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Swedish Radiation Safety Authority

Research

Recent Research on EMF and Health Risk

Sixteenth report from SSM's Scientific Council on Electromagnetic Fields, 2021

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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 in relation 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.

This is a consensus report. This means that all members of the Scientific Council agree with the complete report. This increases the strength of the given conclusions.

The report has the primary objective of covering the previous year's research in the area of electromagnetic fields (EMF) and health but also to place this in the context of present knowledge. The report gives the authority an overview and provides an important basis for risk assessment.

Results

This report reviews studies on electromagnetic fields (EMF) and health risks, published from January 2020 up to and including December 2020. The report is the sixteenth in a series of annual scientific reviews which consecutively discusses and assesses relevant new studies and put these in the context of available information. 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. The result will be a gradually developing health risk assessment of exposure to EMF.

No new established causal relationships between EMF exposure and health risk have been identified.

The studies presented in this report do not resolve whether the consistently observed association between ELF magnetic field (ELF-MF) exposure and childhood leukaemia in epidemiology is causal or not.

Only a very limited amount of new research has been published on tumour risk in relation to mobile phone use. Associations between mobile phone use and insomnia-like symptoms have been observed as in previous years. However, insomnia was associated rather to the time period of use than to the level of radiation exposure. This suggests that other factors than RF-EMF (Radiofrequency-EMF) may explain the observed association. Such factors may include for example stress or other behavioural factors. For insomnia-like symptoms, a significant interaction was found in one study between RF-EMF exposure from mobile phone base stations and environmental concerns, which indicates communication needs with the public about potential health risks from mobile phone base station. New studies in adolescents on cognitive functions and brain volume do not indicate a risk from RF-EMF exposure.

Concerning studies on animals, it is difficult to draw general conclusions other than that under certain circumstances some effects from RF-EMF exposure are observed in experimental animals. The observations of increased oxidative stress reported in previous SSM reports continue to be found, some even below current reference levels. Oxidative stress is a natural biological process that can sometimes be involved in pathogenesis, but under what circumstances oxidative stress due to weak radio wave exposure may affect human health remains to be investigated.

Despite the increasing use of applications in the intermediate frequency (IF) range of the electromagnetic spectrum (300 Hz-10 MHz), scientific evaluation of potential health risks in that range is scarce. However, the few studies identified by the council in this area have not indicated any health effects below current reference levels.

The annual report also includes a section where studies that lack satisfactory quality have been listed. This year, as well as last year, many studies have been excluded due to poor quality (see appendix). From a scientific perspective, studies of poor quality are irrelevant. They are also a waste of money, human resources and, in many cases, experimental animals.

Relevance

The results of the research review give no reason to change any reference levels or recommendations in the field. However, the observations of biological effects in animals due to weak radio wave exposure clearly show the importance of maintaining the Swedish Environmental Code precautionary thinking.

SSM:s hands-free recommendation for mobile phone calls remains even though trends of glioma incidences do not provide support for an increasing risk caused by mobile phone radio wave exposure. However, observed biological effects and uncertainties regarding possible long term effects justify caution.

No new findings that clearly change the suspicion of a causal link between weak low-frequency magnetic fields and childhood leukaemia have emerged in the report. The Swedish authorities' recommendation to generally limit exposure to low frequency magnetic fields due to the observed increased incidence of childhood leukaemia close to power lines remains unchanged.

Need for further research

Despite the fact that no health risks associated with weak electromagnetic fields have been demonstrated up to date, the authority considers that further research is important, in particular regarding long-term effects as more or less the entire population is exposed. One key issue here is to further investigate the relationship between radio wave exposure and oxidative stress observed in animal studies and to establish whether a relationship in humans exists and, if so, to what extent it may affect human health. Another important issue is to clarify the association between weak low frequency magnetic fields and childhood leukaemia as observed in epidemiological studies.

Since epidemiological studies often report impact on cognitive functions (non-specific symptoms such as headache and mental health problems) due to the use of information technology, it is desirable to further investigate if this association to some extent depends on the resulting radio wave exposure. The authority would like to emphasize that innovative approaches allowing differentiating between device usage and physical radio frequency EMF exposure are needed to better understand the causality of radio frequency EMF exposure for health.

Wireless information technology is constantly evolving and new frequency ranges will be used. The fifth generation mobile telecommunication system (5G) will be installed all over the world within the next few years. Even though there is no established mechanism for affecting health from weak radio wave exposure, there is need for more research covering the novel frequency domains used for 5G. The authority also encourages researchers to start undertaking epidemiological studies, i.e. cohort studies, in this area. There are currently very few studies in the 26 GHz band.

New technologies for inductive wireless energy transfer based on intermediate frequency magnetic fields will probably be implemented for many different applications in the near future. In contrast to wireless information communication technology, wireless energy transfer in principle always results in relatively strong local fields. This makes it very important to obtain a robust basis for risk assessment of such fields. Today, there is a lack of studies in this frequency domain, and therefore, there is a special need for research in this area.

Another vital issue to further investigate is whether exposure to low frequency magnetic fields contribute to the slightly increased incidence of childhood leukaemia that has been observed close to power lines in epidemiological studies. When animal studies are planned regarding this issue, the authority encourage the use of the novel mouse design ETV6-RUNX1 (Campos-Sanchez et al. (2019)).

It is also desirable to investigate different health effects based on combinations of electromagnetic fields and other factors, both physical factors and chemical factors.

Project information
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Content

Preface

The Swedish Radiation Safety Authority´s scientific Council for electromagnetic fields (EMF) and health was established in 2002. The Council´s main task is to follow and evaluate the scientific development and to give advice to the authority. In a series of annual 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 2003. A brief overview of whether or how the evidence for health effects has changed over the first decade of reports was included in the eleventh report. The present report is number sixteen in the series and covers studies published from January 2020 up to and including December 2020.

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

Anke Huss, PhD, epidemiology, University of Utrecht, the Netherlands (chair)

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The council would like to thank Dr. D Schürmann, University of Basel, Switzerland, for input on oxidative stress.

Declarations of conflicts of interest are available at the Swedish Radiation Safety Authority.

Stockholm/ Utrecht in January 2022

Anke Huss
Chair

Executive Summary

This report reviews studies on electromagnetic fields (EMF) and health risks, published from January 2020 up to and including December 2020. The report is the sixteenth in a series of annual scientific reviews which consecutively discusses and assesses relevant new studies and put these in the context of available information. The result will be a gradually developing health risk assessment of exposure to EMF.

Oxidative stress is one of the most investigated biological endpoints to evaluate possible effects of electromagnetic fields, also in this period of interest. Several *in vivo* and *in vitro* investigations have been devoted to this topic. Therefore, a short paragraph describing such phenomenon has been included in the report, related to its involvement in physiological and pathological processes and describing the main laboratory techniques applied to detect oxidative stress.

Static fields

Exposure to static (0 Hz) magnetic fields much greater than the natural geomagnetic field can occur close to industrial and medical/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 and therapy monitoring. Volunteer studies show that movement in such strong static fields can generate sensations such as vertigo and nausea. The thresholds for these sensations seem to vary considerably within the population. Personnel exposed to fields from MRI scanners can also be affected by these transient symptoms.

Epidemiology

Occupational exposure from magnetic resonance imaging (MRI) causes acute and transient symptoms, but as stated in previous Council reports, long-term consequences for health remain unclear. Research on occupational MRI exposure is scarce and underlying mechanisms for occasionally observed associations (e.g. accidents, high blood pressure, menometrorrhagia in women using intrauterine devices) are unclear. A new study on sleep problems in persons occupationally exposed to MRI contributes to this pattern. Given that MRI exposure is relatively high, and the number of occupationally exposed persons is increasing, more systematic and comprehensive research on this topic is warranted.

Human studies

In 2020 no experimental study was published that contributes to the knowledge about effects of static fields on humans.

Animal studies

Addressing MRI, exposure for one hour to strong static magnetic fields (SMF) in the range of 7 to 33 T did not significantly affect general health, blood cell count, blood biochemistry, and organ morphology in mice. Furthermore, orientation of homing pigeons was temporarily but reversible affected after a 15 min lasting MR imaging exposure of 3 T.

New immature neural cells occurred following exposure of 4.3 mT-12.9 mT SMF to the brain of rats. In spontaneously hypertensive rats differently orientated SMF of 16 mT reduced anxious-like behavior. Using various mouse models, exposures of 58 – 116 mT showed a trend towards a MF intensity-dependent antithrombotic effect, but no clear-cut effect on type 1 and type 2 diabetes was observed. Increased locomotion in cockroaches was triggered by chronic exposure to a 110 mT SMF. Finally, MF along high voltage direct current (HVDC) subsea cables increased exploratory behaviour more in electro-sensitive skates than in lobsters.

Cell studies

A large number of *in vitro* studies dealing with the effect of static fields have been published in the year 2020. In most cases they lack sham-controls, or the exposure has been performed using commercial devices without adequately described exposure parameters, therefore they have not been considered. In addition, other studies were not included in the report since they were related to biomedical applications of static fields. On the whole, only one study, dealing with the expression of genes that are regulated by reactive oxygen species was included in the report. The results suggest that static fields at very low level (200 nT) are able to induce slight variations in the biological endpoints considered, such as protein conformation, cell viability and chemically-induced oxidative stress.

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, from electric devices and wiring in buildings. Regarding the exposure to ELF magnetic fields and the development of childhood leukaemia associations have been observed, but a causal relationship has not been established.

Epidemiology

The current studies do not resolve whether the consistently observed association between ELF magnetic field (ELF-MF) exposure and childhood leukaemia in epidemiology is causal or not.

New epidemiological studies on childhood leukaemia in relation to paternal exposure or residential exposure are in line with previous research: studies indicated an absence of associations with paternal exposure, whereas previously observed associations with residential exposure were observed again in Mexico City. A Californian study did not indicate that dwelling type may be a critical confounder for this research question.

Several studies on adult cancer did not observe increased risks, whereas one small study on brain tumours in relation to proximity to power lines reported rather implausibly high risk estimates, indicating that chance or bias may play a major role in this study. A large new study on motor neuron disease indicated that electric shocks rather than magnetic fields could be relevant. This is in contrast to the results of new meta-analyses, leaving it still unanswered whether magnetic fields or shocks are underlying the previously observed associations.

Human studies

The number of studies continued to be very low, last year only three were published. A methodologically weak study observed effects of chest exposure in four out of six parameters of heart rate variability, which were not observed in a group of unexposed subjects. The second, methodologically sound, study did not observe any effects on postural modulation in subjects with right-sided ELF-EMF exposure at the vestibular system. The third study underlines that ELF-MF exposure induces phosphene perception at individually varying thresholds when the head is exposed to a homogeneous 50 Hz sinusoidal signal.

Animal studies

Again, and similar to the previous Council reports, studies used mostly 50/60 Hz ELF and exposure levels around 1 mT magnetic fields (MF) or between 5 and 35 kV/m electric fields (EF), respectively. Rats' chronic exposure to 50 Hz, 0.03 mT to 1.5 mT ELF-MF had no significant clinical and biological effects in the animals. Short-term application of different pulsed magnetic fields (PMF) of 1 mT led to contradictory answers on pain sensitivities in rats. A further mouse study addressing ultra-high voltage (UHV) transmission technology and using ELF-EF (50 Hz, 35 kV/m) demonstrated morphological kidney alterations after up to 3 weeks exposure, which recovered after longer lasting exposure. An ELF-EF of 50 Hz and 5.4 kV/m caused oxidative stress and spermatogonia degeneration in rats. In honeybees exposed to the same range of 50 Hz EF (5 – 34.5 kV/m) increased enzyme activities of the antioxidant and proteolytic systems are interpreted as a general first defence mechanism against an environmental stressor. Also, cockroach nymphs were shown to be stressed by a

5 months lasting exposure to 50 Hz, 10 mT ELF-MF. And in the nematode *C. elegans*, chronic exposure to a 50 Hz 3 mT MF over multiple generations can increase body length and boost antioxidant capacity.

MF around 0.2 mT, i.e., at intensities comparable to those produced by high power submarine cables at their close proximity, do not significantly impact the behaviour of juvenile European lobsters. But short-term (up to one week) exposure of the mollusc *Onchidium struma* to a similar low intensity of <0.5 mT elicits some immune response. Finally, embryonic development of Japanese quail and zebrafish was not affected following exposures in and below the mT range.

Overall, the diverse animal models describing dissimilar effects following ELF-MF exposure in the 1 mT range and below again demonstrate the absence of knowledge on biologically relevant mechanisms of ELF-MF, except oxidative stress.

Cell studies

In vitro studies published in the year 2020 evaluated the effect of ELF fields on cell proliferation, cell cycle progression, apoptosis, redox cell state and DNA integrity. In one study the sensitivity to ELF fields on traditional and 3D cell cultures was compared. In most cases cell viability increased or decreased on the basis of the experimental conditions adopted (exposure duration, frequency, field intensity). The inconsistent patterns mean that the results are difficult to interpret. Several studies have been recognized but not considered, due to the scanty quality of the experimental design (lack of appropriate sham-controls).

Intermediate frequency (IF) fields

The intermediate frequency (IF) region of the electromagnetic spectrum (300 Hz-10 MHz) is defined as being between the extremely low frequency and the radiofrequency ranges. Despite increasing use of IF magnetic field-emitting sources such as induction hobs 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. Experimental studies on IF electromagnetic fields do not show any adverse health effects below current guidelines, but since there is only a very limited number of such studies available, no conclusions can be drawn at present. Additional studies would be important.

Epidemiology

Only one new study on IF-MF was published, which does not allow any firm conclusions regarding possible health effects from exposure to IF-MF.

Human studies

As for the previous reporting periods, there was no human experimental study in the intermediate frequency range.

Animal studies

Within the kHz frequency range, relevant for wireless power transfer (WPT) systems, one study was identified. Exposure of mice in a model WPT system (47 kHz, 0.27 mT average magnetic induction intensity) resulted in increased cytokine level and mostly unaffected organ morphology except liver in males, spleen in females and gonads of both sexes. The study may provide some first experimental data for a safety assessment of WPT.

Cell studies

No cell studies on effects of IF exposure have been identified in 2020.

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, base stations and wireless local area networks. Among parts of the public there is concern about possible adverse health effects associated with exposure to radiofrequency fields. Exposure to environmental sources such as mobile phone base stations can be, in principle, continuously for 24 hours a day, whereas own communication activity is generally much shorter. This may create the impression that environmental sources are most relevant for individual exposure. However, new measurements have shown that devices operating close to the body like mobile and cordless phones or tablets and laptops cause much higher local exposure of the body than environmental sources. And even if cumulated over 24 hours and calculated for the whole body, own communication activities dominate RF-EMF dose to the population. According to new dosimetric calculations, environmental sources play mostly a minor role for cumulative exposure and even less so for local peak exposure on the body.

A topic of particular interest and growing concern with the public is the development of the fifth-generation mobile telecommunication system, or 5G. This is intended to provide better service through higher data rates and faster response rates. The main concern pertains to the use of frequencies that are considerably higher than those currently used for the 3G and 4G systems. To date, however, the 5G technology is rolled out by using frequencies near those currently used by mobile telephony and Wi-Fi such as the 700 MHz and 3.6 GHz bands. In order to provide higher data rates and faster connection, frequency bands of around 26 GHz will be used in the future, although these communication standards have not been defined yet. While quite a lot of scientific studies have been performed into currently used frequency bands up to 3 GHz, only about 100 *in vivo* and *in vitro* studies are available which have considered exposures to frequencies higher than about 6 GHz. There are currently very few studies in the 26 GHz band. Electromagnetic fields at frequencies >30 GHz are called millimetre waves and do not penetrate further than skin-deep in the body. This may be of relevance to take into account in future health evaluations. The Council will report on such studies as they become available.

Epidemiology

Little new research has been published on tumour risk in relation to mobile phone use. A French study found an association between maternal mobile phone use and foetal growth restriction, but retrospectively collected mobile phone use data is a limitation for this study. A new analysis from the COSMOS cohorts including more than 24,000 participants found weak indications for an association between operator recorded mobile phone use and sleep quality. However, insomnia was associated rather to the length of use than to the level of radiation exposure. This suggests that other factors than RF-EMF may explain the observed association. Such factors may include for example stress or other behavioural factors.

In a French cross-sectional study including exposure measurements, no associations were observed between RF-EMF from base station and non-specific or insomnia-like symptoms. However, for insomnia-like symptoms, a significant interaction was found between RF-EMF exposure from mobile phone base stations and environmental concerns, which indicates communication needs with the public about potential health risks from mobile phone base station. New studies in adolescents on cognitive functions and brain volume do not indicate a risk from RF-EMF exposure.

Human studies

The studies published in 2020 underline the following: Heart rate variability is probably not affected by RF-EMF exposure, RF-EMF exposure effects on the resting state waking EEG are less consistent than previously reported (the latest study did not find an effect), and exposure effects on the macrostructure of sleep need to be considered separately for males and females, since at least in the elderly population females seem to be more affected than males. On the other hand, age differences in RF-EMF effects on the macrostructure of sleep seem to be less pronounced – at least in males. Finally, isolated effects of an all-night Wi-Fi exposure on sleep and sleep related memory consolidation seem to be due to chance.

Animal studies

As in previous years, there is again a variety of endpoints with mixed results. This year, most included studies show effects of exposure, a few do not. The exposure parameters, such as frequency, duration and exposure level, again vary considerably between studies. It is therefore difficult to draw general conclusions other than that under certain circumstances some effects from RF EMF exposure are observed in experimental animals. The observations of increased oxidative stress reported in previous SSM reports continue to be found. It is of concern that no less than 30 out of the 54 retrieved studies had to be excluded from analysis because of various reasons. Analyses that include all studies regardless of these flawed studies will provide a biased picture.

Cell studies

In vitro studies published in the year 2020 evaluated the effect of RF exposure on several endpoints, such as genotoxicity, apoptosis, cell cycle progression, gene and protein expression, oxidative stress and autophagy. As for the previous years, in most cases no effect of the exposure was detected, although in a few publications, authors reported effects. However, results across studies were inconsistent. In one study the effect of RF in combination with UV radiation has been evaluated. As for the past years, several studies have been recognized but not considered, due to the scanty quality of the experimental set-up.

Oxidative stress

In recent years, there is an increasing interest in the possible effects of exposure to electromagnetic fields on the balance between oxidative and reductive processes (redox homeostasis). In many *in vivo* and *in vitro* studies effects on the this balance are observed, manifesting mostly in an increase in reactive oxygen species (Schuermann and Mevissen [1]). Does this implicate an adverse health effect?

Reactive oxygen species (ROS) can represent as free radicals. They are generated in a variety of biochemical reactions by oxidising enzymes or as by-products of the normal metabolism of oxygen. Free radicals are unstable molecules that have an unpaired electron in their outer shell and are therefore highly chemically reactive. They can react with several cellular components, potentially harming them. Free radicals can also be generated by exogenous factors, such as alcohol, cigarette smoke, environmental pollutants and ionizing radiation (Møller, Wallin [2]).

For the main part, ROS are beneficial to cells, supporting basic cellular processes and viability. At low or moderate concentrations, they are of crucial importance for several physiological processes, such as regulation of vascular tone, sensing of oxygen tension, regulation of functions controlled by the oxygen concentration and enhancement of signal transduction from various membrane receptors (Droge [3]). They also play a key role in immune responses, especially in the phagocytic processes, intracellular signaling cascade, mitogenic response and in the synthesis of some cellular structures (Genestra [4]; Pacher, Beckman [5]).

In the normal cellular biochemistry, there is a balance between free radical formation and scavenging by the action of an antioxidative system. A number of primary antioxidant enzymes, such as dismutases, catalases, reductases or peroxidases are known to neutralise free radicals. Moreover, several compounds such as reduced glutathione (GSH) and some vitamins also scavenge free radicals. Disturbance of the redox homeostasis by increased quantities of ROS and other free radicals, or by the inhibition of the action of antioxidants, can lead to cellular oxidative stress causing direct oxidative damage in cells and tissues, and may also initiate inflammatory processes. Long-lasting and excessive levels of free radicals can lead to a number of pathological consequences in cells and organisms, including lipid peroxidation, protein damage, deactivation of enzyme activities, and DNA modification as well as inflammation (Droge [3]; Halliwell [6]). Furthermore, modulations in cell functions via signal transduction processes can be induced. Thus, oxidative stress plays a role in cytotoxicity and inflammation eventually leading to the onset of pathophysiological alterations and pathogenesis (Pizzino, Irrera [7]). In addition, oxidative damage has been hypothesised to promote aging and degenerative diseases such as cancer and cardiovascular disease, even though causal relationships are not fully elucidated.

Oxidative stress is a state that cannot be measured in a simple way, also because free radicals have very short half-lives. Various biomarkers have been proposed to represent the state of oxidative stress, such as the release of ROS or the activity or abundance of proteins and antioxidants, regulating the redox homeostasis. Oxidative stress can also be investigated indirectly by detecting e.g. molecular damage on the DNA or proteins.

Notably, changes of ROS as a result of EMF exposure without additional parameter cannot be directly interpreted as oxidative stress. The relevance of changes in ROS production should be estimated by temporal observations and additional endpoints assessing for instance the state of the antioxidative defence system. Nevertheless, it is important to critically assess studies on ROS, because it could provide evidence for a mechanism by which exposure to electromagnetic fields might affect health.

Sammanfattning

I rapporten granskas studier av elektromagnetiska fält och hälsorisker, publicerade från januari 2020 till och med december 2020. Det är den sextonde rapporten i en serie årliga vetenskapliga granskningar som fortlöpande diskuterar och utvärderar relevanta nya data och värderar dessa i förhållande till redan tillgänglig information. Granskningarna leder till en successivt förbättrad uppskattning av hälsorisker från exponering för elektromagnetiska fält.

Oxidativ stress är en av de mest undersökta biologiska parametrarna för att utvärdera möjliga effekter av elektromagnetiska fält och är även under denna period av intresse. Flera *in vivo* och *in vitro* undersökningar har ägnats åt detta ämne. Därför har ett kort stycke om oxidativ stress inkluderats ovan. Det är relaterat till dess inblandning i fysiologiska och patologiska processer och beskriver de viktigaste laboratorieteknikerna som används för att upptäcka oxidativ stress.

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 medicinsk/vetenskaplig utrustning som använder likström, som t.ex. elsvetsutrustningar och olika typer av partikelacceleratorer. Den viktigaste källan till exponering för starka statiska magnetfält (> 1 T) är användningen av magnetkamera 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 exponeras för fält från magnetkameror kan påverkas av dessa övergående fenomen.

Epidemiologi

Yrkesmässig exponering från magnetisk resonanstomografi (MRT) ger akuta och övergående symtom, men som konstaterats i rådets tidigare rapporter är de långsiktiga konsekvenserna för hälsan fortfarande oklara. Forskning om yrkesrelaterad MRT-exponering är knapphändig och bakomliggande mekanismer rörande tillfälligt observerade samband (t.ex. olyckor, högt blodtryck, menometroragi hos kvinnor som använder intrauterina enheter) är oklara. En ny studie om sömnproblem hos personer som är yrkesmässigt exponerade för MRT bidrar till detta mönster. Det faktum att MRT-exponeringen är relativt hög och antalet yrkesexponerade personer ökar, motiverar mer systematisk och heltäckande forskning i detta ämne.

Studier på människa

År 2020 publicerades ingen experimentell studie som bidrar till kunskapen om effekter av statiska fält på människor.

Djurstudier

Vid MRI-undersökning under en timme med starka statiska magnetfält (SMF) i intervallet 7 till 33 T påverkade exponeringen inte signifikant den allmänna hälsan, antalet blodkroppar, blodets biokemi och organmorfologi hos möss. Vidare påverkades brevduvors navigering tillfälligt efter 15 minuters långvarig MR-exponering på 3 T.

