levels below standard limits and as encountered under real-life conditions, the extent of heating is too low for such effects and thus the potential underlying biological mechanism remains unclear. The main problem in the available studies is that none of these studies made an attempt to estimate RF-EMF exposure of the testicles but rely only on mobile phone use. These studies can thus not solve whether observed associations are due to radiation or other factors related to mobile phone use as such, for example lack of physical activity or stress level. Lack of confounding adjustments in many of these studies remains a strong limitation.

Thus, any further studies just addressing frequency or duration of mobile phone use and sperm quality will likely remain uninformative.

Similar issues hold for various observed associations between behaviour and health-related quality of life in children and adolescents. Most of the studies observed associations but the underlying causal pattern is difficult to elucidate. A Dutch study that compared effect estimates for sleep outcomes hypothesized to be related to radiofrequency field exposure (e.g. sleep onset delay, sleep duration, night wakenings) with those a priori not related to electromagnetic fields (e.g. sleep anxiety, sleep disordered breathing) indicates that associations are rather due to other factors related to mobile phone use. The same conclusion was made in a Swiss study that compared effects for cumulative radiofrequency exposure of the brain with usage variables that produces small amounts of electromagnetic fields (texting, gaming), because stronger associations were observed for the latter. Strikingly, a different pattern was seen for memory performance, where stronger associations were found for radiofrequency field exposure than for usage variables not related to electromagnetic fields. Also the results of a laterality analysis were in favour of a radiofrequency exposure effect. However, other recent studies on cognitive performance and radiofrequency fields in children and adolescents did not find such an association. New publications on EHS could not identify physiological characteristics that may help diagnosing or developing effective therapeutic options.

In general, study quality has been quite heterogeneous in the last two years. On the one hand, many low-quality studies appeared which did not fulfil basic quality criteria and were thus excluded from this review. On the other hand, some new approaches are promising to obtain new insights into potential health effects from radiofrequency field exposure.

5. Recent expert reports

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

5.1. Mobile phones and cancer: Part 3. Update and overall conclusions from epidemiological and animal studies

Health Council of the Netherlands, Mobile phones and cancer: Part 3. Update and overall conclusions from epidemiological and animal studies. The Hague: Health Council of the Netherlands, 2016; publication no. 2016/06. ISBN 978-94-6281-098-3

Summary

Why this report?
Exposure to radiofrequency electromagnetic fields has considerably changed in the past decades, due to the fast growth of mobile telecommunication, wireless internet access and other sources. This has increased concern about possible adverse health effects of such exposures. In 2012, the International Agency for Research on Cancer (IARC) classified radiofrequency electromagnetic fields as 'possibly carcinogenic to humans'. This classification was primarily based on epidemiological data, with additional support from animal studies.

The Electromagnetic Fields Committee of the Health Council of the Netherlands has performed systematic reviews of both the epidemiological and animal experimental data using a priori defined protocols, taking into account the scientific quality of the studies. The analysis of the epidemiological data has been published in a report issued in 2013.1 The analysis of the data on carcinogenesis in experimental animals was published in 2014.2 This report provides an update of the two previous reports and the overall conclusions of the Committee on the basis of all described data that was announced in the previous reports.

Epidemiological evidence was sought for indications of an association between exposure to radiofrequency fields from mobile phones and tumours in the brain and various other tissues in the head and neck (e.g. meninges, acoustic nerve, parotid glands). Studies investigating other sources of exposure to radiofrequency fields and other cancers are not discussed in this report. The animal carcinogenesis studies had a broader scope and included all possible cancers, as well as exposure to radiofrequency fields alone and co-exposures to carcinogenic agents.

What has been observed?
Overall, the epidemiological data show some weak indications for an association between prolonged and intensive use of a mobile phone and an increased incidence of gliomas (brain tumours) and acoustic neuromas (tumours on the acoustic nerve). In some cases these findings lack biological plausibility. Some studies showed for instance increased risks after a short period of use, which is not compatible with the long period of development of the tumours in question. In other studies an increase in the number of tumours was not observed with the highest exposure level, but only with lower ones. This is also in contrast to expectations. Furthermore, data on the incidence of the relevant tumours from the Netherlands and other countries worldwide do not provide support for a causal relationship. For meningiomas, pituitary tumours and parotid gland tumours, no indications for an association with mobile phone use have been observed.