Efter exponering för 4,3 mT-12,9 mT SMF uppstod nya omogna neurala celler i hjärnan hos råttor. Hos spontant hypertoniska råttor minskade olikorienterade SMF på 16 mT ångestliknande beteende. Olika musmodeller som exponerades för magnetfältsnivåer runt 58 – 116 mT visade en trend mot en MF-intensitetsberoende antitrombotisk effekt, men ingen tydlig effekt på typ 1 och typ 2 diabetes. Ökad rörelse hos kackerlacka triggades av långvarig exponering för ett 110 mT SMF. Slutligen ökade MF längs undervattenskablar med högspänningslikström (HVDC) det utforskande beteendet mer hos elkänsliga rockor än hos humrar.

Cellstudier

Ett stort antal *in vitro*-studier som undersöker effekten av statiska fält har publicerats år 2020. I de flesta fall saknar de oexponerade kontroller, eller så har exponeringen utförts med kommersiella utrusningar utan adekvat dosimetri. De har därför har de inte inkluderats. Dessutom har studier som är relaterade till biomedicinska tillämpningar av statiska fält inte heller inkluderats. Sammantaget inkluderades endast två studier, de handlar om genuttrycket som regleras av reaktiva syrearter och med förmågan att stimulera eller undertrycka neuroexcitabilitet. Resultaten av de *in vitro*-studier som identifierats under denna period tyder på att statiska fält kan inducera små biologiska förändringar när det gäller proteinkonformation, cellviabilitet och kemiskt inducerad oxidativ stress.

Lågfrekventa fält

Allmänheten exponeras för lågfrekventa fält (>0-300 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 årens studier inte entydigt på samband. Inga nya undersökningsmetoder har emellertid använts i dessa 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 något orsakssamband har inte kunnat fastställas.

Epidemiologi

Aktuella studier kan inte fastställa om det finns ett orsakssamband mellan det frekvent observerade sambandet mellan exponering för lågfrekventa magnetfält och barnleukemi eller inte.

Nya epidemiologiska studier om samband mellan barnleukemi och föräldrars exponering eller exponering i hemmet ligger i linje med tidigare forskning; studierna indikerade inga samband med föräldrars exponering, medan tidigare observerade samband med exponering i hemmet återigen observerades i Mexico City. En kalifornisk studie visade ingen indikation på att bostadstyp skulle vara en kritisk förväxlingsfaktor för denna forskningsfråga.

Flera studier om vuxencancer observerade inte ökade risker, medan en liten studie om hjärntumörer kopplat till närhet till kraftledningar rapporterade osannolikt höga riskestimat, vilket indikerar att slump eller metodfel kan ha stor betydelse för slutsatserna i denna studie. En stor ny studie om motorneuronsjukdom visade att elektriska stötar snarare än magnetfält kunde vara relevanta. Detta i motsats till resultaten av nya metaanalyser, vilka fortfarande lämnar det obesvarat huruvida magnetfält eller stötar kan vara orsak till de tidigare observerade associationerna.

Studier på människa

Antalet studier som identifierats är fortfarande litet med endast tre publicerade studier under rapporteringsperioden. En metodologiskt svag studie observerade effekter av bröstexponering i fyra av sex parametrar för hjärtfrekvensvariabilitet, som inte observerades i en grupp oexponerade försökspersoner. Den andra, metodologiskt sunda, studien observerade inga effekter på postural modulering hos personer med högersidig ELF-EMF-exponering vid det vestibulära systemet. Den tredje studien understryker att ELF-MF-exponering inducerar fosfenperception vid individuellt varierande tröskelnivåer när huvudet exponeras för en homogen 50 Hz sinusformad signal.

Djurstudier

I likhet med rådets tidigare rapporter, baserades studierna mestadels på 50/60 Hz ELF och exponeringsnivåer runt 1 mT magnetfält (MF) och 5-35 kV/m elektriska fält (EF).
Långvarig exponering av råttor för 50 Hz, 0,03 mT till 1,5 mT ELF-MF hade inga signifikanta kliniska eller biologiska effekter på djuren. Kortvarig användning av olika pulserade magnetfält (PMF) på 1 mT ledde till motsägelsefulla resultat avseende smärtkänslighet hos råttor. En musstudie kopplat till ultrahögspänningsöverföringsteknologi (UHV) och med användning av ELF-EF (50 Hz, 35 kV/m) visade morfologiska njurförändringar efter upp till 3 veckors exponering, vilka återställdes efter längre pågående exponering. En ELF-EF på 50 Hz och 5,4 kV/m orsakade oxidativ stress och

degeneration av spermatogoni hos råttor. Hos honungsbin som utsätts för samma intervall av 50 Hz EF (5 – 34,5 kV/m) tolkas ökade enzymaktiviteter hos antioxidant- och proteolytiska systemen som en allmän första försvarsmekanism mot en miljöstressfaktor. Dessutom stressades kackerlacksnymfer av en 5 månader lång 50 Hz, 10 mT ELF-MF-exponering. Och hos nematoden *C. elegans* kan kronisk exponering för en 50 Hz 3 mT MF under flera generationer öka kroppslängden och öka antioxidantkapaciteten.

MF runt 0,2 mT, det vill säga vid intensiteter jämförbara med de som produceras i närheten av högeffektssjökablar, påverkar inte nämnvärt beteendet hos unga europeiska humrar. Men kortvarig exponering (upp till en vecka) av mollusk *O. struma* för en liknande låg intensitet på < 0,5 mT framkallar visst immunsvar. Slutligen påverkades inte embryonal utveckling av japansk vaktel och zebrafisk efter exponeringar i och under mT-intervallet.

Sammantaget uppvisar de olika djurmodellerna, som beskriver effekter av exponering för ELF-MF upp till 1 mT, fortfarande kunskapsluckor när det gäller biologiskt relevanta mekanismer för ELF-MF, förutom oxidativ stress.

Cellstudier

In vitro-studier som publicerades år 2020 utvärderade effekten av ELF-fält på cellers tillväxt, cellcykelprogression, apoptos, redoxcellstillstånd och DNA-integritet. I en studie jämfördes känsligheten för ELF-fält i traditionella och 3D-cellkulturer. I de flesta fall ökade eller minskade cellviabiliteten på basis av de antagna experimentella förhållandena (exponeringens varaktighet, frekvens och fältintensitet). De inkonsekventa mönstren gör resultaten svårtolkade. Flera studier har noterats men inte beaktats på grund av den experimentella designens knappa kvalitet (avsaknad av lämpliga oexponerade kontroller).

Intermediära fält

Det intermediära frekvensområdet (300 Hz-10 MHz), IF, 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 eventuella hälsorisker utvärderats endast i mycket liten utsträckning. Exponeringsuppskattningen, särskilt för inducerade elektriska fält i kroppen, är fortfarande en utmaning för den här typen av exponeringskällor. De experimentella studierna avseende exponering för intermediära fält visar inte på några skadliga hälsoeffekter under gränsvärdena, men eftersom det endast finns ett mycket begränsat antal studier tillgängliga kan inga slutsatser dras för närvarande. Ytterligare studier skulle vara värdefulla.

Epidemiologi

Endast en ny studie om IF-MF publicerades, utifrån vilken man inte kan dra några säkra slutsatser om möjliga hälsoeffekter av exponering för IF-MF.

Studier på människa

Liksom för de tidigare rapporteringsperioderna fanns det ingen experimentell studie på människor i det intermediära frekvensområdet.

Djurstudier

Inom kHz-frekvensområdet, som är relevant för trådlös kraftöverföring (WPT), identifierades en studie. Exponering av möss i ett WPT-system (47 kHz, 0,27 mT genomsnittlig inducerad magnetisk flödestäthet) resulterade i ökad cytokinnivå och mestadels opåverkad organmorfologi förutom levern hos hanar, mjälten hos honor och gonader hos båda könen. Studien kan ge några inledande experimentella data för en säkerhetsbedömning av WPT.

Cellstudier

Inga nya studier på effekter av intermediära fält har identifierats under 2020.

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 eventuella negativa hälsoeffekter som skulle kunna orsakas av exponering för radiofrekventa fält. Exponering för radiofrekventa fält från omgivningskällor som basstationer för mobiltelefoni kan i princip pågå dygnet runt, medan exponeringen från den egna mobiltelefonen i allmänhet är mycket kortare. Det kan skapa intrycket av att omgivningskällor har större betydelse för den personliga exponeringen. Mätningar har dock visat att de högsta exponeringsnivåerna orsakas av användning av egen mobiltelefon, läsplatta och bärbar dator. Även om exponeringen summeras över dygnet och beräknas för hela kroppen så dominerar den egna kommunikationsutrustningen den samlade exponeringen. Enligt nya dosimetriberäkningar spelar omgivningskällor för det mesta endast en mindre roll för den kumulativa helkroppsexponeringen och ännu mindre för lokal exponering.

Utvecklingen av den femte generationens mobila kommunikationssystem, 5G, är av särskilt intresse och medför ökande oro hos delar av allmänheten. Avsikten med att införa 5G är att öka kommunikationssystemens användbarhet genom högre datahastigheter och snabbare svarstider. Den huvudsakliga oron rör avsikten att utnyttja frekvenser som ligger avsevärt högre än de som används idag för 3G- och 4G-systemen. Hittills har dock den 5G-teknologi som tagits i bruk utnyttjat frekvenser som ligger nära de som redan används i 3G- och 4G-systemen, dvs. frekvensband runt 700 MHz och 3,6 GHz. För att kunna nå högre datahastigheter och snabbare uppkoppling kommer frekvensband på cirka 26 GHz att börja användas på längre sikt. Dessa kommunikationsstandarder har dock inte definierats ännu. Medan ett stort antal vetenskapliga studier har genomförts för de frekvensband upp till 3 GHz som används idag, finns bara cirka 100 *in vivo*- och *in vitro-studier* tillgängliga för frekvensband högre än 6 GHz. Mycket få studier är gjorda på frekvenser i 26 GHz-bandet. Elektromagnetiska fält med frekvenser över 30 GHz kallas millimetervågor och tränger inte in längre i kroppen än huden. Detta är viktigt att ta i beaktande i framtida utvärderingar av hälsoeffekter. Rådet kommer att rapportera om sådana studier när de blir tillgängliga.

Epidemiologi

Lite ny forskning har publicerats om tumörrisk i relation till mobiltelefonanvändning. En fransk studie fann ett samband mellan moderns mobiltelefonanvändning och begränsning i fostrets tillväxt, men retrospektivt insamlad mobiltelefonanvändningsdata är en begränsning i denna studie. En ny analys från COSMOS-kohorterna bestående av mer än 24 000 deltagare fann svaga indikationer på ett samband mellan operatörernas registrerade mobiltelefonanvändning och sömnkvaliteten. Emellertid var sömnlöshet snarare förknippad med användningstiden än exponeringsnivån. Det tyder på att andra faktorer än RF-EMF kan förklara det observerade sambandet. Sådana faktorer kan till exempel inkludera stress eller andra beteendefaktorer.

I en fransk tvärsnittsstudie med noggranna exponeringsmätningar observerades inga samband mellan RF-EMF från basstationer och ospecifika eller sömnlöshetsliknande symtom. Men för sömnlöshetsliknande symtom fann man en signifikant samband mellan RF-EMF-exponering från basstationer för mobiltelefoni och omgivningsfaktorer, vilket visar behovet av kommunikation med allmänheten om möjliga hälsorisker från mobiltelefonbasstationer. Nya studier på ungdomar om kognitiva funktioner och hjärnvolym tyder inte på någon risk kopplat till RF-EMF-exponering.

Studier på människa

Studierna som publicerades 2020 understryker följande: Hjärtfrekvensvariationer påverkas troligen inte av RF-EMF-exponering, RF-EMF-exponeringseffekter på vakna vilotillståndets EEG är mindre konsekventa än vad som tidigare rapporterats (den senaste studien hittade ingen effekt), och exponeringseffekter på sömnens makrostruktur måste beaktas separat för män och kvinnor eftersom kvinnor verkar vara mer påverkade än män, åtminstone i den äldre befolkningen. Å andra sidan verkar åldersskillnaderna när det gäller effekter av RF-EMF på sömnens makrostruktur vara mindre uttalade, åtminstone hos män. Slutligen verkar effekter från en nattlång Wi-Fi-exponering på sömn och sömnrelaterad minneskonsolidering bero på slumpen.

Djurstudier

Liksom tidigare år har det återigen undersökts en mängd olika parametrar med blandade resultat. I år visar de flesta ingående studier effekter av exponering, medan ett fåtal inte gör det. Exponerings-parametrarna, såsom frekvens, varaktighet och exponeringsnivå, varierar återigen avsevärt mellan studierna. Det är därför svårt att dra några andra generella slutsatser än att vissa effekter från RF EMF-exponering har observerats i djurförsök under vissa omständigheter. Observationerna av ökad oxidativ stress som rapporterats i tidigare SSM-rapporter förekommer fortfarande. Det är oroande att inte mindre än 30 av de 54 funna studierna har behövt exkluderas från sammanställningen på grund av olika brister. Analyser som inkluderar även dessa bristfälliga studier kommer ge en snedvriden bild.

Cellstudier

In vitro-studierna som publicerades år 2020 utvärderade effekten av RF-exponering på flera parametrar, däribland genotoxicitet, apoptos, cellcykelprogression, gen- och proteinuttryck, oxidativ stress och autofagi. Liksom för tidigare år upptäcktes i de flesta fall ingen effekt av exponeringen, även om författarna i ett fåtal publikationer rapporterade effekter. Dock var studiernas resultat inkonsekventa. I en studie har effekten av RF i kombination med UV-strålning utvärderats. Som för de senaste åren har flera av de funna studierna inte beaktats på grund av den bristfälliga kvaliteten på experimentens upplägg.

Oxidativ stress

Under de senaste åren har intresset ökat för möjliga effekter på balansen mellan oxidativa och reduktiva processer vid exponering för elektromagnetiska fält. I många *in vivo*- och *in vitro*-studier observeras effekter på denna balans, vilket främst visar sig i en ökning av reaktiva syrearter (Schuermann och Mevissen [1]). Men innebär det negativa hälsoeffekter?

Reaktiva syreföreningar (ROS) kan representeras som fria radikaler. De genereras i en mängd olika biokemiska reaktioner genom att oxidera enzymer eller som biprodukter av den normala syremetabolismen. Fria radikaler är instabila molekyler som har en oparad elektron i sitt yttre skal och därför är mycket kemiskt reaktiva. De kan reagera med flera cellulära komponenter och potentiellt skada dem. Fria radikaler kan också genereras av externa faktorer, såsom alkohol, cigarettrök, miljöföroreningar och joniserande strålning (Møller, Wallin [2]).

ROS är till största delen fördelaktiga för celler, genom att de stöder grundläggande cellulära processer och livskraft. Vid låga eller måttliga koncentrationer är de av avgörande betydelse för flera fysiologiska processer, såsom reglering av vaskulärt motstånd, avkänning av syrespänning, reglering av funktioner som styrs av syrekoncentrationen och förstärkning av signaltransduktion från olika membranreceptorer (Droge [3]). De spelar också en nyckelroll i immunsvar, särskilt i fagocytiska processer, intracellulär signalering, mitogena svar och i syntesen av vissa cellulära strukturer (Genestra [4]; Pacher, Beckman [5]).

I den normala cellulära biokemin finns det en balans mellan bildning och avlägsnande av fria radikaler genom inverkan av ett antioxidativt system. Ett antal primära antioxidantenzymer, såsom dismutaser, katalaser, reduktaser eller peroxidaser är kända för att neutralisera fria radikaler. Dessutom avlägsnar flera föreningar såsom reducerat glutation (GSH) och vissa vitaminer också fria radikaler. Störning av redoxhomeostasen genom ökade mängder ROS och andra fria radikaler, eller genom hämning av av antioxidanters verkan, kan leda till cellulär oxidativ stress som orsakar direkt oxidativ skada i celler och vävnader, och kan också initiera inflammatoriska processer. Långvariga och överdrivna nivåer av fria radikaler kan leda till ett antal patologiska konsekvenser i celler och organismer, inklusive lipidperoxidation, proteinskador, deaktivering av enzymaktiviteter och DNA-modifiering samt inflammation (Droge [3]; Halliwell [6]]). Vidare kan moduleringar i cellfunktioner via signaltransduktionsprocesser induceras. Sålunda spelar oxidativ stress en roll i cytotoxicitet och inflammation som slutligen leder till uppkomsten av patofysiologiska förändringar och patogenes (Pizzino, Irrera [7]). Dessutom har oxidativ skada antagits främja åldrande och degenerativa sjukdomar som cancer och hjärt-kärlsjukdom, även om orsakssambanden inte är helt klarlagda.

Oxidativ stress är ett tillstånd som inte kan mätas på ett enkelt sätt eftersom fria radikaler har mycket korta halveringstider. Olika biomarkörer har föreslagits för att representera tillståndet av oxidativ stress, såsom frisättning av ROS eller aktiviteten eller överflöd av proteiner och antioxidanter, som reglerar redoxhomeostasen. Oxidativ stress kan även utredas indirekt genom att detektera exempelvis molekylär skada på DNA eller proteiner.

Noterbart är att förändringar av ROS som ett resultat av EMF-exponering utan ytterligare parameter inte direkt kan tolkas som oxidativ stress. Relevansen av förändringar i ROS-produktion bör uppskattas genom tidsmässiga observationer och ytterligare biologiska parametrar som bedömer till exempel tillståndet för det antioxidativa försvarssystemet. Det är ändå viktigt att kritiskt bedöma studier om ROS, eftersom det kan ge bevis för en mekanism genom vilken exponering för elektromagnetiska fält kan påverka hälsan.

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, animals and *in vitro* studies. Where relevant, studies on biophysical mechanisms, dosimetry, and exposure assessment can also be considered. A health risk assessment evaluates the evidence within each of these sectors with the aim to eventually weigh together the evidence across the sectors to provide a combined assessment. Such a 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 (e.g. therapeutical studies), 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]. Reasons why individual studies were excluded are listed in the appendix to the report. Systematic reviews and meta-analyses are mentioned and evaluated, whereas narrative and opinion reviews are generally not considered.

The Council considers it to be of importance to evaluate both studies indicating that exposure to electromagnetic fields has an effect as well as studies indicating a lack of an effect. In the case of studies indicating effects, the evaluation focuses on alternative factors that may explain the result. For instance, in epidemiological studies it is assessed with what degree of certainty it can be ruled out that an observed effect is the result of bias, e.g. confounding or selection bias, or chance. In the case of studies that do not indicate effects, it is assessed whether this might be the result of (masking) bias, e.g. because of too small exposure contrasts or too crude exposure assessment. It also has to be evaluated whether the lack of an observed effect could be 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 and external 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(s) 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

[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] 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).

sector with respect to a given outcome. This includes taking into account the observed magnitude of the effect and the quality of the studies.

In some cases, in an overall evaluation phase, the available evidence may be 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 such a 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* studies and other data depends on how much weight is given on each line of evidence from different categories. For assessing effects on humans, 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 higher 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. Where this is relevant and possible, also effects on other species are taken into account.

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 exposure to 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 the International Agency for Research on Cancer (IARC) to the overall evaluation of ELF magnetic fields as “possibly carcinogenic to humans” (Group 2B).

1 Static fields

1.1 Epidemiological studies

Occupational exposure from magnetic resonance imaging (MRI) causes acute and transient symptoms, but as stated in previous Council reports, long-term consequences for health remain unclear. Among sporadic observed associations are possible risks of menometrorrhagia in women using intrauterine devices, accidents during commuting and high blood pressure. This could reflect true causal associations or alternatively underlying other factors related to MRI work and the outcomes under investigations.

1.1.1 Sleep

Because of earlier findings of a possible increased accident risk among exposed imaging technicians Huss, Schaap [8] discussed in SSM report 2019:08), the association between occupational exposure to MRI-related magnetic stray fields and sleep quality was investigated in a cross-sectional study of 490 imaging technicians in the Netherlands Huss, Özdemir [9]. Imaging technicians filled in questionnaires about MRI exposure, lifestyle, work practices and sleep quality and quantity. Of six sleep domains and three different MRI exposure proxies, two significant associations were observed after adjustment for several potential confounders (e.g. age, sex, evening- and night shifts). Study participants who were present in an MRI room during image acquisition in the past 4 weeks had a higher risk for sleep disturbances (OR 1.93, 95% CI 1.00–3.70), and among participants who entered an MRI room more often (7–20 days) in the past 4 weeks non-optimal sleep duration was observed more often (OR 1.95, 95% CI 1.11–3.44) than among technician who entered MRI room sometimes (1–6 days).

This is a unique observation in a cross-sectional study, which needs confirmation in a larger study, preferably with better time resolution and improved exposure assessment, given the well-established fact that MRI exposure causes acute symptoms.

1.1.2 Conclusions epidemiology

Research on occupational MRI exposure is scarce and underlying mechanisms for occasionally observed associations are unclear. This new study contributes to this pattern. Given that MRI exposure is relatively high, and the number of occupationally exposed persons is increasing, more systematic and comprehensive research on this topic is warranted.

1.2 Human studies

Overall, the number of studies investigating the impact of static magnetic fields in humans was low during the past years. While in 2019 there was at least one experimental human study, in 2020 none was published.

1.2.1 Conclusions on static field human studies

In 2020 no experimental study was published that contributes to the knowledge about effects of static magnetic fields on humans.

1.3 Animal studies

For the reporting year 2020, five experimental studies using rats and mice were identified, while four papers described exposures of non-mammalian species. In one study rats' brain was exposed to static magnetic fields (SMF) in the range of 4.3 – 12.9 mT. A second rat study tested differently orientated SMF with mean induction of 16 mT. Two series of mouse studies were run with SMF strengths of 58 – 116 mT, while in another mouse experiment strong magnetic fields up to 33 T were applied.

Studying behaviour, the non-mammalians covered homing pigeons, lobster, skates, and cockroach. Except the pigeon study with 3 T, the field intensities were in the range from 50 µT to 10 mT and aimed to address anthropogenic SMFs like subsea cables and high voltage power lines.

1.3.1 Brain and behaviour

Ben Yakir-Blumkin, Loboda [10] exposed the brain of five male adult (approx. 300 g) Sprague Dawley rats by use of an implanted magnetic disc. The average SMF strength at the subventricular zone (SVZ) was 4.3 mT and 12.9 mT at the inner neocortex. Another five (non-magnetic disc-implanted) rats served as sham controls. A further five males (not implanted) formed the naïve control group. After 21 days of SMF exposure cell proliferation in the SVZ was enhanced, and in the neocortex new immature doublecortin expressing cells were observed. Therefore, the findings demonstrate a pro-neurogenic effect of the applied SMF. This effect should be supported by an independent further study.

Tasic, Lozic [11] evaluated potential effects of sub-chronic SMF exposure on behaviour, haematological parameters, and organ morphology of spontaneously hypertensive rats (SHR). Groups of n=11 male SHR were continuously exposed to upward and downward oriented 16 mT SMF for a period of 30 days. A further 11 rats exposed to the natural GMF (48µT, 61°44' inclination) served as controls. Behavioural tests (elevated plus maze, open field, and grooming) were performed. Brain, heart, kidney, spleen, bone marrow of tibia and blood were analysed. SMF of either orientation caused less anxious-like behaviour compared to controls. In downward oriented SMF-exposed SHR a significant decrease in grooming microstructure demonstrated the lowest stress level. SMF of both orientations significantly decreased the numbers of platelets number in blood, and granulocytes in spleen and bone marrow, whereas the number of erythrocytes in the spleen was increased. Upward oriented SMF significantly decreased the number of blood lymphocytes and bone marrow erythrocytes. Bone marrow lymphocytes were increased following exposure to downward oriented SMF. Histomorphological changes of heart and kidneys were not seen.