The animal studies do not provide evidence for induction of tumours by exposure to radiofrequency electromagnetic fields. Such exposure may have a promoting effect on the development of tumours, but the indications for this are weak and have been observed in only one, very specific, animal model.

What are the overall conclusions?
The Committee jointly considered the epidemiological and experimental data to formulate its conclusions. The Committee feels that it is not possible to state that there is a proven association between long-term and frequent use of a mobile telephone and an increase in the risk of tumours in the brain and head and neck region in humans. Based on the strength of the evidence it can only be concluded that such an association cannot be excluded. The Committee considers it unlikely that exposure to radiofrequency fields, which is associated with the use of mobile telephones, causes cancer. The animal data indicate a possibility of a promoting effect, but it is not clear whether this could explain the increased risk for tumours in the brain, head and neck that has been observed in some epidemiological studies. The Committee feels it more likely that a combination of bias, confounding and chance might be an explanation for the epidemiological observations.

Is there reason to limit exposure?
From the conclusions formulated above it follows that the value of any measures to reduce exposure is unclear. Nevertheless, the Committee would like to repeat its previous suggestion: apply the ALARA principle. This means that exposures should be As Low As Reasonably Achievable. There is, for instance, no need for any device to transmit with greater power or for a longer period of time than needed for an adequate connection. This is fully in line with the suggestions from the Health Council's advisory report *Prudent precaution*.

Is more research necessary?
There is still very limited information on really long-term effects in humans. Some epidemiological studies have follow-up times of more than 13 years, but with generally few subjects in the highest exposure categories. The latency times for development of the relevant tumours are most likely longer. The Committee therefore considers it important to continue the ongoing cohort studies evaluating the health effects of mobile phone use, in order to provide more conclusive human evidence. The exposure characterization in all currently available studies is very poor. It is therefore very important that ongoing and future studies incorporate more accurate and objective assessment of RF exposure. This is even more important since personal exposure to RF continues to change due to evolving patterns of use and new mobile telecommunication devices.

5.2. The 2016 ANSES Recommendations on exposure to radiofrequency waves.

Following a request by the Ministries of Health, Ecology and Consumer Affairs, ANSES conducted an expert assessment on the specific impact of radiofrequency waves on children. The conclusions of this assessment were published in July 2016.

Recommendations of the Agency
All of the potential health effects of radiofrequency waves, both carcinogenic and otherwise, were studied and their levels of proof classified using a method based on that used by the WHO's International Agency for Research on Cancer (IARC).

The conclusions of the risk assessment published in 2013 do not show any proven health effects. Certain publications do however show a possible increase in the long-term risk of brain tumours for intensive users of mobile telephones. The conclusions of the risk assessment therefore coincide with the suggested classification of radiofrequency waves by the IARC as a "possible carcinogen" for intensive users of mobile phones. The assessment also highlighted, with limited levels of proof, various biological effects in humans and in animals, some of which had already been reported in 2009,

concerning sleep, male fertility and cognitive performance. Indeed, biological effects corresponding to generally reversible alterations in internal bodily function were observed, as in the case of exposure to various everyday stimuli. However, the Agency's experts were not able to establish a causal link between the biological effects described in cell models, animals or humans and any possible resulting health effects. Because of this, it would appear unfounded to propose new exposure limit values for the general public with regard to health.

However, the Agency emphasises that risk assessment cannot currently be made on the different potential effects without data for humans or animals, and that the potential impact of the communication technology implemented (2G, 3G, 4G) appears to be insufficiently documented. The Agency also emphasises the massive development of radiofrequency wave use in outdoor and indoor environments, leading to an increase in population exposure.

In addition, while recent studies conducted nationally have revealed low overall exposure levels as compared to the exposure limits currently set for the geographical areas under investigation, they also demonstrate that the exposure areas have expanded greatly. These areas could be reduced through technological means.

In this context, while mobile phones are the main source of exposure for users, environmental exposure of the general population and its variations over time need to be better documented.

Therefore, to limit exposure to radiofrequency waves, especially by the most vulnerable population groups, the Agency recommends:

- that in “talk” mode, adult intensive users of mobile telephones use hands-free accessories more systematically, and more generally that all users choose telephones with the lowest SAR[1] values;
- reducing exposure in children by encouraging moderate mobile telephone use;
- continuing to improve exposure characterisation of the public in outdoor and indoor environments through the implementation of measurements campaigns;
- that studies be conducted prior to the development of new mobile telephone network infrastructures in order to characterise exposure, and that the consequences of the installation of additional relay antennas in order to reduce environmental exposure levels be examined in depth;
- documenting the existing installation set-ups that cause the highest exposure in the public and studying to what extent this exposure could be reduced by technical means.
- that maximum exposure levels (the SAR, for example) be displayed on all common devices emitting electromagnetic fields designed to be used close to the body (DECT telephones, touch-screen tablets, baby monitors, etc.), as is already the case for mobile phones.

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ZHANG, G., YAN, H., CHEN, Q., LIU, K., LING, X., SUN, L., ZHOU, N., WANG, Z., ZOU, P., WANG, X., TAN, L., CUI, Z., ZHOU, Z., LIU, J., AO, L. & CAO, J. 2016a. Effects of cell phone use on semen parameters: results from the MARHCS cohort study in Chongqing, China. *Environ Int,* 91**,** 116-121.

ZHANG, Y., LAI, J., RUAN, G., CHEN, C. & WANG, D. W. 2016b. Meta-analysis of extremely low frequency electromagnetic fields and cancer risk: a pooled analysis of epidemiologic studies. *Environ Int,* 88**,** 36-43.

ZHOU, L., WAN, B., LIU, X., ZHANG, Y., LAI, J., RUAN, G., HE, M., CHEN, C. & WANG, D. W. 2016. The effects of a 50-Hz magnetic field on the cardiovascular system in rats. *J Radiat Res,* 57**,** 627-636.

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Appendix: Studies excluded from analysis

Articles were identified in relevant scientific literature data bases such as PubMed as well as in the specialized database EMF Portal. Further, reference lists of articles were screened for relevant papers. Several studies had to be excluded from further analysis as they did not fulfil quality criteria. In this Appendix, these studies[5] are listed and the reasons for exclusion are indicated. The list is divided into cell studies, animal studies, human studies and epidemiological studies.

Cell studies

Static fields

Reference	Reason for exclusion
Boda et al. (2015)	No sham-control
Cai et al. (2015)	No sham-control
Kim et al. (2015)	No sham-control
Luo et al. (2016)	No sham-control
Maredziak et al. (2017)	No sham-control
Mizuno et al. (2015)	No sham-control
Pawlowska-Goral et al. (2016)	No sham-control
Reddig et al. (2015)	No sham-control

Extremely low frequency (ELF) fields

Reference	Reason for exclusion
Ardeshirylajimi and Soleimani (2015)	No sham-control
Destefanis et al. (2015)	No sham-control
Mohamed et al. (2015)	No sham-control
Lewicka et al. (2015)	No sham-control
Maes et al. (2016)	No sham-control
Moraveji et al. (2016)	No sham-control
Pasi et al. (2016)	No sham-control; no exposure system description
Patruno et al. (2015)	No sham-control
Yin et al. (2016)	No sham-control

Radiofrequency (RF) fields

Reference	Reason for exclusion
Kazemi et al. (2015)	No sham-control
Lippi et al. (2016)	No sham-control; Smartphone employed for exposure
Danese et al. (2017)	No sham-control; Smartphone employed for exposure
Rogowska et al. (2016)	No sham-control; no dosimetric information

[5] The articles are primarily identified through searches in relevant scientific literature data bases. However, the searches will never give a complete list of published articles. Neither will the list of articles that do not fulfil quality criteria be complete.