In summary, moderate intensity SMF (16 mT) reduced anxious like behaviour in SHR and showed some varying effects of differently oriented SMF on cell counts in bone marrow, spleen, and blood.

1.3.2 Physiology, pathophysiology and oxidative stress

Li, Liao [12] used three different thrombosis models testing the effects of three SMF intensities on thrombosis in rats and mice. Each model comprises one intact animal group and four thrombosis groups, i.e. one sham- and three SMF-exposed groups. SMF exposure was performed by use of magnetic sandwich boards utilizing three kinds of magnets with MF strengths of 200, 400, and 600 mT, respectively. The boards were placed at the bottom of the SMF exposure cages. Scans in the animals' housing area at 0.5, 2, or 4 cm above the plates resulted in peak intensities of 58±8 mT, 107±5 mT, and 116±3 mT, respectively. In the following and to simplify, SMF groups are labelled as "200 mT, 400 mT, and 600 mT," respectively.

Male Sprague-Dawley rats (2 x 40, n = 8 per group) and 50 male ICR mice (n= 10 per group) were used. Thrombosis was induced after 60 days of exposure: 1) The carrageenan- induced thrombosis model was made by injecting 2% carrageenan (10 mg/kg/rat) subcutaneously, 2) the $FeCl_3$- induced

thrombosis was established with an intraperitoneal (ip) injection of pentobarbital sodium (50 mg/kg/rat) and 3) for the adrenaline-induced thrombosis model mice were given 0.6 mg/kg adrenaline ip.
1) In the carrageenan- induced thrombosis model, the SMF treatments (600 mT) reduced the black tail length (an indicator of thrombosis) of rats, extracorporeal thrombus (200 mT, 400 mT, 600 mT), the mass of wet and dry thrombus (600 mT), and fibrinogen level (200 mT, 400 mT, 600 mT).

2) In FeCl3- induced arterial thrombosis, the SMF exposure resulted in some anti- thrombotic effects. Before thrombus induction SMF treatment decreased blood pressure dose-dependently, but not after FeCl3-induced thrombosis. Plasma plasminogen activator and thrombus mass (wet and dry) was not markedly affected after induced thrombosis, but thrombus protein content decreased MF-dependently (200 mT, 400 mT), significantly only in 600 mT exposed rats. Finally, tissue- type plasminogen activator was downregulated at 200 mT.) In the adrenaline- induced thrombosis in mice, the SMF treatment influenced the diameter and blood flow velocity of auricle vessels' microcirculation. Within 5 min of adrenaline treatment the auricle venous and arterial diameter in sham and SMF groups were decreased compared with the (non-adrenaline-treated) normal group. After 10 min, the auricle venous diameter in the 600 mT SMF groups were increased, and after 20 min, auricle venous diameter in all SMF groups (200 mT, 400 mT, 600 mT) were increased, but the values of auricle arterial diameter and auricle blood flow velocity were almost similar between sham- and exposure groups.

In summary, 60 days exposure of moderate intensity SMF improved the blood coagulation index, regulated the blood pressure of rats, and enhanced the auricle microcirculation of mice. The authors explain these effects by a SMF- induced vascular smooth muscle relaxation and blood viscosity reduction. Overall, the applied MF intensities showed a trend towards an anti- thrombotic effect.

In a second paper with an analogous study design, the research group of evaluated the effects of the same SMF (200 mT, 400 mT, 600 mT) on blood glucose of intact and diabetic male ICR mice. Each of the three experiments [1), 2), 3)] comprises one intact (non-treated) animal group and four exposure groups (sham, 200 mT, 400 mT, 600 mT). Per experiment 50 ICR mice (n= 10 per group) were used. Experimental diabetes tests were done after 60 days of SMF exposure.

1) Starch tolerance and glucose tolerance: On day 60 of exposure(s) the mice were fasted overnight for 12 h, with drinking water freely available, and 3.0 g/kg soluble starch was given by gavage. Fasting blood glucose (FBG) levels were determined at 0, 0.5, 1, 1.5, 2, and 3 h after starch loading. Similarly, mice received 3.0 g/kg glucose[4]. The applied three different SMF (200, 400, 600 mT) and sham exposure did not affect the blood glucose (BG) of intact (non-starch or non-glucose-treated) mice. But following starch administration, BG reached a peak at 0.5–1 h, began to drop at 1.5 h and returned to normal at 3 h; in this connection BG tended to decrease but there was no statistical difference with sham. After glucose administration, similar BG concentration curves were seen with highest FBG values after 0.5h. After 1 and 1.5 hours FBG level was slightly but significantly lowered in the 600 mT group only.

2) Alloxan-induced diabetes type 1: Fifty mice were fasted for 12 h and were injected with 100 mg/kg of alloxan intravenously. Groups of n=10 diabetic mice were sham- and SMF exposed or without exposure cage control-housed over a period of 60 days. Additional 10 mice were selected as the normal (non-diabetic non-exposed) control group. Following an overnight fasting on the 30th and 60th days, mice were given 3.0 g/kg po soluble starch. BG levels were determined as above. Sham and exposed diabetic mice showed mostly similar BG levels following 30 and 60 days. Pancreas histopathology demonstrated focal vacuolar degeneration of pancreatic acinar epithelial cells in the sham diabetics, as well as decreased number of islets, and in islets degenerated and necrotic cells. The islets in the 400 and 600 mT groups were smaller than those in sham, and in the 400 mT group the number of islet cells was slightly increased.

[4] It remains dubious if another 40 mice were used for the glucose tolerance test. Additional inaccuracies were found between text and data presenting figures.

3) High- fat diet + streptozotocin (STZ)- induced type 2 diabetic mice: 50 mice were given high-sugar and high- fat feed. Two weeks later, STZ (80 mg/kg) was injected ip at 3 consecutive days. Then diabetic mice were cage-housed, sham- and SMF exposed for 60 days. Again, 10 control mice were added receiving basal feed and no SMF exposure. FBG was determined every 2 weeks, oral starch tolerance test was done after 4 and 8 weeks. Following SMF exposure, serum total cholesterol (TC), triglyceride (TG), and insulin content were measured, and pancreas histopathology was performed. BG levels of sham and exposed diabetic mice was significantly higher than those in the normal control group at different time points (0, 1, 1.5, 2, and 3 h) before and after starch gavage. Compared to sham, 200 mT and 400 mT exposed diabetic mice, an increased starch tolerance was seen in the 600 mT group after 30 days but not after 60 days. TC significantly decreased after 400 and 600 mT, whereas serum insulin increased following 2 months of 200 and 600 mT SMF exposure. Histologically, the 400 and 600 mT pancreatic islets were relatively small; however, the number of islet cells slightly increased compared with sham.

Taking the three experiments together, no strong or clear SMF intensity-dependent effect was reported. Therefore, the authors' conclusion that the data "suggest that SMF has a protective role in diabetic mice" cannot be supported.

In a follow-up "safety study" addressing magnetic resonance imaging (MRI) field strengths, Tian, Lv [13] assessed effects of 7.0–33.0 T SMFs in mice (compare Tian, Wang [14], Swedish Radiation Safety Authority [15]). Eight groups of n=6 male C57BL/6J mice were exposed in different layers of the magnet to 7.0 T, 11.1 T, 17.8 T, 28.7 T (upper part of the magnet, 'hypogravity' conditions, gr. 1 - 4), to 33 T (center, gr. 5), and to 28.7 T, 17.8 T, 11.1 T (bottom part, 'hypergravity' conditions, gr. 6 - 8). Corresponding sham controls (8 x 6 mice) were handled identically, and further 8 mice were tube-restrained outside the magnet. Following the single 1 h-treatment and conventional housing for another 2 months, all mice were humanely killed. Blood count, blood biochemistry, organ weights, and histomorphology were examined.

Most test parameters remained unchanged. Few exemplary exceptions are a decrease in monocytes to 6.0% in group 2 (11.1 T) vs. the normal range of 6.6-9.90%, increased cholesterol (3.38 mmol/L) and high-density lipoprotein cholesterol levels (2.54 mmol/L) in group 5 (33 T) vs. normal ranges of 2.48-3.29 mmol/L and 1.89–2.43 mmol/L, respectively.

Concluding, single exposure to strong SMF of 7.0–33.0 T for 1 h in adult mice did not result in harmful effects 2 months later. The authors announce a further (third) study addressing potential neurological effects.

1.3.3 Studies in Non-Mammalians

Hutchison, Gill [16] quantified behavioural responses of the American lobster (13 groups of females and males) and the (electro-sensitive) little skate (8 groups of females) to MF emissions of a subsea high voltage direct current (HVDC) transmission cable. Enclosures (lwh: 5.0 x 3.5 x 2.5 m) were similar for both lobster and skate. One group of individuals (n= 2-5) was released into each enclosure. The cable crossed the enclosure, off-centre and at an 86° angle; approximately perpendicular to the long side. This presented a gradient of MF within the treatment enclosure allowing two zones of "high" (>52.6 μT) and "low" (<49.7 μT) MF. Comparable spatial zones were defined at the control enclosure (both 51.3 μT [Earth's magnetic field]). Behavioural parameters were analyzed to determine if animal behaviours were associated with "high" or "low" MF. Multiple statistically significant differences in the behavioural parameters were assessed. The assessment of spatial distribution patterns showed that skates and lobsters both used the full extent of the enclosures, however, they spent significantly different periods of time in the central area of the two enclosures. Skates spent more time in the central area of the control enclosure compared to treatment enclosure, lobsters vice versa. Compared to control exposure, the strongest behavioural response to "high" MF (> 52.6 μT) was found in the little skate, where they were observed to differ significantly in the distance travelled per day, speed of movement, their height from seabed, and proportion of large turns. In addition, the different pattern of spatial distribution, distance travelled, and proportion of larger turns was associated with the zone of "high" MF (>52.6 µT). The lobsters, a putative magneto-sensitive species, also demonstrated statistically significant responses to the MF, in the proportion of large turns and height from seabed. But these parameters were not associated with zones of "high" or "low" EMF. Summarizing, MF along HVDC subsea cables increased exploratory/foraging behaviour more in electro-sensitive skates than in lobsters.

Secondary to the behavioural observations and "unexpectedly, a strong AC magnetic and electric field" with a main frequency of 60 Hz was detected from the HVDC cables which "is not predicted by modern DC models." According to the authors, the AC fields originate most likely from the AC/DC converter stations. Therefore, the behavioural responses as a result of DC only may be somewhat questioned.

Parraga, Tyack [17] used homing pigeons (Columba livia domestica) to test whether clinical magnetic resonance (MR) imaging disrupts orientation of animals that sense the earth's magnetic field. Thirty pigeons built three groups (n = 10/group). Two groups were anaesthetized and exposed to either a 1) constant (no sequence) or a 2) varying (gradient echo and echo planar sequences) 3 T MF for 15 minutes. A third group (3) served as sham control. One day after sham or MF exposures the pigeons were transferred to a for the animals' unknown place 15 km from the home loft. Three weeks later, animals were released from a different unfamiliar site 30 km from the loft. On first release, group 2 showed more variability in the vanishing bearing compared to the other groups, indicating some interference with orientation. On second release, there were no significant differences between groups. In summary, regular clinical MR imaging exposure may temporarily affect the orientation of pigeons (and possibly other magnetoreceptive species).

Taormina, Di Poi [18][5] ran two tests with juvenile European lobsters exposed to 225 ± 5 µT MF: an avoidance/attraction test and a test for exploratory and shelter seeking behaviour. For the avoidance/attraction test, lobsters were 45 min exposed to: 1) AC MF (n=30), 2) SMF (n=31), 3) sham (n=31). For evaluating exploratory and shelter seeking behaviour, additional juvenile lobsters were exposed over 1 week to: 4) AC MF (n=38), 5) SMF (n=35), 6) sham (n=38). Day-light conditions were used to stimulate the sheltering behaviour and facilitate the video tracking of each trial. Each video was evaluated a posteriori using video tracking software. The video analyses demonstrated that juvenile lobsters did not exhibit any change of behaviour when submitted to an artificial MF gradient (maximum intensity of 230 µT). Furthermore, either the lobsters' ability to find shelter or their exploratory behaviour following one week of exposure was not significantly affected and remained similar to sham-exposed individuals. Finally, the authors state that static and AC anthropogenic MF, at intensities comparable to those produced by high power submarine cables at their close proximity, do not significantly impact the behaviour of juvenile European lobsters in daylight conditions.

Todorovic, Ilijin [19] published a second paper about the effects of chronic exposure of cockroach nymphs (*Blaptica dubia)* to SMF as well as to ELF-MF (compare Todorovic, Ilijin [20], Swedish Radiation Safety Authority [15]). Again, one month-old cockroach nymphs (n=10 per group) were exposed for 5 months each: (1) 110 mT SMF, (2) 50 Hz, 10 mT ELF-MF[6], (3) sham exposure. The exposure effects on the insects' fat body and locomotor activity were investigated. Locomotion was monitored in the Open Field test for 10 min and expressed as travel distance, time in movement and average speed while in motion. After testing locomotion, fat body mass and content of its main components (glycogen and total lipids) were determined. In addition, nymphs were weighed after 1 and 5 months of treatment.

[5] The same study review can be found in chapter 2.3.4. Reason. AC is addressed too.

[6] The results following exposure to 50 Hz, 10 mT ELF-MF are described in chapter 2.3.4.

SMF exposure significantly decreased nymph body mass and glycogen content in their fat body compared to the control group. But total total lipid content in the fat body was significantly increased, as well as locomotor activity.

Summarizing, SMF exposure affected the fat body and locomotor activity, which according to the authors possibly is a result of stress.

1.3.4 Summary and conclusions on static magnetic and electric field animal studies

Strong MF in the range of 7 to 33 T did not significantly affect general health, blood cell count, blood biochemistry, and organ morphology in mice. Furthermore, orientation of homing pigeons was temporarily but reversible affected after a 15 min-lasting clinical MR imaging exposure of 3 T.
A pro-neurogenic effect in the neocortex of rats occurred following exposure of 4.3-12.9 mT SMF to the brain. In spontaneously hypertensive rats, differently orientated SMF of 16 mT reduced anxious like behaviour.

Using various mouse models, exposures of 58 – 116 mT, showed a trend towards a MF intensity-dependent antithrombotic effect, but no clear-cut effect on type 1 & type 2 diabetes.
Increased locomotion in cockroach was triggered by chronic exposure to a 110 mT SMF. Finally, MF along high voltage direct current (HVDC) subsea cables increased exploratory/foraging behaviour more in electro-sensitive skates than in lobsters

Table 1.3.1. Animal studies on exposure to static fields

Endpoints	Reference	Exposure SMF / SEF	Exposure Duration and Species	Effect
Rodent studies				
Brain and behaviour	Ben Yakir-Blumkin, Loboda [10]	4.3 – 12.9 mT (implanted disc)	21 d Rat	Pro-neurogenic effect in neocortex.
	Tasic, Lozic [11]	16 mT	30 d Rat (SHR)	Anxious behaviour ↓ Hematological parameters ⥮
(Patho)Physiology	Li, Liao [12]	200, 400, 600 mT	60 d 2 x rat + 1 x mouse thrombosis models	MF intensity-dependent antithrombotic effect (trend!).
	Li, Fang [21]	200, 400, 600 mT	60 d Mouse diabetes models	No clear-cut SMF effect in diabetic mice.
	Tian, Lv [13]	7.0, 11.1, 17.8, 28.7, and 33.0 T	1 h exposure + 2 mo. non-exposure Mouse	No severe long-term effects.
Studies in Non-Mammalians				
Behaviour	Hutchison, Gill [16]	<49.7 µT or >52.6 µT	18-24 h Little skate, American lobster	Increased exploratory behavior at >52.6 µT, more distinct in little skates than in lobsters
	Parraga, Tyack [17]	3 T (MRI)	15 min Pigeon	Orientation temporarily affected.
	Taormina, Di Poi [18]	225 µT	45 min & 1 week European lobster	Avoidance/attraction & exploratory and shelter seeking-behaviour unchanged.
	Todorovic, Ilijin [19]	110 mT	5 mo Cockroach *Blaptica dubia*	Locomotion ↑, bw ↓, Fat body: mass ↓, glycogen ↑, lipids ↑

Abbreviations: ⥮: differing; ↓=decrease(d); ↑=increased; bw: body weight; d: day(s); h: hours; m: male(s); mo: months; SEF: static electric field; SHR: spontaneously hypertensive rat; SMF: static magnetic field; wk: week(s)

1.4 Cell studies

In a study conducted by Pooam, Jourdan [22] it was evaluated whether exposure to a static magnetic field could promote comparable effects on cultured cells as exposure to pulsed electromagnetic fields and therefore clarify whether cellular effects are due to the magnetic or induced-electric fields. To this purpose, human embryonic kidney (HEK) 293 cells were exposed for 10 min and 3 h to a SMF of 500 µT, 2 mT and to a field of less than 200nT, called Low Level Field (LLF). The latter in previous studies has been shown to induce physiological effects on biosynthesis of reactive oxygen species (ROS) in mammalian cell cultures.

By applying Quantitative RT-PCR analysis, the expression of three marker genes that are regulated by ROS and are induced immediately after PEMF stimulation has been recorded, namely KIAA1211, RPS16P5 and TAS2R19. By comparing exposed and sham exposed cultures, different effects on gene expression according to the intensity of the static magnetic field, but not with the exposure durations were detected. In particular, no effects were detected after exposure at 500 µT and 2 mT field intensity, while significant changes in the expression of KIAA1211 were detected even at 10 min exposure to LLF and the expression of RPS16P5 and TAS2R19 resulted increased following 10 min and 3 h exposure ($p<0.05$). The results were obtained from three independent experiments for each condition tested. The authors concluded that static magnetic fields can induce effects of PEMF stimulation on ROS-regulated gene expression.

1.4.1 Conclusions on static field cell studies

The new in *vitro* study add interesting information to investigate the interaction mechanisms of static fields with biological systems. Unfortunately, as for the previous years, several studies had to be excluded from the analysis due to the poor quality of the experimental design.

Table 1.4.1. Cell studies on exposure to static magnetic fields

Cell type	Endpoint	Exposure conditions	Effect	References
Human embryonic kidney (HEK) 293 cells n=3	Gene expression	200 nT, 500 µT, 2 mT 10 min and 3 h	Up-regulation of ROS-regulated genes at 200 nT. No effects at 500 µT, 2 mT.	Pooam, Jourdan [22]

Abbreviations: ROS: reactive oxygen species.

2 Extremely low frequency (ELF) fields

2.1 Epidemiological studies

In the previous Council reports it was concluded that most uncertainty consists in terms of residential ELF magnetic field (ELF-MF) exposure and childhood leukaemia as well as occupational ELF-MF exposure and neurodegenerative diseases, in particular amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). For neurodegenerative diseases, electric shocks have been proposed as an alternative explanation for ELF-MF exposure. However, epidemiological study results were inconsistent, and it remained open whether any of these exposures were related to ALS or AD.

2.1.1 Childhood cancer

Kendall, Bunch [23] investigated paternal occupation at time of birth and risk of bone-tumours and soft tissue sarcomas. All cases diagnosed between 1962 and 2010 were identified from the UK national register of childhood tumours. One control for each case matched on sex, period of birth and geographical region of birth registration was extracted from national birth registers. Self-reported paternal occupation was established from birth records. Based on a job exposure matrix, 33 broad exposure groups (e.g. "agriculture", "heat", "rubber") were formed, including occupational exposure to electromagnetic fields. Of the 5,835 eligible cases identified during the study period 5,255 had complete data for conditional logistical regression with adjustment for occupational social class. Paternal ELF-MF exposure was associated with rhabdomyosarcomas (OR: 1.63, 95% CI: 1.19-2.24, cases=1923) with similar OR (1.49, 95% CI: 0.97-2.28, cases) for the subgroup of embryonal rhabdomyosarcomas. There was no evidence of association with other types of sarcomas or with total bone tumours. Looking at the full study, only three significant associations were observed out of 11 analysed outcomes and 33 exposures. The authors emphasize chance as a likely explanation for the ELF-MF result and noted that they saw no significant associations if applying a Bonferroni correction. The study population was nationwide, register-based and had many cases, however only fathers of 299 cases and 301 controls where EMF-exposed. Exposure was assigned to occupations based on expert knowledge, scientific literature and description of jobs but not based on actual measurements. Exposure assignment pertained to exposures at one point in time, not considering changing exposures over time. Similarly, diagnostic practice is likely to have changed over time. These factors may have reduced the ability to detect associations due to non-differential misclassification. The study setup has previously been used to investigate paternal ELF-MF exposure and risk of childhood retinoblastoma, Wilms tumour, neuroblastoma, CNS tumours and lymphomas without finding evidence of an association. An analysis of leukaemia observed increased ORs for "other leukaemia" (see summary in SSM 2014:16.)

Núñez- Enríquez, Correa- Correa [24] used a case-control study to investigate residential ELF-MF exposure and risk of B-lineage acute lymphoblastic leukaemia (B-ALL) in children (age<16) in Mexico City in the period 2010 -2011. Cases were recruited from the nine Mexico City hospitals treating leukaemia patients. Controls, matched on sex, age and health institution, were recruited from the less specialized hospitals of Mexico City. Control children were required to have no known neoplasms, haematological or allergic diseases, acute infections, or congenital malformations. Participation rates for cases and controls where 81.6% and 81.5%, leaving 297 cases and 412 controls for inclusion into the study. Sociodemographic information on cases and controls was collected from questionnaires. ELF-exposure levels (30-800 Hz) were assessed as the geometric mean of 24-h measurements at the site of the child's bed. Traffic load at residence was assessed from a 5 min count of vehicles on the nearest main street. Unconditional logistic regression was used to analyse data with adjustment for sex, age, health institution, paternal education level, whether the dwelling was a house or an apartment and whether it had sealed floors. Information eliminated during model building included birth weight, traffic density and early life infections. Compared to <0.2 µT, exposure to ≥ 0.4 µT was associated with OR 1.87 (1.04-3.35) and <0.2 µT compared to ≥0.6 µT was associated with

OR 2.32 (95% CI: 1.10-4.93, cases 19, controls 15). In a linear analysis, the OR for B-ALL was 1.06 (0.95% CI: 1.01-1.12) per 0.2 µT increase in ELF-MF. The authors concluded that "ELF-MF evaluated as a continuous variable was associated with a moderate risk of developing B-ALL" and that "exposure to ≥ 0.4 µT was associated with a high risk of B-ALL". The observation that children with high ELF-MF exposure may be at increased risk to develop leukaemia is in accordance with previous studies. The 24 h measurements for exposure assessment is a strength. However, a 5-minute count of traffic load at not standardized hours is very crude and in addition, previous research did not find strong confounding in such studies from traffic.

Amoon, Crespi [25] investigated the potential for dwelling type to confound or modify a possible relationship between ELF from overhead power lines and childhood leukaemia. The study was nested within the California Power Line Study (CAPS), which included 4,879 leukaemia cases diagnosed in California between 1988 and 2008 and matched 4,835 cancer free control children. In the original CAPS-study, distance from dwelling to nearest power line (≥200 kV) was determined from spatial data. For 252 subject dwellings (119 cases and 133 controls) where distance was close enough to potentially elevate magnetic fields, a site visit was performed. The full study sample (1019 cases and 1032 controls) for the present study consisted of the 252 site-visited dwellings, as well as a random sample of 1799 additional subject homes. Google Earth and Google Street View imagery was used to classify all dwellings as single family, duplex, apartment, or mobile home. A possible confounding effect of dwelling type was assessed by comparing fully adjusted (age, sex, SES, ethnicity, maternal age data birth and residential mobility) logistic regression models with and without adjustment for dwelling type. In the full sample, when compared to living >600 m from a power line, living <50 m away was associated with an OR of 1.50 (95% CI: 0.88-2.58) for leukaemia when adjusting for dwelling type. Comparing exposure ≥0.4 µT to <0.1 µT, the corresponding OR was 1.41 (95% CI 0.83-2.38). The results in models without dwelling type adjustment were virtually identical. Reducing the data set to only site-visited dwellings produced slightly higher risk estimates (OR 1.75, 95% CI; 0.84-3.64 and OR 1.70, 95% CI 0.95-3.07), but still resulted in very similar risk estimates with and without dwelling type. The authors concluded that there was little evidence of confounding from dwelling type. The strength of conclusions from this study is limited by the wide confidence intervals reflecting the low number of cases (n=23) and controls (n=15) living <50 m from a power line, particularly since only 6 cases and 2 controls lived in apartments/mobile homes. Even fewer children had MF≥0.4 µT. Also, as pointed out by the authors, the study rests on the assumption that there is no other uncontrolled confounding and is mostly applicable to the CAPS study as assessment and association of exposure, SES and other factors may differ between studies and settings.

2.1.2 Adult cancer

Shah, Boffetta [26] investigated a range of occupational exposures and risk for gastric cancer in a case-control study by pooling individual-level data from 11 pre-existing studies. For five of these studies, available information allowed assigning exposure to occupations of study participants. For analyses, exposure was classified based on the Canadian Job Exposure Matrix and defined as exposure to "UV rays, ionizing radiation, radiation sources, and low-frequency magnetic fields". Based on 426 cases of gastric cancer and 1071 controls and adjusting for a range of factors including diet and H. pylori status, the OR for gastric cancer in this exposed group was 1.30 (95%CI: 1.13-1.50). This broad pooling of exposures including ionizing X- and gamma rays, classified by IARC as group 1 gastric carcinogens, means that the study allows no conclusion as to whether non-ionizing radiation is associated with risk of gastric cancer.

Carlberg, Koppel [27] investigated acoustic neuroma (aka vestibular schwannoma) in relation to occupational ELF-MF exposure in a case-control study based on the previous Swedish case-control studies on use of mobile phones (Hardell et al 2006, Hardell et al 2013). Cases and controls aged 18 to 80 were recruited in the years 1997-2003 and 2007-2009. For the present study, all cases diagnosed with acoustic neuroma (n=310) and all controls in the study (n=3485) were used. Exposure was assessed from self-reported job histories coded according to the Nordisk Yrkesklassificering. These codes were translated to the International Standard Classification of Occupations (ISCO88 and ISCO68) and ELF-MF exposure was subsequently assigned according to the Interocc ELF magnetic field job exposure matrix. In logistic regression models adjusting for age, sex, year of diagnosis and socioeconomic index, cumulative lifetime exposure ≥8.52 µT (90% percentile) was associated with OR 1.2 (0.8-2.0) for acoustic neuroma when compared to exposure <2.33 µT (25% percentile) with no indication of exposure-response associations. Similarly, there was no indication of associations with average or maximum lifetime exposure, or exposure 1-14 years or >14 years before diagnosis. The authors concluded that their study does not indicate an association of occupational ELF exposure and acoustic neuroma. Some exposure misclassification is inevitable when assigning exposure from JEMs and may have driven risk estimates towards the null. Vestibular schwannoma has been previously primarily analysed in association with mobile phone use. The study is in line with two earlier studies that also found no association between occupational ELF-MF exposure and vestibular schwannoma (Baldi, Coureau [28], Forssén, Lönn [29]).

In the framework of the French CERENAT case-control study, Carles, Esquirol [30] investigated whether people living near a high-voltage power line were more likely to develop brain tumours. The study included 273 glioma patients and 217 meningioma patients diagnosed in France between 2004 and 2006 (participation rate: 73%). A total of 980 control subjects (participation rate: 45%) were randomly selected from electoral rolls. The distance of the geocoded home address to the nearest high-voltage power line (<45 kV to 400 kV) was used for exposure assessment, with no distinction made between overhead and underground lines. Various exposure proxies were formed based on duration of exposure and distance to the power line. The data analysis took several possible risk factors (gender, age, education, tobacco and alcohol consumption, pesticide exposure, residential magnetic field exposure and mobile phone use) into account. The majority of the analyses indicated an increased brain tumour risk in relation to various ELF-MF exposure proxies, although the number of exposed cases was small and the risk estimates had wide confidence intervals. As an example, based on 7 exposed cases and 6 exposed controls, the brain tumour risk was 4.33 times higher for people who lived near (<50m) to any high-voltage power line for more than 15 years (confidence interval: 1.11-16.9).

In principle, distance to high-voltage power line is a suitable exposure measure, as recently shown by Amoon, Swanson [31]. The advantage of this approach is that other factors associated with high-voltage power lines can also be accounted for, such as the electric field or electrically charged ions due to corona discharges in highest-voltage power lines. A limitation of this study is that for 31% of the participants, the coordinates of their place of residence were unknown, and substituted by the coordinates of the municipality's town hall building or a main church location. The fact that no distinction was made between overhead and underground lines is another source of uncertainty. The participation rate in control persons is relatively low (45%), which is a potential risk for selection bias. The small number of exposed persons makes the study susceptible for chance findings. It can be assumed that an increased risk by a factor of four in connection with all high-voltage power lines would have already been discovered in earlier studies. For instance, a substantially larger study from England based on 6,781 brain tumour patients and 20,343 control persons did not find evidence of an increased brain tumour risk for persons living within 50 m of the highest-voltage power lines (≥275 kV) (OR =1. 22, 95% CI: 0.88-1.69) or who were exposed to more than 1 µT (OR=1.02, 95% CI 0.47-2.22) or between 0.40 and 0.99 µT (OR=0.92, 95% CI: 0.54-1.55) (Elliott et al. (2013) discussed in SSM report 2014:16).

To explicitly test the hypothesis that charged ions from high voltage power lines may increase the cancer risk among adults, Toledano, Shaddick [32] modelled air ion density within 600 m of high voltage overhead power lines in England and Wales. Tumours of the mouth, lung, and respiratory system diagnosed between 1974–2008 were included. Further, incidence of non-melanoma skin cancer was compared with electric fields within 25 m of power lines. With adjustment for age, sex, area deprivation index and degree of rurality, risk of the 20% highest net air ion density exposed individuals compared with the lowest 20% was not increased for mouth cancer (n=3,061, OR: 0.94, 95% CI: 0.82–1.08), lung cancer (n=26,087, OR: 1.01, 95% CI: 0.95–1.07) and for respiratory system cancers (n=28,134, OR: 1.03, 95% CI: 0.97–1.09), with no trends in risk across exposure categories. Keratinocyte carcinoma was not associated with electric field (OR in the highest compared with the lowest third: 1.23, 95% CI 0.65–2.34). This is a very large study that does not provide evidence that air ion density or electric fields in the vicinity of power lines are a risk factor for adult cancer. A limitation of the study is that the air ion density model was not validated, and it remains unclear how well it reflects long term exposure. The study did not have access to lifestyle information, which may be a relevant confounder (e.g. smoking).

2.1.3 Neurodegenerative diseases

Chen, Mannetje [33] performed a case-control study in New Zealand to analyse if exposure to ELF magnetic fields or risk of electric shocks could be underlying increased risks of motor neuron disease (MND). Of MND cases, about 85% are amyotrophic lateral sclerosis (ALS). Incident and prevalent MND cases identified through the MND registry as well as the hospital outpatient registry were recruited between 2013-2016. Overall, 396 cases and 605 controls, selected from electoral rolls (92% and 48% response rate, respectively) were included into the study. Occupational history was assessed, as were a range of potential confounders, occupations were coded into the NZ Standard Classification of Occupations, and exposures were based on previously developed job exposure matrices. People who had never worked in an exposed job were grouped into the referent category. Logistic regression analyses were adjusted for a range of potential confounders, such as smoking and alcohol consumption, educational level, spine injuries, occupational solvent exposures and a few more. The authors report a range of sensitivity analyses, such as stratified analyses by sex, age (<65, >=65) and latency analyses. Results indicated increased risks for workers in jobs at risk of electrical shocks but not in jobs exposed to higher levels of magnetic fields. For example, workers who were grouped as having ever worked in a job at high potential for electric shocks (compared to low potential) had an OR of 2.01 (95% CI 1.31 - 3.09). In contrast, exposure to magnetic fields mostly resulted in risk estimates below unity. For example, workers ever exposed to high levels of magnetic fields (compared to background) had an OR of 0.71 (95% CI 0.39 - 1.28). Lag time analysis did not provide clear indication of relevant exposure windows. Associations for shocks were more pronounced in the age group below 65 years of age. This is a well performed case-control analysis that managed to analyse the full lifetime history of workers, and where a range of potential confounders were taken into account. Cases were identified via a registry which is certainly a plus, while it is unclear what kind of effect the lower participation rate in controls as compared to cases had on the effect estimates. Overall, the study is interesting and contributes further to the - as yet unclear - evidence as to whether it is magnetic fields, electric shocks or both, that contribute to observed higher risks of MND among exposed workers.

Filippini, Tesauro [34] reported results of an Italian case-control study on occupational and residential exposures and risk of amyotrophic lateral sclerosis (ALS). Cases were recruited from ALS registries between 2008–2011 in the provinces Catania, Modena, and Reggio Emilia, and in the period 2002–2012 in the Novara province. The authors aimed for including four controls per case, recruited from the National Health Service directory of the residents in the study provinces, matched by sex, age (+/-5 years), and province of residence. Response rate was 19%. In total, 95 cases and 135 controls filled in questionnaires that inquired about occupational and residential history, and about occupational and residential exposures. Regarding magnetic field exposures, three risk estimates were reported: one for workers with occupations using “electric or electronic equipment”: OR 0.85 (0.44–1.62); one for “exposure to electromagnetic fields” OR 1.69 (0.70–4.09), and one for “having lived near overhead power lines” OR 2.41 (1.13–5.12). This is a relatively small study with rather low response rate. Of the risk estimates, only the one pertaining to occupations in electric and electronic equipment may be comparable to what has been previously reported in the scientific literature for electrical workers. The others risk estimates rely on self-reported exposures and the reported increased risks could therefore be introduced by recall bias. In particular, the question “having lived near overhead power lines” may be interpreted differently by the responders. Unfortunately, a validation was not performed, which could likely be done by comparing to existing maps of such lines.

Huang, Hu [35] systematically reviewed and meta-analysed cohort and case-control studies that had assessed occupational exposures and risk of dementia, Alzheimer's disease, and vascular dementia. Five cohort and seven case-control studies assessing magnetic field exposures were included. Both cohort and case-control studies found higher risks of dementia (all outcomes combined) for workers in occupations exposed to magnetic fields, with risk estimates 1.26 (95% CI 1.01-1.57, cohort) and 1.30 (95% CI 1.01-1.60, case-control), respectively. Heterogeneity between studies was moderate to high. As such, this meta-analysis is in line with previous similar assessments showing increased risks for dementia or Alzheimers disease (García, Sisternas [36], Jalilian, Najafi [37]) and indicating moderate to high heterogeneity between studies.

Jalilian, Najafi [37] systematically reviewed studies that had assessed occupational exposure to magnetic fields and risk of electric shocks and amyotrophic lateral sclerosis (ALS). The study highlights that summary risk estimates suggest associations of magnetic fields, but not electric shocks, with ALS. However, heterogeneity was high for both associations, and the authors identified study characteristics that were associated with strength of the reported risks. It is therefore unclear if the reported summary risk estimates across very different types of reports are able to separate presence from absence of possible risks.

2.1.4 Reproduction

Ingle, Mínguez-Alarcón [38] included women aged 18-46 years who visited the Massachusetts General Hospital fertility centre. The study was embedded in a larger study with a reported 60% response rate. This particular sub-study included 119 women recruited between 2012 and 2018 who underwent intrauterine insemination (n=123 cycles) or *in vitro* fertilisation (n=163 cycles), who consented to wearing an ELF-MF meter. Outcomes were implantation, pregnancy and pregnancy loss, and live birth (all assessed as successful or not). ELF-MF exposure was assessed with and Emdex Lite, worn by the women for up to three 24h cycles, separated by several weeks. As ELF-MF exposure metrics, the authors evaluated mean, median as well as peak exposures in the separate days but also as a combined metric. Data were analysed using cluster weighted generalized estimating equation (CWGEE) log-binomial models, taking multiple cycles per women into account, and adjusting for a range of potential confounders. Overall, authors reported no evidence for a relationship between personal exposure to MF and the fertility treatment or pregnancy outcomes. Strength of the study include the prospective design applying measurements in the relevant time periods of pregnancy or fertility treatment, and the use of repeated measurements across women. Also, a range of previously criticized factors were taken into account, such as activity profiles, or nausea. Limitations are the small sample size.

Migault, Garlantézec [39] pooled two existing French cohort studies to assess effect of maternal occupational ELF-MF exposure on birth outcomes in 19,894 singleton births. Children were included using the ELFE and EPIPAGE2 cohort, both general-population cohorts. In both cohorts, mothers were included from randomly selected maternity wards in 2011. Information regarding maternal characteristics including occupation was assessed by means of a questionnaire during pregnancy. Occupations were coded into ISCO-88 and ELF-MF exposures were assigned using the INTEROCC job exposure matrix. The authors evaluated extreme (<28 completed weeks), very (28-32 completed weeks) and moderate (32-37 completed weeks) preterm birth. Small for gestational age (SGA) was defined as birth weight below the 10th percentile of the French reference curves. Cumulative exposure calculated over trimesters was evaluated in logistic regression models, adjusted for a range of possible confounders. In analyses of preterm birth, all births were included when evaluating exposure in the first trimester (period 1), extreme preterm birth was excluded from the analysis assessing first and second trimester (period 2), and extreme and very preterm birth was excluded from the analysis of exposure in all three trimesters (period 3). Sensitivity analyses were performed on spontaneous preterm birth (excluding preterm induced labour and preterm caesarean before labour) and on restricting the data set to mothers who worked. For SGA, results did not indicate exposure-response functions, although an increased OR among most exposed mothers in period 3 was observed, with an OR of 1.25 (95% CI 1.02-1.53). For prematurity, the results were more heterogeneous, with two estimates above and one below unity, but for intermediate exposure categories. For spontaneous preterm birth, an increased risk in period 3 was observed in the highest exposed group, with an OR of 1.40 (95% CI: 1.03 - 1.81). Strength of the study include the prospective design. Weakness of the study is that even though the authors managed to include a relatively large group of participants, the number of high exposed women was nevertheless low, with only about 75 women exposed to average workplace levels exceeding 0.4 µT. Only few studies have previously assessed maternal ELF-MF exposure, with mixed results. The current study does not prove or disprove the existence of an association between ELF-MF exposure and birth outcomes.

Zhao, Guo [40] examined the association between exposure to common electrical appliances in early pregnancy and congenital heart disease (CHD) in a case-control study of 585 cases and 1,754 controls from six hospitals in Northwest China recruited from 2014 to 2016. CHD were diagnosed according to ICD-10 classification and all other information including exposure to electrical appliances during pregnancy was obtained by personal interviews with the mothers. According to multiple logistic regression models, mothers exposed to computers (OR: 1.33, 95% CI: 1.03, 1.71), induction cookers (OR: 2.79, 95% CI: 2.19, 3.55), and microwave ovens (OR: 1.53, 95% CI: 1.01, 2.31) during early pregnancy were more likely to give birth to infants with CHD. Reduced risks were observed for neonates whose mothers who wore radiation protection suits (OR: 0.67, 95% CI: 0.52, 0.87) during early pregnancy. Many potential confounding factors have been considered as dichotomized variables. Because the cases and controls differed in many aspects, residual confounding is still of concern in this study. Further, the retrospective exposure assessment is vulnerable to bias and overestimation of the risk. From a physical point of view, radiation protection suits cannot protect from ELF-MF. The fact that this appeared to be protective indicates the presence of bias in this study. The results of this study are not in line with a substantial larger study from Canada with more than 20,000 newborns with heart defects discussed in 15th SSM report Swedish Radiation Safety Authority [15] (Auger, Arbour [41]).

2.1.5 Other outcomes

Zendehdel, Asadi [42] conducted a pilot study on using Fourier Transform Infrared Spectroscopy (FTIR) to investigate DNA and haemoglobin alterations associated with occupational ELF exposure. From an unspecified power plant presumably situated in Iran, the authors recruited 29 exposed and 29 unexposed workers. Exposed workers were males aged 30-46 working as controllers at the plant for 5-12 years. Unexposed workers were volunteering administrative employees. Exposed and unexposed persons were matched on age, work experience and smoking habit, exactly how and how precise is not detailed. By means of a TES-1393 (TEX Electrical electronic corp. Taipei, Taiwan) magnetic field strengths were assessed on four occasions for each of 78, 16 by 16 m squares covering the power plant area. Each cell was assigned the mean field strength of the four measurements and the 29 exposed workers were assigned exposure based on checklists on time spent in each cell during their shifts. The mean magnetic field strength was 0.85 µT among exposed and 0.5 µT among unexposed. Blood was sampled from all participants and DNA and haemoglobin extracted and after preparation, FTIR spectra were obtained and normalized. Students t-test, Mann-Whitney U-tests and principal component analysis were used to compare the two groups. Analyses were not adjusted for potential confounders. Haemoglobin level in exposed (15.67 +- 1.42 g/dL) was reported to be significantly higher (p=0.0001) than the (unreported) level among unexposed. There were also significant differences in spectral bands related to haemoglobin structure and functional base groups in DNA. The authors conclude that their findings support that ELF magnetic field cause qualitative changes in DNA and haemoglobin structure and that the method can be used to present the effect of ELF magnetic field toxicity.
The study is limited by its small size, and multiple comparisons increase the risk of chance findings. Cross-sectional studies comparing two different groups have a high risk for bias and it is not substantiated that the observed differences are associated with the magnetic fields as many other

factors may vary between the two groups. Finally, it is not clear if the observed effects are outside the norm or medically relevant.

Hosseinabadi, Khanjani [43] investigated the possible effect of occupational exposure to ELF-EMF on burnout syndrome and the severity of depression including the role of oxidative stress among thermal power plant workers. In this cross-sectional study, they compared 115 exposed power plant workers with 124 unexposed administrative employees. According to measurements at the workplace, ELF-MF were on average 23.8 µT for power plant workers and 1.4 µT for administrative personnel (electric fields 24.9 and 3.8 V/m). Oxidative stress markers malondialdehyde and superoxide dismutase (SOD) were significantly higher in the exposed group compared to the unexposed group, although no confounders were considered in the analysis. The exposed group reported a higher prevalence of burnout syndrome and higher depression severity. Cross-sectional studies comparing two different worker groups like in this study, have a high risk for bias. Since this study did not consider other risk factors such as age or job demand, the cause for the observed associations remains unclear. Apparently, the same data have also been published in Bagheri Bagheri Hosseinabadi, Khanjani [44], which is not further discussed here.

2.1.6 Conclusions on ELF epidemiological studies

New epidemiological studies on childhood leukaemia in relation to paternal exposure or residential exposure are in line with previous research: Studies indicated an absence of associations with paternal exposure, whereas previously observed associations with residential exposure were observed again in Mexico City. A Californian study did not indicate that dwelling type may be a critical confounder for this research question.

Several studies on adult cancer did not observe increased risks, whereas one small study on brain tumours in relation to proximity to power lines reported rather implausibly high-risk estimates, indicating that chance or bias may play a major role. A large new study on Motor Neuron Disease indicated electric shocks rather than magnetic fields could be relevant, but this contrasts with new meta-analyses, leaving this question still unanswered.

2.2 Human studies

While for the two previous reporting periods only one study each could be considered with the endpoint mu-EEG rhythm (Swedish Radiation Safety Authority [45]) and postural control (Swedish Radiation Safety Authority [15]), in 2020 two studies were published, addressing the outcomes cardiovascular system and postural control. One additional study, which did not directly investigate RF-EMF effects but used the exposure to induce phosphene perception, included a brief report on phosphene perception thresholds.

Binboga, Tok [46] investigated the effect of extremely low-frequency electromagnetic field exposure on heart rate (HR) and heart rate variability (HRV) in 34 healthy young males (18-27 years). Subjects were randomly assigned to two study groups, one with sham and one with EMF exposure. Exposure was delivered by a one-dimensional custom-made Helmholtz coil system resulting in a field strength of 26-30 µT at the heart position (sternum) and 3-5 µT at the head position (nasion). Subjects, data analyst, and statistical analyst were blind to the exposure condition, but not the person conducting the experiment. An experimental session consisted of three consecutive 5 min intervals, a pre-exposure period, an exposure period and a post exposure period, during which blood volume pulses were recorded with a photoplethysmographic sensor while the subjects were in a supine position. Changes in six variables characterising time and frequency domains of heart rate variability were analysed separately for each group by a repeated measures ANOVA design. Four of the six parameters increased over time in the EMF group, while they were stable in the sham group. From these results the authors concluded that short-term exposure of the chest region to ELF-EMF could potentially enhance parasympathetic predominance. The researcher conducting the experiment knew the exposure condition and the study was not performed in a double-blind manner. The parallel-group design, and the fact that the person conducting the experiment was not blind, certainly are considerable methodological limitations of the study.

Bouisset, Villard [47] pursued their earlier research on effects of ELF-MF exposure on postural control. Thirty-eight healthy young participants (16 females and 22 males, 24.3 ± 3.51 years old) were analysed with lateral ELF-EMF stimulations of the vestibular system. Direct and alternating current (DC and AC) stimulation of the right vestibular system were delivered by a customized headset coil exposure system. DC stimulation was used as a positive control. Exposure conditions consisted of five seconds of MF (100 mT_{rms}), DC (2 mA), AC (peak ± 2 mA), or no stimulation (CTRL). All trials were randomly distributed. MF and AC stimulations were delivered at 20 Hz, 60 Hz, 90 Hz, 120 Hz, and 160 Hz. Postural modulations were investigated based on spatial orientation and quantity of movement variables. Effects on postural control were seen in the DC stimulation condition, which served as positive control, but, regardless of frequency, not with the lateral ELF-MF stimulations regardless of frequency condition.

In a study with 20 healthy young volunteers (10 females and 10 males, 23.4 ± 1.4 years) Modolo, Hassan [48] aimed at inducing magnetophosphene perception to characterize non-invasively the associated ignition process in men. Ignition is a process of coordinated activation of distant brain regions thought to occur during conscious perception. Participants were exposed to a 50 Hz magnetic field at 11 flux density conditions given in a random order (5 mT steps ranging from 0 -sham- to 50 mT, each repeated 5 times). Each of the 55 exposure conditions had a duration of 5s. EEG was recorded from 64 channels. Each time that the participant began to perceive magnetophosphenes he/she had to press as fast as possible on a button directly synchronized with the EEG acquisition system. As expected, participants did not perceive phosphenes in the sham condition. In the MF exposure condition, phosphene perception began with a 0.28 probability at a threshold of 20 mT when the entire head was stimulated by the homogeneous 50 Hz, sinusoidal signal. At 50 mT, the maximal flux density used in this study, the probability of magnetophosphene perception was close to 1 (0.96). With regard to the ignition process induced by phosphene perception, two functional networks were considered: a network, which reflects local information processing (network segregation) and a network, which reflects global information processing (network integration). Results showed that conscious phosphene perception activated frequency-specific networks. Network integration increased within an alpha-band functional network, while changes in segregation occurred in the beta band.