Shahbazi-Gahrouei et al. (2016)	No sham-control; cell phone employed for exposure
Taheri et al. (2017a)	No sham-control; No dosimetry (wifi-router)
Zalata et al. (2015)	No sham-control
Liu et al. (2015)	Sham-control quoted but not described
Liu et al. (2013)	cell phone employed for exposure

Animal studies

Static fields and extremely low frequency field

Reference	**Reason for exclusion**
Abreu et al. (2016)	Treatment of cranial bone defects in rats using implanted neodymium iron boron magnets (0.84mT)
Ahmadi et al. (2016)	Improper description of MF and animal housing
Ambalayam et al. (2016)	Treatment (50Hz, 18µT) of secondary effects after spinal cord injury
Bainbridge et al. (2016)	No health risk relevant data -> Magnetic orientation in C. elegans & integrity of AFD magnetosensory neurons
Bazalova et al. (2016)	No health risk relevant data -> Cry2-dependence of directional magnetoreception in cockroaches
Belova and Acosta-Avalos (2015)	Review -> animals' magnetoreception and effects of alternating magnetic fields
Chen et al. (2016)	Treatment (6Hz, 20mT rotary non-uniform MF) of nerve injury (decapitated planarians) at early regeneration stages
Gerardi et al. (2016)	Imprecise description of study design, time-point of mating during the "100-day trial" and therefore duration of pre-conceptual 60Hz 38-47 µT ELF-MF exposure of CD1 mice
Khaki et al. (2016)	Exposure not defined [no MF data for the "50-60 Hz magnetic field" presented]. Improper description of in vivo part,
Seifpanahi-Shabani et al. (2016)	No description of ELF-MF exposure system. Very brief paper, entitled « Correspondence », describing that a 50Hz 100µT, 2h/d, 30mo –exposure did not change the melatonin levels in serum and supernatant of whole blood culture of male Wistar rats.
Sheppard et al. (2017)	Only ex vivo work on mT MF-effects on photocycle of Drosophila cryptochrome (*DmCry)* and interpretation in terms of radical pair mechanism. Spectroscopic measurements of photo-induced FAD and Trp radicals in *DmCry*
Rostami et al. (2016)	Improper description of 3Hz & 60 Hz 4mT ELF-MF exposure (system) and dosimetry.
Umarao et al. (2016)	No description of MF & Treatment-related study of Fe-NP and MF-exposure in a PD rat model
Wu et al. (2016)	No health risk relevant data -> Magnetoreception regulates male courtship activity in Drosophila
Xu et al. (2016)	Imprecise description of 1) EF near to HVDC transmission lines, 2) exposure days for outdoor exposed ICR mice
Zhang et al. (2016a)	Imprecise and improper description of study design (species [mix-up of species rat and mouse, group size 10?

	(≥3 replicates with 3 mice), no description of exposure. Finally, more a study of immunoprevention of LSPC than of ELF-MF effects.
Zmejkoski et al. (2017)	Incomplete methodological description (group sizes of Drosophila larvae and flies, "fitness components" etc.). Health relevance questionable: "…various responses of D. obscura IF lines to the applied ELF-MF depending on their genetic background."

Radiofrequency (RF) fields

Reference	Reason for exclusion
Bin-Meferij and El-Kott (2015)	No dosimetry, mobile phone in cage
Celiker et al. (2016)	No dosimetry
Cetkin et al. (2017)	No dosimetry
Erdem Koc et al. (2016)	Incomplete dosimetry (no SAR provided).
Erkut et al. (2016)	No dosimetry.
Esmekaya et al. (2016)	Incomplete dosimetry, mobile phone in cage, but SAR calculated for phone under cage; no frequency provided..
Hussein et al. (2016)	No dosimetry, mobile phone in cage.
Kerimoğlu et al. (2016)	No dosimetry.
Kouchaki et al. (2016)	No source and exposure levels provided.
Mortazavi et al. (2016d)	No dosimetry
Mugunthan et al. (2016)	No dosimetry, mobile phone in cage.
Oyewopo et al. (2017)	No dosimetry.
Shehu et al. (2016)	No dosimetry, mobile phone in cage.
Shekoohi Shooli et al. (2016)	No dosimetry, no information on frequency.
Shekoohi-Shooli et al. (2016)	No dosimetry.
Yuksel et al. (2016)	Unclear experimental design, no sham exposure.