2.2.1 Conclusions on human studies

The number of studies continued to be very low, last year only three were published. A methodologically weak study observed effects of chest exposure in four out of six parameters of heart rate variability indicating a decrease in stress (increase of parasympathetic activity), which were not observed in a group of unexposed subjects. The other, methodologically sound, study did not observe any effects on postural modulation in subjects with right-sided ELF-EMF exposure at the vestibular system. The third study underlines that ELF-MF exposure induces phosphene perception at individually varying thresholds when the head is exposed to a homogeneous 50 Hz sinusoidal signal.

2.3 Animal studies

Compared to the previous Council report a similar number of studies and endpoints was identified for the reporting year 2020. Eight studies evaluated effects of ELF fields on inflammation, physiology and reproduction in rodents. A further eight studies in highly different non-mammalians described effects on Japanese quail, honeybees, lobster, mollusc, round worm (*C. elegans*) and cockroaches.

2.3.1 Inflammation

Mert and Yaman [49] tested possible effects of two different pulsed magnetic fields (PMF) of 1 mT on inflammation in rats. After baseline measurements, carrageen (CG) was intraplantarly injected in the hindpaw of 35 adult male Wistar rats to induce inflammation. Another 35 males were saline-injected. The 1 mT PMF exposures were performed 3 times (1, 4, and 23 h after CG or saline injection). Two designed different frequencies (PMF-1: 1, 3, 5, 7 Hz or PMF-2: 9, 12, 14 Hz) were applied. Frequencies in sequences were chosen on the basis of literature and researchers' own data. PMF-1 and PMF-2 each were presented in three repeated sequences, and each sequence included four different consecutive pulse trains, each pulse train took 4 min, and the interval between each pulse train was 1 min. I.e., one exposure session lasted 1 h. In total, 70 rats were allocated to groups of 7 animals each: 1) rats with inflammation (CG injection), 2) CG + PMF-1, 3) CG + [PMF-1]sham, 4) CG + PMF-2, 5) CG + [PMF-2]sham, 6) saline-injected rats (control for CG), 7) saline + PMF-1, 8) saline + PMF-2, 9) sham-treated rats with saline, and 10) non-treated intact rats. Following each exposure inflammatory symptoms such as abnormal pain behaviors, hyperalgesia and allodynia, edema, and fever were investigated[7]. All animals were sacrificed after 24 h. Paw tissues were weighed and histologically examined. CG injection gradually decreased the thermal latencies and mechanical threshold and caused significant increases in temperature and mass of paw. Both PMF treatments significantly reduced the temperature and mass in the CG-treated paw. At 24 h post CG injection PMF-1 caused significant increases in the (paw withdrawal) latencies and thresholds after heat and mechanical stimulus. But PMF-2 treatment significantly decreased the latency and threshold. Paw histology showed some anti-inflammatory effects of PMF-1, but no differences between sham and PMF-2 exposure. Summarizing the findings, different pulse designs of PMF treatments may result in contradictory answers on pain sensitivities.

2.3.2 Physiology and Pathophysiology

Di, Dong [50] tested renal function and morphology in continuation of previous research Di, Kim [51] and Di, Kim [51]. Again, groups of n=10 male ICR mice were 24 h/d continuously exposed to ELF-EF (50 Hz, 35 kV/m) for 7, 14, 21, 35 and 49 days[8], added by two groups exposed for 25 and 52 days, another n=10 mice per time-point served as non-exposed controls. The exposure unit was the same as previously used by Di, Gu [52], Di, Kim [51]. Following 7, 14, 21, 35 days of SEF-exposure, serum levels of urea nitrogen (BUN) and creatinine (CREA) were significantly increased, whereas after 49 days both BUN and CREA returned to normal levels. Histopathology and electron microscopy revealed an enlarged Bowman's space, vacuolation of renal tubular epithelial cells and foot process effacement of podocytes after 25 days of exposure, but not after 52 days compared to the respective control groups. The authors conclude that a short-term exposure of mice to a 50 Hz EF caused kidney alterations, which may recover after a longer lasting exposure.

Gunes, Buyukakilli [53] studied the effects of chronic 7 months-exposure of rats to a 50 Hz 1.5 mT MF on the diaphragm. A total of 29 weaned rats were randomly divided into the following groups:
1) MF exposure of 7 male rats,
2) MF exposure of 8 females,
3) sham exposure of 7 males,
4) sham exposure of 7 females.
At the end of the exposure period (4 h/d, 7 months), all rats were sacrificed and examined. Regarding electrophysiological parameters, peak latency and depolarization time of action potentials were significantly increased in MF-exposed male rats (group 1 compared to group 3). Current intensity and the area of action potentials were significantly decreased and increased, respectively, in exposed female rats (group 2 compared to group 4). Muscle contractility was significantly reduced in exposed male and female rats. Serum Ca^{2+} level was significantly decreased in exposed males and K^{+} and Ca^{2+}

[7] Data for the timepoints 1 h (correct 2h!) and 5 h post CG are not referred because they are confusingly presented and there are discrepancies between text and fig. 2 & 3 of the paper.

[8] For the timepoints, 7, 14, 21, 35, and 49 days, it remains questionable whether the mice were the same as used by Di, Kim [48]).

levels were significantly increased in exposed females. The total antioxidant status was significantly decreased in diaphragm tissue of exposed males and significantly decreased in serum of exposed female rats. Electron microscopic evaluation demonstrated normal morphology of the diaphragm. The authors summarize that only few effects of chronic exposure of rats to a 50 Hz magnetic field on the diaphragm were found, which were relatively small and unlikely to be clinically relevant. However, these effects seemed to be gender dependent.

Keser, Bozkurt Girit [54] assessed the acute effects of combined extremely low-frequency magnetic field (ELF-MF) and pterostilbene (Pte) treatment on renal ischemia-reperfusion (I/R) damage. Pte (10 mg/kg daily) was chosen as an antioxidant and anti-inflammatory compound. Adult male Wistar rats were divided in 4 experimental groups: 1) control (n = 9), I/R injury (n = 10), ELF-EMF treated I/R injury (n = 8), and combined Pte and ELF-EMF treated I/R injury (MF-P) (n = 7). After induction of renal I/R, rats were exposed to 50 Hz, 1 mT ELF-MF alone or in combination with Pte for 3 h/d on 5 consecutive days. Kidney homogenates were analyzed by Fourier transformation infrared spectroscopy. Renal ischemia reperfusion resulted in: an altered protein and lipid structure with the dominance of longer acyl chains; a significantly decreased protein to lipid ratio; a slight decrease in lipid, protein, unsaturated lipid content, an unsaturated/saturated lipid ratio; and an increase in membrane fluidity and lipid peroxidation in rat kidneys. After ELF-MF treatment alone those ischemia-induced alterations were partly restored, whereas the combined treatment of Pte + ELF-MF showed a stronger effect towards control values. The authors discuss that due to increased vascular permeability and antioxidant enzyme activities following ELF-MF exposure alone, the combined treatment may have increased the efficacy of endogenous antioxidants by facilitating the delivery of Pte to damaged cells in the I/R affected kidneys.

Zhang, Li [55] exposed 24 male Sprague Dawley rats to a 50 Hz, 500 µT ELF-MF over a period of 24 weeks and 20 h/d. Another 24 rats were sham-exposed. Systolic, diastolic, mean blood pressure (bpm) and heart rate were measured every 4 weeks. After termination of exposure the following parameters and methods regarding the cardiovascular system were looked at: cardiac rhythm (ECG), echocardiography, hemodynamics of left ventricle (ejection fraction, fractional shortening, left ventricular internal diameter, thickness of the interventricular septum and left ventricular posterior wall; cardiac catheterization); morphology and arrangement of cardiomyocytes; gene and protein expression of cardiac remodelling-related genes (ANP, BNP and Myh6; quantitative RT-PCR and western blot), ratio of heart weight to body weight.

ELF-MF exposure had no influence on heart rate, bpm, and pulse rate. Morphology and arrangement of cardiomyocytes were not different to sham-exposed controls. Also, mRNA and protein levels of the above cardiac hypertrophy-related genes were not affected by ELF-MF exposure. After all, cardiac function (detected by echocardiography and cardiac catheterization) was similar between the two groups. Summarizing, significant differences between ELF-MF and sham exposed rats were not seen in any of the parameters relevant for the cardiovascular system.

In continuation, investigated blood, kidney and liver of rats following chronic exposure to 50 Hz MF. Groups of n=30 male Sprague Dawley rats built the following groups: 1) exposure to 30 µT, 2) exposure to 100 µT, 3) exposure to 500 µT MF, 4) sham exposure. During the 24- week exposure period (20 h/d), body mass was recorded weekly, water and food intake biweekly. Hematologic parameters were examined after 12 and 24 weeks, and every 4 weeks blood chemistry was analysed. Following sacrifice, histopathological and immunohistochemical staining of liver and kidney tissue were done; fibrosis- related gene expression (fibronectin and collagen type I/III alpha 1; protein expression of alpha- smooth muscle actin, collagen type I α1 chain and transforming growth factor-β1) and oxidative stress status (hydrogen peroxide, nitric oxide, enzyme activities of the antioxidant enzymes catalase, superoxide dismutase, and total antioxidant capacity) were also detected. Compared to sham, exposure to 30 µT, 100 µT, or 500 µT did not show any effect on body mass, food or water intake. Also, hemogram and blood chemistry were similar between all groups. Microstructure of liver and kidneys were unaffected, too. Finally, fibrosis- related gene expression and oxidative stress status were comparable in the four groups. Concluding, there were no indications for an effect of chronic exposure of rats to a 50 Hz MF on the tested parameters in blood, liver, and kidneys.

A third study using the same study design was published by Wang, Yang [56]. Again, potential effects of ELF-MF on hematologic and biochemical parameters were addressed but a higher MF-intensity (1 mT) was used. Thirty adult male Sprague-Dawley rats were sham-, another 30 animals were ELF-EMF-exposed at 1 mT for 24 weeks and 20 h/d. Blood was taken every 4 weeks. After 24 weeks liver and kidneys were histopathologically evaluated. Compared to (sham) controls no statistical difference of hematologic parameters (total white blood cell count, neutrophil ratio, lymphocyte ratio, red blood cell count, haemoglobin concentration and platelets count) was seen. Also, blood biochemistry (glucose, lipid profile, liver, and renal functional parameters), were similar to sham. Finally, morphology of liver and kidneys was comparable between the groups. In summary, chronic 50 Hz, 1 mT ELF-MF exposure did not alter haematology, blood biochemistry and organ morphology of liver and kidneys.

Summing up the above studies (Zhang, Li [55], and Wang, Yang [56]), in rats chronically exposed to 50 Hz, 30, 100, 500, and 1000 µT ELF-MF no significant effect on the cardiovascular system, on haematology, blood biochemistry, function and morphology of liver and kidneys was seen.

2.3.3 Reproduction

Gazwi, Mahmoud [57] studied 1) the antimicrobial activity and 2) the antioxidant effect of rosemary extract on rat testicular tissue after exposure to an ELF-EF of 50 Hz and 5.4 kV/m. Sixty 2 month-old male albino rats were divided into six groups of 10 animals each: Control, rosemary (5 mg/kg bw), ELF-EF-only (2 h), ELF-EF-only (4 h), ELF-EF (2 h) + rosemary, and ELF-EF(4 h) + rosemary. After 30 days, 5 d/wk, 2 or 4 h/d of ELF-EF exposure, serum samples and testes were obtained.
First, the ethanolic extract of rosemary leaves was active against pathogenic bacteria.
Second: following ELF-EF-only-exposure follicle stimulating hormone (FSH), testosterone, and luteinizing hormone (LH) were significantly decreased in serum. In testes' homogenates of ELF-EF-only-exposed rats, catalase (CAT) activity was low and malondialdehyde (MDA) levels were increased in comparison to the control and rosemary groups. In co-exposed rats (ELF-EF + rosemary) the above hormonal changes, CAT activity, and MDA levels were less pronounced but did not return to control values. Histology of testicular tissue showed degeneration of spermatogonia and some interstitial oedema in ELF-EF-only- treated animals, while pre-treatment with rosemary extract inhibited these effects. The authors conclude that ELF-EF has a "detrimental impact on testicular function by stimulating oxidative stress", whereas rosemary extract suppresses lipid peroxidase and normalizes MAD and CAT levels. Unfortunately, the paper lacks some experimental details such as an exact description of the rat strain, no real sham exposure and an imprecise EF description in the animals' living area.

2.3.4 Studies in non-mammalians

Koziorowska, Depciuch [58] evaluated the effect of ELF-MF (50 Hz, 1.6 mT) at different durations of treatment (2, 6, 12, 24 and 48 h) on honeybees. A total of 400 *A. mellifera carnica* workers were placed on eight Petri dishes 10 cm in diameter (filled with an aqueous sugar solution,10 bees per dish). Four dishes formed a control group (incubated under the same conditions as the corresponding ELF-MF group), the next four were exposed to ELF-MF. This scheme was used for bees incubated/exposed for 2, 6, 12, 24 and 48 h. After exposure bees were frozen (-18°C) for analysis using Fourier Transform Infrared (FTIR) spectroscopy. Following 2 hours ELF-MF exposure the smallest changes were observed in the FTIR spectrum. Compared to controls and after exposures of ≥6 hours pronounced alterations were seen in chemical structures, especially in the IR region corresponding to DNA, RNA, phospholipids and protein vibrations. A further distinct exposure duration-dependency was not obvious.

Lola Costa, Silva Araújo [59] exposed eggs of the of Japanese quail (*Coturnix japonica*) to 60 Hz MF with two different intensities (0.16 mT and 0.65 mT) and performed a morphometric evaluation of embryos and blood vascular network of the yolk sac membranes (YSM). A total of 30 fertilized eggs were divided into the following groups (n=10, respectively): 1) sham exposure, 2) exposure to a 0.16 mT, and 3) exposure to a 0.65 mT MF. After 24 h of egg incubation, an opening of approximately 3 cm^2 was made in each eggshell and subsequently covered with parafilm. This opening allowed the embryo and YSM to be visualized. A 6 h exposure to the MF (3 x 2 hours, with 6-hour intervals in between) started at 54 h of incubation and finished exactly at 72 h. Stereomicroscope images of the vascular network of YSM were evaluated by two methods of fractal dimension: box-counting dimension and information dimension. Embryos were evaluated by body mass, percentage cephalic length and body area.

Embryos exposed for 6 h to the 0.65 mT MF showed a significantly smaller body area and percentage cephalic length compared to 0.16 mT and sham exposure. The fractal dimensions revealed no difference among groups. Consequently, the authors concluded that ELF-MF (60 Hz, 0.16 mT and 0.65 mT) exposure of Japanese quail embryos did not affect vascular network of the yolk sac but might decrease the development of the embryonic body.

Migdał, Roman [60] studied the antioxidative and proteolytic system in honeybees, after exposure to four different intensities of 50 Hz electric fields (EF). Homogeneous 50-Hz EF were generated in the exposure system in the form of a plate capacitor with distance of 20 cm between two electrodes constructed as a squared wire mesh cage (1 m × 1 m, 10 mm × 10 mm grid diameter). Wooden cages containing bees (20 x 15 x 7 cm) were placed in the EF exposure system with field intensities of 5.0 kV/m, 11.5 kV/m, 23 kV/m, and 34.5 kV/m. The duration of exposure was 1 h, 3 h, and 6 h. The study involved 15 groups, each consisting of 10 wooden cages containing 100 two-day-old honeybee workers per cage: Exposure to an electric field of 1) 5.0 kV/m for 1 h, 2) 5.0 kV/m for 3 h, 3) 5.0 kV/m for 6 h, 4) 11.5 kV/m for 1 h, 5) 11.5 kV/m for 3 h, 6) 11.5 kV/m for 6 h, 7) 23.0 kV/m for 1 h, 8) 23.0 kV/m for 3 h, 9) 23.0 kV/m for 6 h, 10) 34.5 kV/m for 1 h, 11) 34.5 kV/m for 3 h, and 12) 34.5 kV/m for 6 h. Groups 13 -15 were the controls for each exposure duration (1 h, 3 h, 6 h). Following exposure, hemolymph was taken and the biochemical parameters superoxide dismutase (SOD), catalase (CAT), ferric ion reducing antioxidant power (FRAP) as well as acidic, neutral, and alkaline proteases were analyzed. The applied E-field increased activities of antioxidant systems. Highest SOD and CAT activities were seen after 1 h in the 34.5 kV/m group. Also increased activities within the proteolytic systems were seen, i.e., in all EF groups the acidic and neutral protease activities were higher than in the corresponding control group. A time-dependent linear increase of acidic protease activities was observed in the 5 kV/m, 11.5 kV/m, and 23 kV/m groups and in the 5 kV/m groups in the case of alkaline protease. Summarizing, all exposure groups revealed a significant increase in one or more enzyme activities of the antioxidant and proteolytic systems, compared to the respective control groups.

In a second study, Migdal, Murawska [61] looked at the effects of exposure of honeybees to a 50 Hz EF in the antioxidative system only. The very same exposure system and EF were used. But the exposure duration was prolonged to 12 hours. Again, 2-day-old honeybee workers were divided into the following groups: 1) 5.0 kV/m, 2) 11.5 kV/m, 3) 23.0 kV/m, 4) 34.5 kV/m and 5) control. Each group consisted of 10 cages with 100 bees, respectively. Hemolymph analysis demonstrated that SOD activity was significantly increased in all EF groups. CAT was slightly but significantly decreased in group 1 and significantly increased in groups 2-4 compared to the control group. The total antioxidative capacity (FRAP) was significantly decreased in group 2 and significantly increased in group 4 compared to the control group 5. The highest values of SOD, CAT and FRAP occurred following 34.5 kV/m exposure but clear-cut EF strength-dependencies were not seen. According to the authors, EF strengths of 5 kV/m and 11.5 kV/m are common in the environment and honeybees can be exposed to them during foraging. EF of 23.0 kV/m and 34.5 kV/m were used to investigate whether higher values will cause different changes in the antioxidative system. Since the antioxidant system is a general first defence system, the results may be discussed in terms of honeybee health in urban and rural environments.

Taormina, Di Poi [18] ran two tests with juvenile European lobsters exposed to 225 ± 5 µT MF: an avoidance/attraction test and a test for exploratory and shelter seeking behaviour. For the avoidance/attraction test, lobsters were 45 min exposed to: 1) AC[9] MF (n=30), 2) SMF (n=31), 3) sham (n=31). For evaluating exploratory and shelter seeking behaviour, additional juvenile lobsters were exposed over 1 week to: 4) AC MF (n=38), 5) SMF (n=35), 6) sham (n=38). Day-light conditions were used to stimulate the sheltering behaviour and facilitate the video tracking of each trial. Each video was evaluated posteriori using a video tracking software. The video analyses demonstrated that juvenile lobsters did not exhibit any change of behaviour when submitted to an artificial MF gradient (maximum intensity of 230 µT). Furthermore, either the lobsters' ability to find shelter or their exploratory behaviour following one week of exposure was significantly affected and remained similar to sham-exposed individuals. Finally, the authors state that static and AC anthropogenic MF, at intensities comparable to those produced by high power submarine cables at their close proximity, do not significantly impact the behaviour of juvenile European lobsters in daylight conditions. The DC part of the study is described in chapter 1.3.3.

Todorovic, Ilijin [19] published a second paper about the effects of chronic exposure of orange-spotted cockroach (*Blaptica dubia*) nymphs exposed to SMF as well as to ELF-MF (compare Todorovic, Ilijin [20], Swedish Radiation Safety Authority [15]). Again, one month-old cockroach nymphs (n=10 per group) were exposed for 5 months each: (1) 110 mT SMF, (2) 50 Hz, 10 mT ELF-MF, (3) control. The exposure effects on the insects' fat body and locomotor activity were investigated. Locomotion was monitored in the Open Field test for 10 min and expressed as travel distance, time in movement and average speed while in motion. After testing locomotion, total nymph body mass, mass of fat body and content of its main components (glycogen and total lipids) were determined. ELF-MF (50 Hz, 10 mT) exposure for 5 months significantly decreased nymph body mass, and mass, glycogen and lipid content of the fat body but significantly increased locomotor activity compared to the control group. Summarizing, ELF-MF exposure affected the fat body and locomotor activity slightly different to SMF. The authors conclude that "*B. dubia* nymphs are sensitive to the applied MFs and possess different strategies for fuel usage in response to the SMF and ELF-MF in order to satisfy increased energy demands and to overcome stressful conditions". The static field part of the study is described in chapter 1.3.3.

Wang, Sun [62] determined effects of chronic exposure to a 50 Hz, 3 mT ELF-MF over multiple generations on growth, metabolism, and antioxidant capacity in the nematode *C. elegans*. The exposure system was already used by Sun, Huang [63], compare Swedish Radiation Safety Authority [15]. Eggs from *C. elegans* were divided in an exposure (50 Hz, 3 mT) and a control group. The hatched individuals were recorded as F1 generation and when they laid eggs, these were collected and after hatching, these individuals were defined F2. This process was continued until the F15 generation. Tests were conducted with worms from different generations. Each test was repeated three times. Body length of ca. 100 each F1, F5, F10, and F15 worms was analyzed at 60 h. In a total number of 20,000 F1 and F15 adult worms (60 h) ATP level and ATPase, and the expression levels of genes encoding ATP synthase (r53.4, hpo-18, atp-5, unc-32, atp-3) were detected by RT-PCR. Furthermore, the level of reactive oxygen species (ROS) was evaluated by dichlorofluorescein staining, and the total antioxidant capacity (T-AOC), superoxide dismutase (SOD) and catalase (CAT) activity were investigated. Finally, the expression of genes encoding superoxide dismutase (sod-1, sod-2, sod-3) was determined in F1 and F15 worms. Compared to controls body length of exposed F15 worms increased significantly but not of F1, F5, and F10. ATP content and ATPase activity were significantly higher increased in exposed F15 worms. Accordingly, the gene expression levels of the r53.4, hpo-18, atp-5, unc-32, and atp-3 genes were significantly upregulated in exposed F15. In addition, SOD activity increased significantly, and the gene expression levels of the sod-1, sod-2, and sod-3 genes were also

[9] Remark: The AC part of the study is incompletely described.

significantly upregulated in exposed F15 worms compared to the control group. The authors summarized that chronic exposure to a 50 Hz MF over multiple generations can increase body length, induce metabolism, and boost antioxidant capacity of *C. elegans*.

Zhang, Wang [64] exposed the mollusc *Onchidium struma* without shell to environmentally relevant ELF-MF and tested the immune response based on immune-related enzyme activities and gene expression. Three experimental groups with exposure durations of 24 h, 72 h, and 168 h each were set: 1) C: unexposed control group, 2) E1: ELF-EMF (50 Hz, 100 µT), and 3) E2: ELF-EMF (50 Hz, 500 µT). Following exposure coelomic fluid was collected and analyzed. All experiments were done in triplicate. Growth performance (body weight, length, width, and height) did not differ between the 3 groups. Compared to groups C and E2, total coelomocyte and spherulocyte density in group El increased significantly (with highest cell counts after 168 h). Amoebocyte and chromatocyte[10] density was similar between the groups. In the coelomic fluid of *O. Struma* enzyme activities of acidic phosphatase, alkaline phosphatase, antioxidative capacity, catalase, superoxide dismutase, and polyphenol oxidase were significantly increased in both ELF-MF groups (E1, E2). In coelomocytes there were 341 differentially expressed genes (DGEs) between E1&E2 versus C, including 209 up-regulated and 132 down-regulated unigenes. After allocation of DGEs to pathways, five pathways were associated with immune response. The authors conclude that short-term (up to one week) exposure of the mollusk *O. struma* to low MF (< 500 µT) elicits an immune response.