Human studies

Radiofrequency (RF) fields

Reference	Reason for exclusion
Lv et al. (2015)	not published in a peer-reviewed journal
Singh (2015)	lack of a sham condition, lack of information on blindness, no exposure characterisation

Roggeveen et al. (2015a), Roggeveen et al. (2015b)	single-blind experiments, no within subject control of time-of-day (experiments were carried out between 9 am and 5 pm), no detailed dosimetric characterisation of exposure (use of a 3G smartphone with SAR information according to the manual: 0.69 W/kg), no clear sham exposure control condition (one of the four consecutive conditions always was a real exposure – "dialling" – condition). There is no information on the control of interference exposure system and recording device (EEG and "Radiation" were recorded simultaneously). Experiments were performed in a non-shielded room. EEG was recorded with shielded electrodes (no specification on how shielding of electrodes was achieved), no information on the reference for EEG recordings (linked mastoids or contralateral ear).

Epidemiological studies

In a first step, all articles that were not relevant for this report were discarded, i.e.

A) papers that did not study non-ionizing electromagnetic fields (i.e. static, extremely low frequency, intermediate frequency or radiofrequency EMF), or
B) did not study any health outcome (including letters, commentaries etc.), or
C) did not in any way study the association between radiofrequency fields and a health outcome (e.g. use of text messages for self-management of diabetes).
D) Studies on using EMF as therapeutic interventions (e.g. diathermy),
E) Case-reports were also excluded.
F) Further, studies that did not include humans were excluded, as well as studies of humans with an experimental design (these studies are included under "human studies").
G) Not a peer-reviewed publication, or published in another language than English,
H) Studies published outside of the time frame of this report (online publication date).

In a second step, the following exclusion criteria were applied after screening the abstracts and the full text:

I) Study base not identified (e.g. self-selection of subjects in cross-sectional or case-control studies, the population intended for inclusion not described)
J) No comparison group or no exposure considered (either no unexposed group or lacking denominator for prevalence/incidence calculation in descriptive or incidence study), with the exception of incidence trend studies from registries applying a systematic data collection.
K) Narrative reviews
L) Duplicate reports, unless new additional analyses are presented (including the first original publication, and information from duplicate reports if new additional results were presented)
M) Addressing exclusively exposure assessment methods which have been proven to be invalid such as self-estimated distance to mobile phone base stations.

In total 175 potentially relevant papers were identified in the literature search. Of them, 83 papers were excluded in the first screening round and 38 after abstract and full text screening. Thus, 54 papers remained for evaluation.

The following papers were excluded from evaluation based on the reasons indicated in the second column:

Reference	**Reason for exclusion**
Pouchieu et al. (2016)	A
Schaap K, Christopher-De Vries Y, Crozier S, de Vocht F, Kromhout H (2015): CORRIGENDUM: Exposure to static and time-varying magnetic fields from working in the static magnetic stray fields of MRI scanners: a comprehensive survey in the Netherlands. Ann Occup Hyg 2015; 59 (6): 817 – 820. http://annhyg.oxfordjournals.org/content/59/6/817.long	A

Kim et al. (2016a)	A
Zhang et al. (2016b)	A
Jarideh et al. (2015)	A
Goedhart et al. (2015)	B
Batistatou et al. (2016)	B
Carpenter (2015)	B
Carpenter and Belpomme (2015)	B
Lewis et al. (2016)	B
Mortazavi and Mortazavi (2015)	B
Porsius et al. (2016)	B
Redmayne and Johansson (2015)	B
Toledano et al. (2015)	B
Vila et al. (2016)	B
Yzermans et al. (2016)	B
de Vocht and Olsen (2016)	B
Gallastegi et al. (2016)	B
Mortazavi et al. (2016a)	B
Radwan et al. (2016)	B
Sudan et al. (2016)	B
Berthelot (2016)	B
Domotor et al. (2016)	B
Foster and Moulder (2015)	B
Freudenstein et al. (2015)	B
Johansson (2015)	B
Kandel et al. (2016)	B
Kaplan et al. (2016)	B
Kim et al. (2016b)	B
Mortazavi et al. (2016c)	B
Mortazavi et al. (2016b)	B
Schuz et al. (2016)	B
Terzi et al. (2016)	B
Warille et al. (2016)	B
Say et al. (2016)	B
Keevil A. Safety in magnetic resonance imaging. Medical Physics International Journal, vol.4, No.1, 2016. http://mpijournal.org/pdf/2016-01/MPI-2016-01-p026.pdf	B
Feychting (2016)	B
Yu G. 30 Years of Cellular and Health Populations (There is a Realization, Forecast of Dangerous, Recommendations). Review Pub Administration Manag 2015, 3:1. http://www.omicsonline.com/open-access/30-years-of-cellular-and-health-populations-there-is-a-realizationforecast-of-dangerous-recommendations-2315-7844-1000173.php?aid=66493	B
Belyaev et al. (2016)	B
Moradi et al. (2016)	B
Maes and Verschaeve (2016)	B
Boehmert et al. (2017)	B
Markov and Grigoriev (2015)	B
Malisuwan S, Wassana Kaewphanuekrungsi, Noppadol Tiamnara and Pollawich Apintanapong. A study of electromagnetic radiation effects from mobile phone base stations on human health. International Journal of Advanced Research in	B