2.3.5 Summary and conclusions on ELF animal studies

Again, and similar to the previous Council reports, rodent studies used mostly 50 Hz ELF and exposure levels in the mT range.

Rats' chronic exposure to 50 Hz, 30 µT, 100 µT, 500 µT, and 1000 µT ELF-MF had no significant effect on the cardiovascular system, on hematology, blood biochemistry, function and morphology of liver and kidney, and oxidative status. Also, in rats relatively small but clinically non-relevant effects on the diaphragm were observed after a chronic 50 Hz, 1.5 mT exposure. And in renal ischemia-reperfused rats, vascular permeability and antioxidant enzyme activities increased following a short-term exposure to a 50 Hz, 1 mT ELF-MF. In addition, two different pulsed magnetic fields (PMF) of 1 mT may result in inconsistent effects on inflammation and pain sensitivities in rats.

A further mouse study addressing ultra-high voltage (UHV) transmission technology and using ELF-EF (50 Hz, 35 kV/m) demonstrated after a short-term (up to 25 days) exposure kidney alterations, which may recover after longer lasting exposure. And an ELF-EF of 50 Hz and 5.4 kV/m applied to rats caused oxidative stress and spermatogonia degeneration. In honeybees exposed to the same range of 50 Hz EF (5 kV/m – 34.5 kV/m) increased enzyme activities of the antioxidant and proteolytic systems are interpreted as a general first defence mechanism against an environmental stressor. Exposure of cockroach nymphs to 50 Hz, 10 mT ELF-MF affected the insect's fat body in its glycogen and lipid content, and increased locomotor activity. Also, these observations were interpreted as reaction to stress.

Furthermore, chronic exposure to a 50 Hz 3 mT MF over multiple generations can increase body length, induce metabolism, and boost antioxidant capacity of *C. elegans*.

AC and static[11] anthropogenic MF around 0.2 mT, i.e., at intensities comparable to those produced by high power submarine cables at their close proximity, do not significantly impact the behaviour of juvenile European lobsters. But short-term (up to one week) exposure of the mollusk *0. struma* to a similar low intensity of < 500 µT elicits some immune response.

[10] Spherulocytes, amoebocytes and chromatocytes are subtypes of coelomocytes which are phagocytic leukocytes in animals with a coelom.
[11] see chapter 1.3.3 and 1.3.4

Finally, embryonic development of Japanese quail was not affected following exposures in the mT range (50/60 Hz, 0.1 mT – 4 mT).

Summarizing, the very different animal models describing dissimilar effects following ELF-MF exposure in the 1 mT range and below demonstrates again the absence of knowledge on biological-relevant mechanisms of ELF-MF, except oxidative stress.

Table 2.3.1. Animal studies on exposure to ELF fields

Endpoint	Reference	Exposure ELF –MF & -EF	Exposure Duration and Species	Effect
Rodent studies				
Inflammation	Mert and Yaman [49]	PMF 1, 3, 5, 7 Hz, 1 mT 7, 9, 12, 14 Hz, 1 mT + CG inflammation	3 x 1 h (1, 4, 23 h CG injection) Rat	Temperature ↓, paw mass ↓ PMF-1 only: antiinflammatory effects
Physiology & Pathophysiology	Di, Dong [50]	35 kV/m	7, 14, 21, 25, 35, 49, 52 d 24 h/d Mouse	7, 14, 21, 35d: BUN ↑, CREA ↑; 49 d: BUN & CREA normal. Kidney cells affected at 25 d but not at 52 d.
	Gunes, Buyukakilli [53]	50 Hz 1.5 mT	7 mo. 4 h/d Rat	Diaphragm: muscle contractility↓; TAS ↓m. Serum: TAS ↓f ; Ca^{2+}↓m, K^{+} & Ca^{2+}↑f
	Keser, Bozkurt Girit [54]	50 Hz 1 mT + Pte	5 d 3h/d Rats with renal I/R injury	Partly restoration of altered protein and lipid structures in damaged (I/R) kidney.
	Wang, Yang [56]	50 Hz 1 mT	24 wk 20 h/d Rat	Hematology, blood chemistry, and morphology of liver & kidneys not affected.
	Zhang, Li [55]	50 Hz 500 µT	24 wk 20 h/d Rat	Cardiovascular system not affected.
	Zhang, Wang [65]	50 Hz 30, 100, 500 µT	24 wk 20 h/d Rat	Hematology, blood chemistry, morphology & oxidative status of liver & kidneys unaffected.
Reproduction	Gazwi, Mahmoud [57]	50 Hz 5.4 kV/m EF + rosemary extract	30 d Rat	Serum levels of LH, testosterone, FSH↓. Testicular CAT↓ & MAD↑. Degeneration of spermatogonia.
Studies in non-Mammalians				
Whole body chemical composition	Koziorowska, Depciuch [58]	50 Hz 1.6 mT	2, 6, 12, 24, 48 h Honeybee	After ≥ 6h changes in DNA, RNA, phospholipids and protein
Embryonic development	Lola Costa, Silva Araújo [59]	60 Hz 0.16, 0.65 mT	3 x 2 h Japanese quail embryos	Vascular network of the yolk sac unaffected. But embryonic body development decreased at 0.65 mT.
Antioxidant & proteolytic system	Migdał, Roman [60]	50 Hz 5, 11.5, 23, 34.5 kV/m	1, 3, 6 h Honeybee	Enzyme activities ↑ of the antioxidant (SOD, CAT) and proteolytic systems.
Oxidative stress	Migdal, Murawska [61]	50 Hz 5, 11.5, 23, 34.5 kV/m	12 h Honeybee	SOD ↑, CAT ↑, FRAP ↑ (highest values at 34.5 kV/m)
Behaviour	Taormina, Di Poi [18]	50/60 Hz? 225 µT	45 min & 1 week	Avoidance/attraction

			European lobster	& exploratory and shelter seeking-behaviour unchanged
Locomotion and insect's fat body	Todorovic, Ilijin [19]	50 Hz 10 mT	5 mo Cockroach *(Blaptica dubia)*	Locomotion ↑, bw ↓ , Fat body: mass ↓, lipids ↓, glycogen ↓
Development, ATP, antioxidant capacity	Wang, Sun [62]	50 Hz 3 mT	60 h Nematode *C. elegans* (F1-F15)	F15: body length ↑, ATP ↑, ATPase ↑, SOD ↑
Immune response	Zhang, Wang [64]	50 Hz 100, 500 µT	24, 72, 168 h Mollusk (*O. struma)*	No effect on growth. Coelomocyte count ↑, T-AOC ↑, CAT ↑, SOD ↑, PO ↑, and Immune-related gene expression affected.

Abbreviations: ↑=increase(d); ↓=decrease(d); ATP: adenosine triphosphate; ATPase: adenosine triphosphatase; BUN: blood urea nitrogen; bw: body weight; CAT: catalase; CREA: creatinine; d: day(s); EF: electric field; ELF-MF: extremely low frequency magnetic field(s); f: female(s); FSH: follicle stimulating hormone; FRAP: ferric ion reducing antioxidant power; h: hours; I/R: ischemia-reperfusion; mo: month(s); LH: luteinizing hormone; m: male(s); MAD: malondialdehyde; NOS: nitric oxide synthase; PO: polyphenyl oxidase; Pte: pterostilbene; SOD: superoxide dismutase; T-AOC: total antioxidative capacity / TAS: total antioxidant status.

2.4 Cell studies

Compared to the previous Council report a similar number of studies and endpoints was identified for the reporting year 2020. They were carried out on several cell types of human and rodent origin, dealing with proliferation, apoptosis, genotoxicity, gene expression and oxidative stress.

2.4.1 Proliferation

Human amniotic (FL) cells were employed by Chen, Xia [66] to investigate the effects of 50 Hz exposure on sphingosine-1-phospate (S1P) activation pathway. S1P is produced by two sphingosine kinases (SphK1 and SphK2) and has been reported to regulate different cell functions, including the promotion of proliferation. To this purpose cell cultures were exposed/sham-exposed to a 50-Hz MF at 0.4 mT for 15, 30, 60 min or 24 h. The results showed that 1 h MF exposure increases the level of S1P by activating SphK1 by approximately 20% (three independent experiments; $p<0.05$). Following 23 h from the exposure, cell proliferation was increased. The same results were obtained following 24 h exposure. The addition of SKI II, a specific inhibitor of SphKs, abolished the cell proliferation induced by the MF. No effect of the exposure was detected on either total or phosphorylated SphK2, suggesting that MF exposure increases the level of S1P by activating SphK1 through extracellular signal-regulated kinase (ERK) signalling. In fact, by adding ERK inhibitors the effect of MF on proliferation was negated.

2.4.2 Other cellular endpoints

A study was devoted to compare the response to an ELF magnetic field (50 Hz, 1 mT) of human neuroblastoma cells SH-SY5Y, cultured in a three-dimensional (3D) scaffold and in a conventional two-dimensional (2D) monolayers Consales, Butera [67]. In a first step, the authors verified that the growing phenotype of proliferating cells was not affected by the culturing conditions (2D *vs.* 3D cultures), as morphology, cell cycle distribution, proliferation/ differentiation and gene expression. Next, 2D and 3D cultures were exposed/sham-exposed for 72 h. No change in the proliferation index and in the distribution of cell cycle phases were detected. These results were also confirmed by evaluating the expression on several genes involved in modulation of cell proliferation and neuroblastoma aggressiveness (Ki-67, CCND1, MYCN, and Nestin genes). No effects of the exposure in both cell cultures were also detected in terms of invasiveness and neovascularization in neuroblastoma cells by monitoring the expression of the hypoxia-inducible factor 1-alpha (HIF-1α), the vascular endothelial growth factor (VEGF), and the platelet-derived growth factor (both PDGF-A and PDGF-B variants). Similar results were also obtained when the expression of neuroblastoma-specific MicroRNAs related to epigenetic regulation were investigated, such as miR-21-5p, miR-222-3p, and miR-133b. At variance, when the effect of the exposure was analyzed in terms of cell redox state, the content of intracellular reduced glutathione (GSH) was significantly decreased with a significant increase in superoxide dismutase (SOD-1) RNA level in exposed samples ($p<0.05$), but only in 3D cultures. Moreover, the exposure to 50 Hz concurrent to treatments with retinoic acid and phorbol 12-myristate 13-acetate to stimulate neuroblastoma differentiation into a dopaminergic phenotype also gave different results in 2D and 3D cultures: the exposure enhanced the differentiation pattern in 3D cultures only. For all the experimental condition tested three independent experiments were performed. The authors concluded that the 3D cultures of human neuroblastoma cells are a more reliable experimental model for studying cell response to ELF-MF if compared to 2D conventional monolayer, as it allows the identification of cellular and molecular events that might be underestimated or missing in 2D growing conditions.

Xu, Wang [68] investigated the effects of an ELF magnetic field on MCF-7, ZR-75-1, T-47D and MDA-MB-468 breast cancer cell lines. Cell cultures were exposed/sham-exposed to 1 mT at 50, 125, 200 and 275 Hz for 6, 12, 24, or 36 h in a pair of Helmholtz coils. The exposure resulted in a decreased viability with the increased duration of treatment (statistical significance not reported) in all the breast cancer cells investigated and the stronger effect was recorded at 200 Hz. Human umbilical vein epithelial cell (HUVEC) were used as normal reference cells and no effects were detected for all the exposure conditions investigated. The four breast cancer cell lines were also tested for apoptosis following 24 h exposure at 200 Hz, 1 mT and a statistically significant increase was detected by flow cytometry (Annexin-V/PI method; $p<0.05$). MCF-7 and ZR-75-1 cells were employed to confirm this result by measuring the expression of some apoptosis-related proteins. In addition, they were tested to evaluate cell cycle progression, that resulted affected following exposures for 6, 12, and 24 h ($p<0.05$). ROS formation also was increased following 2 h exposure ($p<0.01$) and the effect was attenuated by adding N-acetyl-l-cysteine, a ROS scavenger ($p>0.05$). Finally, the PI3K/AKT/ GSK3 signalling pathway, one of the signal transduction pathways with an anti-apoptosis and survival-promoting role, was inactivated by the exposure, contributing to the cell proliferation inhibition and apoptosis. For each experimental conditions three independent experiments were carried out.

In a study carried out by Zuo, Liu [69] rat pheochromocytoma cells (PC12) were employed to evaluate the effect of 24 h exposure to a 50 Hz, 100 μT, magnetic field. Cells were also induced into an Alzheimer's Disease (AD) neuronal model using nerve growth factor and Amyloid β25–35. Changes in the morphological structure, cell viability and apoptosis were investigated 3, 6 and 12 h post-exposure in three independent experiments. Cell viability was evaluated by the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) test; 6 and 12 h after exposure viability was increased in normal neuronal model (MF vs. sham; $p<0.05$) and in AD model (AD+MF vs. AD; $p<0.05$) cells and in the latter case a decrease of ultrastructural damage was also detected by transmission electron microscopy (AD+MF vs. AD; $p<0.05$), suggesting that the exposure has a positive effect on AD neuronal model cells, and could promote their metabolic activity. Compared to sham controls, apoptosis was increased in the exposed neuronal model (MF vs. sham, $p<0.05$) while the exposure decreased the apoptotic rate in the AD model (AD+MF vs. AD, $p<0.05$). Such an increase was also confirmed by measuring the expression of apoptosis-related proteins. It is known that Bcl-2 and Bax proteins are the most important regulators of the progress of apoptosis, and an increased Bcl-2/Bax ratio usually indicates the enhanced capabilities against apoptosis. Since in this study in AD cells the exposure inhibited the decrease of Bcl-2/Bax ratio the authors suggested that the effect of MF exposure can be related to the mitochondria apoptotic pathway.

Mononuclear cells extracted from umbilical cord blood of healthy newborns after full-term pregnancies were used by Zastko et al to evaluate viability, DNA double strand breaks and ROS formation following 48 and 72 h exposure/sham-exposure to an intermittent (250 s on/250 s off) triangular pulse trein with 7.8 Hz repetition rate of 24, 17, 13, 10, 8 and 6 μT, Zastko, Makinistian [70]. No effects were detected, except for a decrease in viability following 72 h exposure at 13, 10, 8 and 6 μT ($p<0.05$).

Ye and co-workers employed a neuroblastoma cell line (SH-SY5Y) to investigate neurochemical changes induced by low-intensity magnetic stimulation Ye, Lee [71]. An exposure system was designed and fully characterized using a computational electromagnetic modelling technique. Three different stimulation protocols were applied for 30 min to differentiated neuroblastoma cells and then the resultant neurochemical changes were assessed. In particular, the authors applied repetitive high-frequency (rHF; 10 Hz, 18,000 pulses), intermittent high-frequency (iHF; 10 Hz, 1800 pulses), and low-frequency (LF; 1 Hz, 1800 pulses) stimulation.

For each protocol six independent experiments were carried out to evaluate glutamate, calcium and Ɣ-aminobutyric acid (GABA) concentrations. Such measurements were performed soon after 30 min exposure, 1 h and 3 h after the exposure.

The results obtained by comparing sham-exposed and exposed samples indicated that HF stimulation increased levels of glutamate, while LF stimulation increased levels of GABA ($p<0.05$), suggesting that the effects are frequency-dependent. In addition, calcium changes were closely associated with glutamate changes in response to different stimulation parameters.

The authors concluded that low-intensity magnetic stimulation induces a protocol-dependent effect is that HF stimulation facilitates neuroexcitability while LF stimulation suppresses neuroexcitability.

Table 2.4.1. Cell studies on exposure to Extremely low frequency (ELF) fields

Cell type	Endpoint	Exposure conditions	Effect	References
Human amniotic (FL) cells n=3	Proliferation	50 Hz, 0.4 mT 15, 30, 60 min and 24 h	Increased proliferation after 1 and 24 h exposure due to increased level of S1P related to SphK1 activation.	Chen, Xia [66]
Human neuroblastoma (SH-SY5Y) cells 2D and 3D cultures n=3	Proliferation, cell cycle, gene expression, differentiation, redox cell state	50 Hz, 1 mT 72 h	No effect in proliferation and cell cycle. Decreased GSH content and increased SOD-1 RNA and enhanced differentiation pattern in 3D cultures only.	Consales, Butera [67]
Breast cancer cells (MCF-7, ZR-75-1, T-47D and MDA-MB-468 n=3	Viability, apoptosis, cell cycle, gene expression, ROS formation	50, 125, 200, 275 Hz, 1 mT 6, 12, 24, or 36 h	Decreased viability; 200 Hz: Increased apoptosis, decreased cell cycle progression, increased ROS formation	Xu, Wang [68]
Rat pheochromocytoma cells (PC12); AD neuronal model n=3	Morphology, viability, apoptosis	50 Hz, 100 µT 24 h	Increased viability 6 and 12 h post-exposure; decreased ultrastructural damage in AD cells; increased apoptosis in normal; decreased apoptosis in AD cells	Zuo, Liu [69]
Mononuclear cells from human umbilical cord blood n= not reported	Viability, DSB, ROS formation	Intermittent triangular pulse train, 7.8 Hz 24, 17, 13, 10, 8 and 6 µT 48 and 72 h	Decreased viability after 72 h exposure to 13, 10, 8 and 6 µT; No effects in the other experimental conditions	Zastko, Makinistian [70]
Human neuroblastoma cells (SH-SY5Y) n = 6	Glutamate, calcium and GABA concentration	10 Hz, 18000 pulses (rHF); 10 Hz, 1800 pulses (iHF); 1 Hz, 1800 pulses (LF) 30 min	rHF and iHF protocols increased levels of glutamate and calcium; LF protocol increased levels of GABA	Ye, Lee [71]

Abbreviations: AD: Alzheimer's Disease; DSB: double strand breaks; GABA: Ɣ-aminobutyric acid; GSH: reduced glutathione; iHF: intermittent high frequency; LF: low frequency; rHF: repetitive high frequency;ROS: reactive oxygen species; SOD-1: superoxide dismutase -1; SphK: sphingosine kinases

3 Intermediate frequency (IF) fields

In the last years' report, it was stated that research on intermediate frequency (IF) fields was scarce despite increasing use of IF-MF emitting sources (for example induction cooking, anti-theft devices, wireless power transfer systems). Only one epidemiological and one animal study was reported for this years' reporting period, summarised below.

3.1 Epidemiological studies

Sato, Kiyohara [72] performed an ecological study in all 47 Japanese prefectures. Per prefecture, the spontaneous foetal death rate (per 1000 births), the foetal death rate after the 22nd week of pregnancy (per 1000 births), the perinatal mortality rate (per 1000 births), and the proportion of newborns weighing less than 2500 g in 2009 and 2014 (per prefecture; only singleton births) were extracted from Vital Statistics Japan. Data on the coverage (presence) of induction heating cookers in two- or more person households by prefecture in 2009 and 2014 were extracted from a national survey. Neither cross-sectional analyses for 2009/2014, nor an analysis of trends using interpolated data between these two time points resulted in statistically significant correlations across the prefectures.
This is not an informative study in the sense that no exposure assessment was performed, nor were there any data pertaining to possible confounding factors. The analysed birth outcomes may also be affected by a range of other exposures (such as smoking). Therefore, evaluation of any trends could be driven by entirely different underlying changes of exposures or lifestyles and would be uninformative regarding a possible association (in this case of induction cooker coverage and perinatal mortality rate).

3.1.1 Conclusions epidemiology

Only one new study on IF-MF was published, which does not allow any firm conclusions regarding possible health effects from exposure to IF-MF.

3.2 Human studies

As for the previous reporting periods, there was no human experimental study in the intermediate frequency range.

3.3 Animal studies

One animal study was identified.

Zhao, Wu [73] tested whether mice are affected in a wireless power transfer (WPT) system. First, a model of the WPT system was established and the peak values of induced EF intensity and temperature changes of the mouse main organs were calculated. Second, 20 one-month-old Kunming mice were divided in 4 groups (n=5 each): 1) female control, 2) female IF exposed, 3) male control, 4) male IF. Group 2 and 4-mice were exposed in the WPT system at 47 kHz and average magnetic induction intensity of 270 µT for 12 wk, 6 d/wk, 5 h/d. Following exposure, cytokines (TNF-α, IL-6, IL-1β), testosterone and progesterone in blood, and organ morphology of some main organs were evaluated. Cytokines in serum of IF exposed mice all increased compared to controls, whereas progesterone levels in IF females and testosterone in male IF mice decreased. Compared to non-exposed controls, male IF mice developed hepatocyte edema (4/5), in spleens of female IF mice interstitial hypertrophy and "loose cell arrangement" (4/5) was seen. Ovaries of female IF mice were significantly reduced in size and had polycystic changes (2/5). Testicular morphology of IF males was mostly unaffected, but "the intercellular space increased, some cells became blurred borders and cell glands shrank" (4/5). Heart morphology of IF exposed and control mice was similar.

According to the authors, the simulation outcome with peak values of induced EF intensity of the liver (1.43 V/m) and a temperature rise of the kidney with 2.736 x10^{-6} °C are the largest, but the "calculation results of all organs are lower than the ICNIRP safety standards". However, the authors' correlation between liver pathology and liver peak value of induced EF should not be drawn since "hepatocyte edema" was reported in males only. In summary, exposure of mice in a model WPT system (47 kHz, 0.27 mT) showed increased cytokines and mostly unaffected organ morphology except liver in males, spleen in females and gonads of both sexes. Finally, and besides some experimental inaccuracies (i.e., no real sham control, lack of basic data like body weight, organ weight, female liver (pathology) and standardized pathology nomenclature), the study offers first data which may be considered for a safety assessment of WPT only following a verification experiment.

3.4 Cell studies

In the period of interest, no cell studies have been published covering the intermediate frequency range.

4 Radiofrequency (RF) fields

4.1 Epidemiological studies

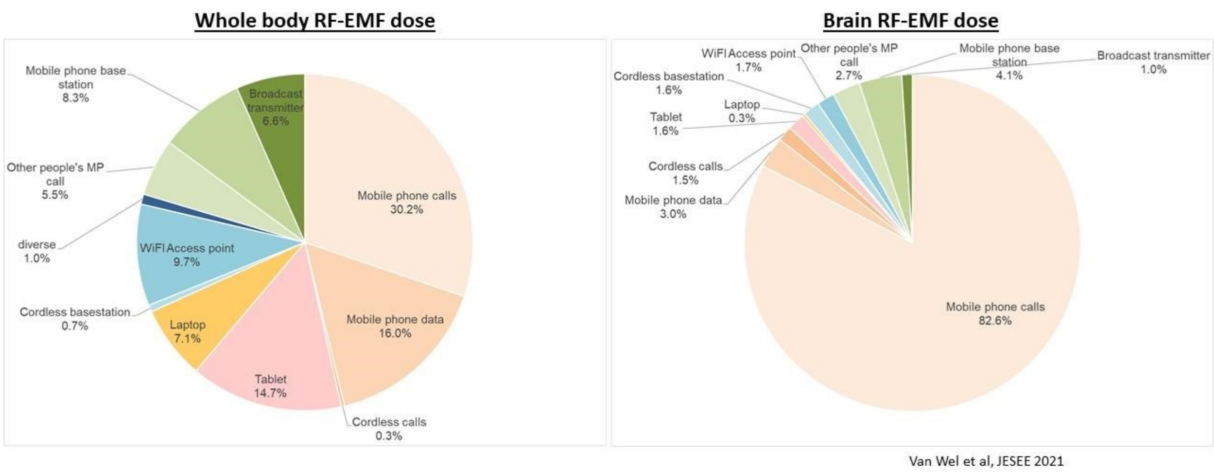
In the last year's report, it was concluded that new research on brain tumours and mobile phone use is in line with previous research suggesting mostly an absence of risk. This conclusion is in line with analyses of cancer incidence time trends, which do not indicate an increase in brain tumours in the last decade.