Engineering and Technology (IJARET) Volume 6, Issue 12, Dec 2015, pp. 25-38	
Marell et al. (2016)	B
Gajsek et al. (2016)	B
El-Zein et al. (2016)	B
Redmayne (2017)	B
Bandara (2016)	B
Chapman et al. (2016)	B
Hardell et al. (2016)	B
Lloyd Morgan et al. (2016)	B
Wojcik (2016)	B
Kiyohara et al. (2016)	B
Roser et al. (2017)	B
Munk and Murphy (2017)	B
Jaffer and Murphy (2017)	B
Lewis et al. (2017)	B
Mortazavi et al. (2017)	B
Budinger and Bird (2017)	B
Liboff (2016)	B
Keevil and Lomas (2017)	B
Dechent and Driessen (2016)	B
Baliatsas et al. (2015)	C
Eyvazlou et al. (2016)	C
Koteles et al. (2016)	C
Kjellqvist et al. (2016)	C
Slottje et al. (2017)	C
van Wel et al. (2017)	C
Hojo et al. (2016)	C
Milham and Stetzer (2017)	C
Wang et al. (2016a)	D
Zhu et al. (2016)	D
Johansson and Redmayne (2016)	E
Milham and Stetzer (2016)	E
Yilmaz et al. (2017)	F
Nakatani-Enomoto et al. (2016)	F
Tran et al. (2017)	F
Brascher et al. (2017)	F
Bhargav et al. (2016)	F
Al-Qahtani (2016)	G
Medeiros and Sanchez (2016)	H
Wang et al. (2016c)	H
Vesselinova (2015)	I
Zarei et al. (2015)	I
Kunt et al. (2016)	I
Ekici et al. (2016)	I
Pachuau L , Zaithanzauva Pachuau: Health Effects of Mobile Tower Radiation on Human — Case Study. International Journal of Applied Physics and Mathematics. Volume 6, number 2, April 2016. http://www.ijapm.org/vol6/352-ST3001.pdf	I