Associations between mobile phone use and non-specific symptoms such as headache or mental health problems were observed, but several studies suggest that these associations were mediated by other factors such as short sleep duration or insomnia. COSMOS, the largest prospective study to date, did not provide indications for an association of mobile phone use with tinnitus and hearing loss. Headache was developed slightly more often in participants with the longest call time, but in-depth analysis suggested that the association was unlikely to be caused by RF-EMF, but rather other aspects correlated with long mobile phone call duration such as a stressful life including high job demands.

Exposure to RF-EMF and dose calculations

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, 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. Measurements and exposure calculations have shown that a person's radiofrequency field exposure is dominated by ones' own mobile phone use. For most people, the exposure from environmental sources such as mobile phone base stations play a minor role. This was shown for example in a study published by van Wel, Liorni [74], calculations of cumulative dose performed for brain as well as for whole body was calculated based on exposure and device use profiles for 1755 individuals from France, Netherlands, Spain, Switzerland that participated in a survey (see Figure below).

Figure 1: Contribution of RF-EMF sources to dose



The Figure shows contributions of various RF-EMF sources to the average daily whole body (290 mJ/kg/day) and brain dose (811 mJ/kg/day) of adults (adapted from van Wel, Liorni [74]). Orange to reddish colours refer to near field (from own device use); blue to mixed, and green to far field sources.

4.1.1 Adult cancer

Chen, Wang [75] systematically reviewed and meta-analysed case-control and cohort studies that had analysed associations between wireless (mobile phone and/or DECT phone) use and risk of meningioma. Eight studies were included, and results were stratified by wireless phone use duration in years (0-5, 5-10, >10 years duration). Overall, no increased risk of meningioma emerged from meta-analysing the studies, with low heterogeneity between study results. In fact, a slightly decreased risk was observed for the category of 0-5 years duration of use, with an OR of 0.85 (95% CI: 0.77-0.94). It is unclear what is underlying this pattern. The authors discuss several possible explanations, including possible recall and selection biases, low case numbers and differences in methodology hampering interpretation. Another possible explanation could be reverse causation: Reverse causation could occur if people with meningioma that have not been diagnosed yet but changed their mobile phone use behaviour. Such changes could be triggered e.g. by headaches or hearing loss, common symptoms of meningioma.

Assi, Hilal [76] investigated demographics, self-reported exposures, and meningioma in 195 Beirut meningioma patients. An analysis was performed if several exposures (e.g. smoking, alcohol consumption, radiotherapy, and “heavy cell phone use”) affected overall survival or progression-free survival over a follow-up duration of 10-16 years. The authors describe that they found no association with mobile phone use. No further details of any sort are provided. This study is not informative regarding any possible association between mobile phone use and survival or progression-free survival after meningioma diagnosis, given the scarce exposure-relevant information.

Choi, Moskowitz [77] published a meta-analysis of 46 case-control studies that investigated associations between mobile phone use and different types of disease (e.g. malignant brain tumours, meningioma, testicular cancer, leukaemia, and melanoma). Analyses were performed across all studies, by a quality score, by tumour subtype, and by investigator group (Hardell group, Interphone group, other). Across different types of cancers combined, no evidence of an increased risk emerged, with an OR of 0.99 (95% CI: 0.0.91-1.07). Stratification by 15 types of disease across all included studies did not result in increased risks of any of the subtypes in mobile phone users. However, stratification of the 15 disease types and by investigator group (38 additional stratifications) resulted in statistically increased risks of malignant tumours/glioma in long-term mobile phone users in the Hardell study group, and statistically decreased risks of overall brain tumours (malignant and benign) in the Interphone group. Further stratifications reported in the publication appear to reflect differences by investigator group rather than by underlying methodological differences as such.

Overall, the publication is in line with previous observations that primarily the Hardell group case-control studies identified increased risks of glioma/malignant brain tumours in wireless phone users. This result has not been confirmed in studies performed by other groups. This observation has been discussed in previous SSM reports. Published commentaries regarding this meta-analysis have discussed various aspects of the methodology and interpretation that will not be further repeated and discussed here. Choi, Moskowitz [77]

4.1.2 Incidence trends

Marinelli, Lohse [78] compared the incidence rates of vestibular schwannoma (aka acoustic neuroma) and the incidence of MRI procedures over the years 1995 to 2016. The study was based on the Rochester Epidemiology Project, which records medical diagnoses and procedures including MRI and vestibular schwannoma for virtually all residents of Olmsted County, Minnesota. Sex specific, age standardized incidence rates of MRI, and symptomatic and asymptomatic vestibular schwannoma were calculated for each calendar year. Over the study period a total of 43,561 MRIs of the head were performed, and 25 asymptomatic and 95 symptomatic vestibular schwannoma were observed. The age standardized incidence of MRI head scans in women increased from around 900/100,000 in 1995 to around 1700/100,000 in 2003; after this time the incidence was fairly stable. The incidence in men followed a similar trend but at a slightly lower level. The incidence of asymptomatic vestibular schwannoma was around 0.7/100,000 from 1995 until around 2006, then increasing reaching 2/100,000 in 2016. For men the trend was similar but lower and the increase after 2005 less pronounced. For symptomatic vestibular schwannoma, there was an increasing incidence from 1995 to around 2011 with a slightly higher incidence in men than in women. It is well known that the incidence of diagnosed vestibular schwannoma is rising, this is generally ascribed to increased use of MRI as well as increased disease awareness. The authors argue that unknown environmental factors may be the cause since the rising incidence of asymptomatic vestibular schwannoma primarily occured after the number of MRI procedures had plateaued. The study is limited by the very small number of asymptomatic cases, i.e. about 1 case per year, and random variation is likely to have influenced the results.

Carlberg, Koppel [79] updated a previous investigation (summarized in SSM 2018) of thyroid cancer incidence in Sweden and the Nordic countries based on data from Nordcan and the Swedish Cancer Register. For Swedish women, there was a fairly constant incidence until 1999, after this time point, the annual percentage chance (APC) in incidence rate was 4.13 (95% CI: 2.48-5.81) until 2010 after which the APC was 9.65 (95% CI: 6.68-12.71). For Swedish men there was little change in incidence before 2001, after which the APC was 5.26 (95% CI 4.05-6.49). For Nordic women the most conspicuous joint point was 2006: from 1976 to 2006 the APC was 0.52 (0.28-0.77), after 2006 the APC was 5.83 (95% CI: 4.56-7.12). For Nordic men the APC before 2005 was 0.35 (95% CI: 0.09-0.61), after 2005 the APC was 5.48 (95% CI: 3.92-7.06). Observational studies such as this will reflect temporal changes in surveillance, diagnosis, medical practice or environmental risk factors. The authors speculate that the common explanation of improved diagnostics is insufficient to explain the observed increase and postulate that RF radiation is the causative factor. They do, however, not present any analysis to support this interpretation.

4.1.3 Reproduction

Kaya, Aykaç [80] retrospectively investigated semen motility in samples from males (n=2147) attending Eskisehir State Hospital Andrology Laboratory during 2017 and 2018 for an analysis of their semen. Males (n=1956) that did not have extremely low-semen volumes or azoospermia were invited to be evaluated by an urologist and to answer a questionnaire. The final sample consisted of 1311 males required to not have preexisting pathological conditions such as chronic disease, prolonged medication use, occupational exposure to heat or chemicals and damage to the testes. Former alcoholics, ex- or passive smokers were also excluded. Participants filled in a questionnaire on a range of factors including if they had used a cell phone for 10 or more years before semen collection. Pearson Chi Square test found that those who did, did not differ with regard to a range of semen parameters and overall, they were not at increased risk of dysspermia (p=0.984).
The study has various limitations. The sample is not representative of the normal population. Exposure assessment was very crude, even more so with regard to EMF exposure of the testes. There was no statistical allowance for factors such as age, income or lifestyle, which might be associated with long-term use of mobile phones and with visiting an andrology clinic.

In the French prospective NéHaVi cohort study of 1368 mothers, the association between mobile phone use during pregnancy and foetal development was investigated Boileau, Margueritte [81]. The personalized AUDIPOG score was used to assess neonatal growth, which considers the height, birth order, and sex of the child, and the age, height, and weight of the mother. The threshold for growth restriction was set at the 10th percentile. Mobile phone use was inquired by means of face-to-face interviews in the post-partum period during stay at the maternity unit and was inquired in general for "phone time". Mean phone time was 29.8 min (range: 0.0–240.0 min) per day. After adjustment for various confounders (e.g. smoking, alcohol consumption), newborns, whose mothers used their mobile phones for more than 30 min/day, were significantly more likely to show growth restriction than those, whose mothers used their mobile phones for less than 5 min/day during pregnancy (aOR = 1.54 [95% CI 1.03; 2.31]). Self-reported exposure information collected after birth is a limitation for this study. In addition, "phone time" was not further specified regarding type of use (e.g. calling, browsing the internet, streaming videos…) or location of the phone (e.g. on the belly, next to the ear). However, such an information would be of relevance when considering possible indirect pathways via the exposure of the mother, or direct pathways via the exposure of the foetus. The high average mobile phone use duration may indicate errors in these self-reported data. The authors also stated that they could not rule out selection bias in their study because some of the medical charts were non-exploitable records, which was related to sociodemographic status of the mothers. In conclusion, it remains unclear whether the observed association is related to RF-EMF exposure or due to other aspects of high mobile phone use like stress, sleep deprivation, diet etc.

4.1.4 Self-reported electromagnetic hypersensitivity (EHS) and symptoms

Kacprzyk, Kanclerz [82] published a survey in electromagnetic hypersensitive individuals in Poland. The survey was advertised on social media and elsewhere. Participants could fill in the survey between Sept and Dec 2018. Participants were regarded as EHS if they answered "yes" to the question "Do the electric/electronic/telecommunication devices negatively affect your well-being?" and indicated at least one device which in their opinion had such an impact. Primary aim of the study was to assess which sources were reported most often and which symptoms participants had. 1028 participants filled in the survey of which 408 self-described as EHS. 71% were women and median age was 33 years. Most frequently listed symptoms were exhaustion followed by headache, eye pain, irritation, and concentration difficulties (more than half of respondents). Most frequently named EMF sources were (mobile) phones (more than half of participants). Less frequently named sources included laptops/computers and Wi-Fi routers. Mobile phone base stations were named by 17% of the participants. As such, the study is in line with previous surveys reporting a range of unspecific symptoms, attributed to multiple sources of electromagnetic fields, including extremely low frequency and radiofrequency fields. This is a younger study collective than several of the previously published EHS publications. No conclusions regarding causal associations can be made in this cross-sectional study with a self-selected participant group.

A possible association between mobile phone use and self-reported sleep quality was investigated in the prospective COSMOS cohort with more than 24,000 participants from Sweden and Finland Tettamanti, Auvinen [83]. Data on mobile phone use (call duration) was collected by means of a questionnaire at the beginning of the study. In addition, objective data on call duration in the GSM (2G) and UMTS (3G) networks were obtained from the mobile phone operators for a period of three months at the start of the study. At the beginning of the study and after four years, the study participants completed a questionnaire regarding sleep disturbance, sleep adequacy, daytime sleepiness, sleep latency, and insomnia. The group of participants with the longest talk duration (>258 minutes/week) had a higher risk of insomnia compared to those with the shortest call duration (OR=1.24, 95% CI: 1.03-1.51). However, the correlation was less pronounced in an analysis accounting for the fact that less radiation is emitted while using the UMTS network compared to the GSM network. For all other aspects related to sleep quality, no significant associations with mobile phone use were observed. Major strengths of this study are the prospective design, large number of participants and the use of objective data from mobile phone operators. Because the correlation with insomnia was associated rather to the length of use than to the level of radiation emissions suggests that other factors than RF-EMF may explained the observed association such as stress and high demands, problematic mobile phone use, displacement of sleep due to mobile phone use, exposure to blue light from screens or other behavioural factors. Similar conclusions were drawn in a previous analysis of this sample in relation to occurrence of headache (Auvinen, Feychting [84]) discussed in the 15th SSM report Swedish Radiation Safety Authority [15].

The association between RF-EMF from mobile phone base stations and non-specific symptoms was examined in a cross-sectional survey conducted between 2015 and 2017 in five large cities in France, Martin, De Giudici [85]. In total, 2641 adults were contacted that were living in buildings located in the main beam of a mobile phone base station at a distance of 250 m or less. Sites were selected based on having been in operation for more than two years and not having been the subject of complaints by local residents at the time of their installation. Among 354 individuals who consented to participate, information on environmental concerns, anxiety, and non-specific and insomnia-like symptoms was collected with a questionnaire administrated by telephone. RF-EMF exposure was measured at five points in each dwelling using a broadband field-meter (100 kHz - 6 GHz), followed by a spectral analysis at the point of highest exposure to obtain source specific exposure contributions. The median exposure from mobile phone base stations was 0.27 V/m (0.44 V/m for total RF-EMF), ranging from 0.03 V/m to 3.58 V/m. Mobile phone base station was the main source of exposure for 64% of the dwellings. No association between RF-EMF from base station and non-specific or insomnia-like symptoms was observed. For insomnia-like symptoms, a significant interaction was found between RF-EMF exposure from mobile phone base stations and environmental concerns: risk for insomnia-like symptoms increased with RF-EMF exposure among worried participants (OR per 0.396 V/m increase: 1.80, 95% CI: 1.14; 2.84) and uninformed participants (2.12, 95% CI: 1.05; 4.26) but not among slightly concerned participants (0.84, 95% CI: 0.55; 1.31). Exposure measurements at the home of the study participants is an asset in this study. An appropriate recruitment strategy was chosen to maximize the exposure contrast in the study collective. As a consequence, exposure levels from mobile phone base stations in this study are somewhat higher than in previous similar studies. The relatively small sample, low participation rate and the cross-sectional design are limitations of this study. Overall, the study does not indicate an association between symptoms and RF-EMF from mobile phone base station. The observed interaction in worried participants may reflect an attribution bias if some of these individuals were aware of their exposure status. In contrast, the increased risk among uninformed participants is interesting, because the analysis in these people is unlikely to be biased by knowledge of their exposure status. Further studies need to confirm whether this observation is causal or due to chance, confounding other type of bias.

4.1.5 Other outcomes

Cabré-Riera, van Wel [86] conducted a cross-sectional study on RF-EMF exposure and cognitive function in children and adolescents. Participants were recruited from a pre-existing Dutch (participants: 8266) and a Spanish birth cohort (participants: 2757). Use of EMF-sources and cognitive function were assessed at age 9-11 and for a small Spanish subcohort at age 17-18. Children (n: 2944) and adolescents (n: 261) with information on RF-EMF exposure information and at least one cognitive test were included into the present study. Whole brain RF-EMF exposure from both near and far field sources was modelled. Near field exposure was based on self-reported or parental reported information about duration of use of: DECT phones or mobile phones for calls, other use of mobile phones and use of Wi-Fi-connected tablets and laptops. The authors assumed no hands-free use, 35% 2G and 65% 3G traffic. Time online was assumed to be spent 40% gaming, 40% streaming video and 20% browsing internet and social media. Far field exposure was modelled based on location of masts around residence. Far field exposure for other sources and locations was estimated as the average of 72 h personal measurements by 56 Dutch and 191 Spanish children and 53 Spanish adolescents. Furthermore, Wi-Fi was assumed to operate at 2.4 GHz with a 54 megabit per second bit-rate. Total and source specific whole-brain RF-EMF dose was calculated. Validated tests were used to assess non-verbal intelligence, information processing speed, attentional function, visual attention, cognitive flexibility, working memory and semantic verbal fluency. Linear regression models, negative binomial regression and linear mixed-effects models with adjustment for maternal education level, maternal social class, maternal smoking during pregnancy as well as maternal anxiety and depression symptoms. Childs' sex, age, physical activity and BMI. The median whole brain dose in children and adolescents was 90.1 and 105.1 mJ/kg/day, primarily from phone calls. In children, but not adolescents, higher total RF-EMF doses were associated with lover non-verbal intelligence score (-0.10 points per 100 mJ/kg/day, 95%CI: -0.19—-0.02) which was also the estimate associated RF-EMF doses from phone calls. No other associations were observed. As the authors point out, the lack of biological established mechanism, small effect size and cross-sectional nature mean that chance or reverse causation cannot be ruled out. Inverse probability weighting was used make the sample representative of the original cohorts, these may however not be representative of the general population. An elaborate exposure algorithm was applied, it is however unclear to what extent it actually led to reordering of the relative brain exposure levels between children compared to self-reported mobile phone use, which was the main predictor. Finally, given the self-reported data and many assumptions, inevitable exposure misclassification may have affected the results.

In the Generation R study from the Netherlands, data from 2592 children aged nine to twelve years were analysed to determine whether there is an association between RF-EMF exposure and the volume of different brain areas, Cabré-Riera, van Wel [86]. The brain volume of all study participants was assessed by magnetic resonance imaging (MRI) between 2013 and 2015. Data on use of wireless communication devices (mobile and cordless phones, as well as tablets and laptops used with WiFi) were collected via questionnaires filled by the parents. Exposure by broadcast transmitters and mobile phone base stations was modelled for the school and residential locations and exposure at other locations was assessed based on personal RF-EMF measurements in a sample of 56 children. Based on all this information on exposure, the absorbed RF-EMF dose was calculated for different brain regions. The statistical analyses were corrected for a series of potential confounders (e.g. maternal education and smoking behaviour, as well as body mass index and intelligence quotient of the child). The volume of all studied brain regions was not associated with the total absorbed RF-EMF dose nor to that from far-field sources. However, the RF-EMF dose from screen activities was associated with a smaller volume of the frontal lobe and the caudate nucleus. The outcome measurements are of high quality and RF-EMF dose estimation is an asset in this study, although, as discussed above, self-reported use is a major input to the modelling and prone to uncertainty. As discussed by the authors, various alternative reasons than RF-EMF dose may explain the observed association in this cross-sectional analysis. Strikingly, in a previous study, a reduced volume of the caudate nucleus was found to be related with attention deficit hyperactivity disorder (ADHD) of preadolescents Carrey, Bernier [87] thus be plausible that the reduced brain regions are the cause and not the consequence of intensive screen use of hyperactive pre-adolescents.

The association of smart mobile phone use with cognitive function was investigated in 251 Saudi adult mobile phone users in a cross-sectional study conducted between September 2019 and January 2020 Al-Khlaiwi, Habib [88]. The Montreal Cognitive Assessment (MOCA) tool was used to assess the cognitive functions. The MOCA score decreased statistically significantly with increasing daily mobile phone usage. In addition, decreased MOCA scores were found for participants who kept their mobile phone near their pillow while sleeping. The latter does involve only very little RF-EMF exposure. No confounding was considered in the statistical analysis. Thus, a likely explanation for the observed associations are other factors related to the extent of mobile phone use or to unfavourable mobile phone use (e.g. nighttime use). A further limitation of the study is the cross-sectional design, the small sample size and the unclear recruitment process.

4.1.6 Conclusions on epidemiological studies

Little new research has been published on tumour risk in relation to mobile phone use. A French study found an association between maternal mobile phone used and foetal growth restriction but retrospectively collected mobile phone use data is a limitation for this study. A new analysis from the COSMOS cohorts including more than 24,000 subjects found weak indications for an association between mobile phone use and sleep quality. Because the correlation with insomnia was associated rather to the length of use than to the level of radiation emissions suggests that other factors than RF-EMF may explain the observed association. Such explanations include for example stress and high demands, problematic mobile phone use, displacement of sleep due to mobile phone use, exposure to blue light from screens or other behavioural factors.

In a French cross-sectional study with careful exposure measurements, no associations were observed between RF-EMF from base station and non-specific or insomnia-like symptoms. However, for insomnia-like symptoms, a significant interaction was found between RF-EMF exposure from mobile phone base stations and environmental concerns, which calls for a vigilance balance in communication with the public about potential health risks from mobile phone base station. New studies in adolescents on cognitive functions and brain volume do not indicate a risk from RF-EMF exposure.

4.2 Human studies

As for previous reporting periods, the number of studies addressing RF-EMF effects in human experimental studies is higher than for other exposure types. In the current reporting period eight human studies were published. Six studies investigating effects of RF-EMF exposure on heart rate variability (Wallace, Andrianome [89]), resting state wake EEG (Nakatani-Enomoto, Yamazaki [90]), as well as sleep and sleep related memory consolidation (four studies, all from the same group: Bueno-Lopez, Eggert [91], Danker-Hopfe, Bueno-Lopez [92], Danker-Hopfe, Dorn [93], Eggert, Dorn [94]) were published. Two additional studies investigated possible effects of sham Wi-Fi exposure on symptom perception (Brascher, Schulz [95], Wolters, Harzem [96]).

4.2.1 Symptoms, perception

In a single-blind study, which aimed to experimentally induce a nocebo effect for somatic symptom perception, Brascher, Schulz [95] investigated 65 healthy volunteers (41 females and 24 males, mean ± SD: 27.3 ± 7.38 years). Participants were randomly and almost counterbalanced allocated to an experimental and a control group with 32 and 33 volunteers, respectively. Both groups had two sessions scheduled one week apart. Prior to the first test session, participants performed a heartbeat detection task, filled out questionnaires on modern health worries and self-perceived electrosensitivity, and then watched either a 6-min film on adverse health effects of EMF or a neutral film on trade of mobile phones. After watching the respective film, participants took place in a cued sham exposure experiment with two kinds of trials: while Wi-Fi was always off, subjects were told that Wi-Fi was on and that Wi-Fi was off in 50% each (randomly assigned). During the trials tactile stimuli of a low, medium, and strong intensity (12 each and per Wi-Fi on/off condition) were presented to the participants' index finger of the dominant hand and subjects had to rate the perceived intensity and aversiveness on visual analogue scales. Electrodermal activity was recorded throughout the experiment as skin conductance on the palm of the non-dominant hand. This cued sham exposure experiment was repeated one week later. Evidence for a nocebo effect was observed in both sessions as reflected by an increased self-reported intensity and aversiveness as well as electrodermal activity during sham Wi-Fi exposure. Contrary to previous findings, no differences were observed between the two groups, i.e. between those subjects who watched the health-related EMF film and those who watched the neutral film. Based on negative instructions, somatic perception and physiological responding can be altered. This finding is consistent with the hypothesis that IEI-EMF could be due to nocebo effects.

Another single-blind study from the same group investigated how expectations about electromagnetic fields affects body perception (Wolters, Harzem [96]). The authors used the same film on adverse health effects of electromagnetic fields and conducted the same sham Wi-Fi on/off paradigm. The somatic signal detection task (SSDT) was used twice at the same day to assess somatosensory sensitivity for tactile stimuli, once with sham Wi-Fi exposure and once without. The experimental conditions were performed in a random order. In 50% of the trials a weak tactile stimulus was used, and no tactile stimulus in the other 50%. The subjects had to decide whether a stimulus was present or not. Eighty-three healthy volunteers participated in the study (72.8% females, mean ± SD: 23.9 ± 4.77 years), two had to be excluded from analysis. This is one of the few studies in the EMF field that performed an *a priori* power analysis. A sample size of 71 is needed to detect an effect size $d = 0.3$ at an α level of 0.05 and a power of 80%. While somatosensory sensitivity was not affected in this study, expecting Wi-Fi exposure significantly liberalized somatosensory response behaviour. This result underlines the role of expectations in body perception and helps to understand the development of IEI-EMF.