Naglaa M. Elsayed1,2, Saddig D. Jastaniah1. Mobile Phone Use and Risk of Thyroid Gland Lesions Detected by Ultrasonography. Open Journal of Radiology, 2016, 6, 140-146. http://file.scirp.org/pdf/OJRad_2016062114145375.pdf	I
Aderinola M, J.S. Kazaure, I. Muhammad. Study on the Effect of Electromagnetic Radiation on Human Health in Kano Metropolis. International Journal of Engineering and Innovative Technology (IJEIT) Volume 5, Issue 8, February 2016 www.ijeit.com/Vol%205/Issue%208/IJEIT1412201602_12.pdf	I
Hegazy AA, Bahaa Aba Alkhail1 Nabil J. Awadalla3,4, Mahdi Qadi and Jawaher Al-hmadi.Mobile Phone Use and Risk of Adverse Health Impacts among Medical Students in Jeddah, Saudi Arabia. British Journal of Medicine & Medical Research. 15(1): 1-11, 2016, Article no.BJMMR.24339 www.researchgate.net/profile/Amal_Hegazy/publication/301342480_Mobile_Phone_Use_and_Risk_of_Adverse_Health_Impacts_among_Medical_Students_in_Jeddah_Saudi_Arabia/links/571a1c0308ae30c3f9f3ce20.pdf	I
Joshi RV & Dr. H.D. Khanna. Effect of electromagnetic fields emitted by cellular phone base stations on human health. Indian Journal of Applied Basic Medical Science, 2016, Vol 17a, Issue 24. http://www.indianjournals.com/ijor.aspx?target=ijor:ijabms&volume=17a&issue=24&article=002	I
Ghadimi-Moghadam A.1,2, Mortazavi S. M. J.2*,Hosseini-Moghadam A.3, Haghani M.2, Taeb S.2,Rastegariyan N.4, Arian F.5, Sanipour L.5, Aghajari S.5,Mortazavi S. A. R.2, Soofi A.2, Dizavandi M. R.6. Does Exposure to Static Magnetic Fields Generated by Magnetic Resonance Imaging Scanners Raise Safety Problems for Personnel?J Biomed Phys Eng. http://www.jbpe.org/Journal_OJS/JBPE/index.php/jbpe/article/viewArticle/399	I
Joshi RV, HD Khanna. Electromagnetic Fields Emitted by Mobile Phone Affects Autonomic Function in Human Being. - Indian Journal of Applied Basic Medical Sciences, 2016, 18b(27)	I
Wang et al. (2016b)	I
Tabrizi and Hosseini (2015)	J
Leng and Zhang (2016)	J
Ortiz Francisco, Fern´andez-Gil Beatriz I, Guerra-Librero Ana, L´opez Luis C, Acu˜na-Castroviejo Dar´ıo, Escames Germaine. Preliminary evidence suggesting that nonmetallic and metallic nanoparticle devices protect against the effects of environmental electromagnetic radiation by reducing oxidative stress and inflammatory status. European Journal of Integrative Medicine. http://dx.doi.org/10.1016/j.eujim.2016.06.009	J
Balekouzou et al. (2017)	J
Alexiou and Sioka (2015)	K
N (2015)	K
Meena JS, Bhavishya Rathore, Abhishek Sahai, Mahesh Gupta. Ill Efects of Using Smart Phones and/Or Laptops 1-2 Hrs Before Sleep, Among Students A Medical College in Central India: An Educational Interventional Study. PARIPEX - INDIAN JOURNAL OF RESEARCH Vol 5 No 5 2016. http://worldwidejournals.in/ojs/index.php/pijr/article/viewFile/5300/5330	K
Sirav B, Nesrin Seyhan. Effects of radio-frequency radiation on the permeability of blood-brain barrier. Medical Science and Discovery. 2016; 3(5): 206-12. http://www.ncbi.nlm.nih.gov/pubmed/27231809	K
Bernabò N , Rosa Ciccarelli, Mauro Mattioli, Barbara Barboni. Effect of Non-Ionizing Electromagnetic Fields of Anthropic Origin on Male Fertility. Current Chemical Biology, 2016	K
Pall (2016)	K
Foster et al. (2017)	K

Havas (2017)	K
Starkey (2016)	K
Meena et al. (2016)	K
Sammet (2016)	K
Garzillo et al. (2016)	K
Wdowiak et al. (2017)	K
Thakur H, Sahu D. Biological Effects of Electromagnetic Waves: Case Studies and Safety Standards. Indian Journal of Science and Technology, 2016, Vol 9(47), DOI: 10.17485/ijst/2016/v9i47/106851	K
Asghari et al. (2016)	K
Pall M. Low intensity microwave frequency electromagnetic fields (EMFs) produce extensive brain damage and widespread neuropsychiatric effects. 24th European Congress of Psychiatry / European Psychiatry 33S (2016) S349–S805	K
Silva et al. (2015)	M
Singh et al. (2016)	M
Mohan et al. (2016)	M
Amin et al. (2016)	M
Taheri et al. (2017b)	M

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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.

Strålsäkerhetsmyndigheten
Swedish Radiation Safety Authority

SE-171 16 Stockholm
Solna strandväg 96

Tel: +46 8 799 40 00
Fax: +46 8 799 40 10

E-mail: registrator@ssm.se
Web: stralsakerhetsmyndigheten.se

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