4.2.2 Heart rate variability

In a double-blind randomized study with a counterbalanced crossover design Wallace, Andrianome [89] investigated effects of a GSM 900 MHz exposure on heart rate variability (HRV) in 26 young healthy volunteers (13 males and 13 females, 23.5 ± 3.1 years). Sessions were scheduled one week apart at the same time of the day to control for circadian variations in HRV. Each session comprised three periods: pre-exposed, exposure, and post exposure. In the current paper only data for the exposure period, which lasted 26 min and 15s are presented and which comprised 3 min recording blocks with open and with closed eyes. ECG was recorded with subjects in a seated position. Exposure was delivered by a commercial dual-band GSM mobile phone (measured max SAR_{10g} = 0.49 W/kg). Ten heart rate variability parameters were analysed in the time (four) and the frequency (six) domain. One significant effect in the time domain and two significant effects in the frequency domain were observed. All time domain parameters and all but one (low frequency) frequency domain parameters were significantly affected by the eyes condition (open vs. closed). Significant EMF effects were observed only for the standard deviation of interbeat intervals (SDNN) in the time domain and for the total power and the low frequency power in the frequency domain. SDNN was higher (12%) in the exposure condition in the eyes open as well as in the eyes closed recording condition compared to sham exposure. Spectral power was significantly higher (30% for the total power and 49% for the low frequency power) under real exposure. The authors conclude from their results that the weak effects observed on HRV parameters are likely to represent chance rather than real effects. This conclusion is confirmed by the fact that a Bonferroni correction of p-values would have led to non-significant results.

4.2.3 Resting state waking EEG

Nakatani-Enomoto, Yamazaki [90] investigated the effect of a long-term evolution (LTE) like 1950 MHz EMF exposure (continuous wave signal) with a max SAR_{10g} of 2.0 W/kg on the resting state wake EEG in a presumably double-blind cross-over design. Exposure was delivered by a specially developed microstrip patch antenna placed in front of the right ear. Maximum SAR_{10g} was 2.0 W/kg at the head surface directly under the antenna. Thirty-eight healthy volunteers (age range 20-36 years) participated in this study, data from 34 subjects (17 men and 17 women) could be used in the analysis. Overall, EEG was recorded for 60 min (15 min prior to, 30 min during, and 15 min post exposure) in an eyes closed condition. Sessions were scheduled on different days at 1 p.m. or 3 p.m. It is, however, not known whether the time was kept constant within subjects. EEG was analysed in frequency bands: delta (0.5–3.8 Hz), theta (4–7.8 Hz), alpha (8–12.8 Hz) and beta (13–30 Hz) separately for 10 electrodes. Results of a repeated measures ANOVA with exposure (LTE or sham) and time (before, during, and after) as factors and their interaction was restricted to the theta, alpha and beta band, and performed separately for location and frequency band. Time had a significant effect for the theta and the alpha frequency bands at five of 10 locations each. However, neither a significant EMF exposure effect, nor a significant interaction effect between EMF exposure and time was observed. That participants were blinded is obvious from the statement that no participant was able to differentiate between sham and real exposure. Furthermore, it is explicitly stated that EEG was analysed by a specialist who was blind to the exposure condition. Unclear is whether the person conducting the experiment was blind to the exposure condition. There is also no information on randomisation and/or counterbalancing.

4.2.4 Sleep and sleep dependent memory consolidation

So far, possible age and sex differences in response to RF-EMF exposure have rarely been considered. Danker-Hopfe, Dorn [93] addressed the question of sex dependent differences in RF-EMF effects on based on data from 60 healthy elderly volunteers (60-80 years, 30 men: 69.1 ± 5.5 years and 30 women: 67.8 ± 5.7 years). Participants were exposed to GSM (900 MHz), TETRA (385 MHz), and sham conditions in a double-blind crossover design. Each participant underwent 10 laboratory nights, scheduled at approximately two-week intervals. The first night served as an adaptation and screening night. During the remaining nights, each participant was exposed in a block-randomized design three times each to the three exposure conditions, and the sequence of the conditions was counterbalanced across all participants. Exposure was applied via a head-worn antenna attached to the left side of the head and set to transmit at a maximum SAR10g of 2 W/kg in the GSM condition and of 6.0 W/kg in the TETRA condition. The antenna had been specially designed to approximate typical exposure patterns resulting from the exposures from mobile or radio handset. The participants were exposed for 30 min prior to sleep and 7.5 hours during sleep. Altogether, 30 parameters characterizing sleep-wake times, sleep latencies, sleep architecture, sleep continuity, and arousal from sleep were analysed together with four self-rated assessments of sleep. Mixed design rmANOVAs with exposure (GSM vs. sham), sex (male vs female) and the interaction between these factors revealed significant sex effects in 50% of the variables. Exposure to GSM900 and/or TETRA resulted in a significant reduction of arousals. Exposure effects depending on sex (significant interactions) were also observed. Latency to sleep stage R was shorter in females and tended to be longer in males under both exposures as compared to sham. Latency to stage N3 was shorter in females under TETRA exposure and almost not affected in males. The time awake within the sleep period under TETRA exposure was shorter in females and only slightly longer in males. Under GSM exposure, the self-rated total sleep time tended to be longer in females and to be shorter in males. Finally, the number of awakenings was lower only in females and tended to be higher in males under GSM exposure. In summary GSM and TETRA led to significantly more exposure effects in females. Regardless of sex, none of the observed changes, however, is indicative of a sleep disturbing effect of RF-EMF exposure. The observed changes in women might reflect a sleep promoting effect.

The data from the elderly men of this study Danker-Hopfe, Dorn [93] were also used to explore age differences in RF-EMF effects in males Eggert, Dorn [94]. Data for young healthy volunteers had been collected in two studies, one with GSM (900 MHz) exposure and one with TETRA (385 MHz) exposure. The age distribution of the young men (20-30 years) in both samples was almost identical: 25.3 ± 2.6 years and 25.4 ± 2.6 years, respectively. The design of the studies was almost identical to the ones in elderly subjects. In the GSM study in young subjects, the second exposure was a UMTS exposure (SAR10g = 2W/kg) and in the TETRA study the second exposure was a TETRA exposure at a lower level (SAR10g = 1.5 W/kg). The investigated endpoints were the same as in the previous study, 30 objective and four self-rated sleep parameters. Comparisons of sleep parameters observed under sham exposure revealed highly pronounced physiological differences between young and elderly men. A main exposure effect was found for a shorter latency to persistent sleep under TETRA exposure reflecting a sleep-promoting effect. Exposure effect modifications by age were observed for two of the four self-reported sleep parameters following GSM900 exposure. The subjective number of awakenings (sAWA) and the subjective total sleep time (sTST) were differentially affected by GSM exposure in young and elderly men. There was a slight decrease in sAWA under GSM900 exposure in young men and a slight increase in sAWA in elderly men. The subjective TST increased in young men under GSM900 exposure and decreased in elderly men. Furthermore, under TETRA exposure with 6 W/kg, significant interaction effects between EMF exposure and age were observed for arousals during REM sleep. The number and index of arousals during REM sleep decreased in elderly men and showed a tendency to increase in young men. Overall all-night RF-EMF exposure effects only occurred sporadically in young and elderly men. Compared to sex differences in EMF effects in the elderly age at least in men, does not seem to matter. However, as long as there are no corresponding data from young healthy women that would allow a comparison with the data from elderly women, this assumption cannot be conclusively verified for women. Nevertheless, as for the effects observed in the elderly females the present results are not indicative of any adverse health effects.

The effect of an all-night 2.45 GHz Wi-Fi exposure on sleep Danker-Hopfe, Bueno-Lopez [92] and sleep dependent memory consolidation Bueno-Lopez, Eggert [91] was investigated in a study with a double-blind, sham-controlled, randomized fully counterbalanced design. Thirty-four healthy male volunteers were recruited for the study (age range 20 to 30 years, mean ± SD: 24.1 ± 2.9 years). Due to protocol deviations in the memory tasks (same version of the task was conducted on both experimental nights) four participants had to be excluded from statistical analysis of effects on sleep dependent memory consolidation. Participants spent five nights in the sleep laboratory, the first served as an adaptation and screening night. Nights with real and sham exposures were scheduled one week apart. The nights preceding the exposure nights served as baseline nights and to control bedtimes and the amount of sleep, respectively, before the exposure night. The exposure system was specially developed for this study (for details see Schmid, Hirtl [97]). The peak spatial SAR10g was set to <25mW/kg, the temporal average of the peak spatial SAR10g was <6.4mW/kg, representing a "strong" Wi-Fi exposure, which is still realistic in a home setting. To prevent the electrode cables from modifying the RF field distribution, electrode cables featuring a high RF impedance were constructed and used for the polysomnography recordings in this study. Exposure (real or sham) was applied for the whole night (8 h from lights out to lights on). To prevent the RF exposure from interfering with the recorded signals, shielding of the recording input device and RF blocking filters were used, and the effectiveness of the prevention was tested by using a melon phantom. Only after a comprehensive artefact detection and removal procedure data were unblinded. Repeated measures analysis of variance revealed that none of the 30 sleep parameters characterising sleep architecture, wake times, sleep continuity and arousals was significantly affected by exposure Danker-Hopfe, Bueno-Lopez [92]. Furthermore, power spectral values were calculated for frequency bands (delta: 0.50–4.00 Hz, theta: 4.00–8.00 Hz, alpha: 8.00–12.00 Hz, beta1: 12.00–16.00 Hz, and beta2: 16.00–20.00 Hz) separately for each electrode. For further analyses, electrodes were grouped into six brain regions. Repeated measures-ANOVAs performed separately for sleep stages N1, N2, N3, NREM and REM with exposure (Wi-Fi and sham) and region (frontopolar, frontal, temporal, central, parietal, and occipital) as well as their interactions as factors revealed a significant exposure effect on alpha during NREM sleep. Post-hoc analysis revealed that the global EEG Power in the alpha frequency band was significantly decreased under Wi-Fi exposure when compared to sham exposure. The authors, who on purpose did not correct the p-value for multiple testing, discussed that this result could be just by chance given the number of statistical tests.

Sleep dependent memory consolidation was analysed for declarative, emotional and procedural memory. Furthermore, EEG activity parameters which are discussed to be involved in the consolidation process (power spectra for slow oscillations and in the spindle frequency range) were considered. Emotional and procedural memory were not affected by exposure, while the overnight improvement in the declarative memory task was significantly better under Wi-Fi exposure. However, none of the post-learning sleep-specific parameters was affected by exposure. Thus, the significant effect of Wi-Fi exposure on declarative memory observed at the behavioural level was not supported by results at the physiological level. Due to these inconsistencies, this result may also be considered to be a random finding Bueno-Lopez, Eggert [91].

4.2.5 Conclusion on human studies

In summary the studies published in 2020 underline that heart rate variability is most probably not affected by RF-EMF exposure, that RF-EMF exposure effects on the resting state waking EEG are less consistent than previously reported (the latest study did not find an effect), and that effects of GSM 900 and TETRA exposure on the macrostructure of sleep need to be considered separately for males and females, since at least in the elderly population females seem to be more affected than males. On the other hand, age differences in RF-EMF effects on the macrostructure of sleep seem to be less pronounced– at least in males. Finally, isolated effects of an all-night Wi-Fi exposure on sleep and sleep related memory consolidation seem to be due to chance.

4.3 Animal studies

This year again a variety of endpoints was investigated, ranging from effects on the brain and on behaviour, genotoxicity, male fertility, early development, and temperature changes.

4.3.1 Effects on brain

Kumar, Deshmukh [98] exposed male Wistar rats in groups of 8 to 900 MHz, 1800 MHz and 2450 MHz RF EMF at a SAR of 5.84×10^{-4} W/kg, 5.94×10^{-4} W/kg and 6.4×10^{-4} W/kg, respectively. Exposure was for 2 h per day during 1, 3 or 6 months. After the last exposure, the animals were sacrificed, and the brains removed. They then assessed epigenetic modulation in the hippocampus and found it to be altered with all treatments, despite the very low SAR, since global DNA methylation was decreased and histone methylation was increased. The effect was larger with increasing frequency and exposure time and may alter gene expression.

Lameth, Arnaud-Cormos [99] exposed Sprague Dawley rats to 1800 MHz fields for 2 h to the head, with a SAR of 3.22 W/kg in the target area, a motor area of the cerebral cortex. Three groups of 6 or 7 animals each were exposed: wild-type rats, rats with an acute neuroinflammation triggered by a lipopolysaccharide (LPS) treatment, and transgenic hSOD1G93A rats as a model for a pre-symptomatic phase of human amyotrophic lateral sclerosis (ALS). In addition, a group of 7 rats was sham-exposed. They observed significant changes (both up- and downregulation) in a number of genes in the animals with neuroinflammation, but not in the other groups. They conclude that the RF EMF exposure can trigger changes in genes, depending on the pathology. However, they did not include a control group with neuroinflammation without RF EMF exposure, so it cannot be excluded that the inflammation itself caused the changes in gene expression, and not the RF EMF exposure.

Zhao, Sun [100] exposed or sham-exposed male Wistar rats (n=30 per group) to 2.856 GHz at a power density of 300 W/m^2 for 15 minutes. They observed that the escape latency in a Morris water maze was significantly increased at 7 and 15 days after exposure but returned to normal levels after 16 or more days. When astragaloside, a compound used in traditional Chinese medicine, was administered after RF exposure, there was no difference in the responses of sham and real exposed groups. Exposure resulted in structural damage of synapses in the hippocampus and an associated reduction of the neurotransmitter acetylcholine. This effect was not observed after administration of astragaloside after exposure. The authors conclude that astragaloside might be used in treatment of RF-induced injuries in the brain. The RF exposure used is much higher than the current exposure limits and might have resulted in heating of the brain.

Er, Basaranlar [101] exposed male Wistar rats in groups of 15 each to 900 MHz fields for 2 h per day and 5 days per week during 1 or 10 weeks, at a brain SAR of 0.66 W/kg. Following the last exposure, auditory brain stem responses were measured. They also assessed oxidative stress parameters in the temporal cortex and performed ultrastructural analysis. Both the latency of auditory brain wave responses as well as oxidative stress were increased at 1 week and decreased at 10 weeks. After both treatment times edema was present in the cytoplasm of neurons and astrocytes and in astrocyte end-feet.

Gao, Chen [102] investigated the blood-brain barrier (BBB) in male Sprague Dawley rats. They exposed the animals (n=18 per group) to a single ultra-wideband pulse of 50, 200 or 400 kV/m and assessed the integrity of the BBB at 0.5, 3, 6 and 24 h after exposure. They observed that the permeability of the BBB increased immediately following exposure to 200 and 400 kV/m, but not after 50 V/m, peaked between 3 and 6 h after exposure and returned to pre-exposure levels 24 h later.

Kaprana, Vardiambasis [103] exposed anesthetized 8 months-old New Zealand rabbits (no sex provided) to GSM-1800 fields to one ear. The E field strength was 0.274 V/m and exposure duration was 1, 15, 30, 45 or 60 minutes. They measured auditory brainstem responses in both ears before (baseline recordings) and after exposure. Several latencies of waves were significantly prolonged in the exposed ear compared to the corresponding baseline values after 30, 45 and 60 min exposure.

4.3.2 Effects on behaviour

Singh, Rohit [104] exposed young male Wistar rats in groups of 6 to 1966.1 MHz EMF at a whole-body SAR of 0.36 W/kg, for 2 h per day during 16 weeks. The animals were then tested for fear memory and after euthanasia the oxidative stress level in the hippocampus was assessed, as well as the level of pro-inflammatory cytokines and hypothalamic-pituitary-adrenal axis hormones. They observed an increase in hippocampal oxidative stress and elevated levels IL-1β, IL-6 and TNF-α in the blood. Adrenocorticotropic hormone and corticosterone were also significantly increased after exposure. Contextual fear memory was not significant altered.

Jeong, Son [105] exposed young and adult female C57BL/6J mice in groups of 12 to 1950 MHz fields for 2 h per day, 5 days per week during 8 months. The exposure took place in a reverberation chamber and the whole-body SAR was 5 W/kg. Body temperature did not increase more than 0.5 °C. They then measured behavioral changes at 10 and 20 months in the open-field test, the Y-maze test, and an object recognition memory task. Biological effects were analyzed via microarray gene profiling of the hippocampus. No effects on memory were observed in the young mice, but in the adult ones memory was improved after exposure. The expression of two genes involved in neurogenesis was increased in adult animals, that of 13 others was not. No changes in gene expression were observed in the young animals.

Gökçek-Saraç, Akçay [106] exposed male Wistar rats (n=11 per group) to 2100 MHz EMF for 2 h per day during 1 week. The animals were exposed/sham exposed while restrained in a tube with their head positioned towards the antenna. The brain SAR was calculated to be 0.41 or 1.3 W/kg. The highest exposure level resulted in impairment of memory in the object location and Y-maze tests. Also, levels of the cholinergic biomarkers acetylcholinesterase, choline-acetyltransferase and vesicular acetylcholine transporters were decreased in that group. No changes were observed in the group exposed to the lower level.

4.3.3 Genotoxicity

Lerchl, Klose [107] exposed pregnant female C57Bl/6N mice to a 1960 MHz UMTS signal from day 7 post-conception (p.c.) at 0 (sham), 0.04, and 0.4 W/kg SAR. At day 14 p.c., the mice were injected with the carcinogen ethylnitrosourea (ENU, 40 mg/kg). 24, 36, and 72 h later, the pregnant females (n=3-6, mostly n=3 per group and timepoint) were sacrificed and the foetuses (n = 24-57) were removed. None of the exposures had an effect on the formation of DNA adducts in the brain, liver, and lung.

Habauzit, Nugue [108] assessed gene expression in the skin of male CD hairless rats after exposure to 94 GHz EMF. Both young and adult animals (n=5 per group) were exposed for 3 h per day, 3 days per week, during 5 months. The incident power density was 100 W/m^2. No effects on gene expression in skin were observed.

Li, Lu [109] exposed male Wistar rats (n=8 per group) to 2856 MHz EMF for 10 min every other day for three days. The power density was 300 W/m^2. At 1, 7 and 14 days after exposure the animals were euthanized, their brains removed, and the hippocampus collected for analysis. The presynaptic marker VGLUT1 was downregulated at day 1 after exposure and at normal level at day 7. No changes in the postsynaptic marker PSD-95 could be detected. miR219, an important molecule in the synaptic vesicle cycle, was upregulated at day 1 and downregulated at day 7 after exposure.

4.3.4 Cancer

de Seze, Poutriquet [110] exposed male Sprague Dawley rats (n=12 per group) to very strong microwave electric fields at 10 and 3.7 GHz. With 10 GHz, the pulse duration was 1 nanosecond and pulse trains were given for 10 seconds every 5 minutes for 1 h, resulting in a peak SAR of 95 MW/kg and an average SAR of 0.34 W/kg. With 3.7 GHz, the pulse duration was 2.5 nanoseconds. These were given continuous for 14 minutes, or for 2 x 8 minutes with 10 minutes interval, either once, or daily for 5 days per week during 8 weeks. The exposure level was varied by increasing the distance to the source. The 14-min exposure resulted in a peak SAR of 90 MW/kg and an average SAR of 22 W/kg. The single 2 x 8 min exposure resulted in a peak SAR of 31 MW/kg and an average SAR of 4.7 W/kg, and the repeated 2 x 8 min exposures resulted in a peak SAR of 3.33 MW/kg and an average SAR of 0.83 W/kg over the exposure. After the short exposure at the very high exposure level of 22 W/kg, an avoidance reflex was shown, not after the other treatments. Groups of animals were sacrified at 2 or 7 days after exposure and the brain inflammation marker GFAP assessed. This was increased after all treatments at some days after exposure. The remaining animals were subsequently kept until the age of 104 weeks or earlier death. With the repeated 3.7 GHz exposures, survival time was 4 months shorter in the exposed group, with an increase in subcutaneous tumours. No such effects were found in the other groups.

4.3.5 Development

Dasgupta, Wang [111] used zebrafish as a model to study the effects of RF exposure on development. They exposed the animals to 3.5 GHz, at an SAR of 8.27 W/kg, from 6 to 48 hours after fertilization, and measured a battery of morphological and behavioral endpoints at 120 hours after fertilization (n=48 per group). They observed no significant impacts on mortality, morphology or photomotor response, with the exception of a modest inhibition of a startle response.

Li, Zhang [112] exposed pregnant female Wistar rats (n=3 or 9 per group) to 1800 and/or 2400 MHz EMF, from the 1st to the 21st day of pregnancy. Exposure was for 12 h per day at a power density of 10 W/m^2 with 1800 MHz and 1 W/m^2 with 2400 MHz. Behavioural testing was done on groups of 12 randomly chosen offspring for the exposed animals and a group of 36 controls. The Y maze test was taken at 3 weeks postnatal, and showed some shortening of searching for the 2400 MHz and the 1800+2400 MHz groups. The open field test at 7 weeks postnatal showed an increase in searching for the 1800+2400 MHz group. The expression of N-methyl-D-aspartate receptors (NMDARs) in the hippocampus at 9 weeks postnatal showed that in the 1800+2400 MHz and 2400 MHz groups, NR2A and NR2B expression was down-regulated, while NR2D, NR3A and NR3B were up-regulated. In the 2400 MHz group, NR1 and NR2C were also up-regulated. According to the authors these effects might be related to the behavioural changes.

4.3.6 Physiology

Furman, Komoshvili [113] exposed female C57BL/6 mice (n=7 per group) locally to the skin (to an area of 20x25 mm), using pulsed 101 GHz EMF. The pulses were of 5-10 µs duration and 20-50 pulses were applied at a power range of 0.5-1.5 kW. No changes were observed in various physical, physiological and behavioral endpoints.

Misek, Veternik [114] exposed non-anaesthetized male and female New Zealand white rabbits (n=10 or 11) to 1788 or 1805-1870 MHz (GSM) EMF for 150 minutes. The E field level at the head was 160 V/m. Heart rate variability (HRV) was measured before, during and after exposure. Both types of exposures resulted in changes in HRV parameters, indicating a lower heart rate.

Ouadah, Blazy [115] investigated pain perception in rats after RF exposure. They exposed male Wistar rats (n=6-12 per group) to a 900 MHz GSM signal. The exposure in restrainers was to the head, lasted 45 min per day and was given 5x per week for 4 weeks. The brain SAR was 1.5 or 6 W/kg. On the 5th day of each exposure week, pain perception was tested. Heat avoidance was significantly increased by +40% in the 6 W/kg, group compared to the sham exposed group. The effect was abolished after treatment with N-methyl d-aspartate (NMDA) immediately before the last weekly exposure, indicating that a modulatory role in heat perception is being played by NMDA receptors.

Fahmy and Mohammed (Fahmy and Mohammed [116]) exposed female Wistar rats (n=6 per group) to 2.45 GHz EMF from a Wi-Fi access point continuously for 40 days at a whole-body SAR of 0.01 W/kg. After the exposure, damage to the liver was investigated. They observed changes in oxidative stress parameters indicating increased oxidative stress. They also found a small effect on liver function, a minor alteration in its molecular structure and severe histological and ultrastructural changes, but these were not quantified.

Guo, Zhang [117] exposed Kunming mice (n=8 per group, no sex provided) to a pulsed ultrawideband signal with a pulse duration of 2 nanoseconds and a repetition rate of 100 Hz, and peak intensities of 98, 168 and 344 kV/m for, respectively, 30 and 60, 10 and 30, and 10 min. They observed significantly increased levels of ALT and AST, increased oxidative stress, and accumulation of lipid droplets in hepatocytes, which were intensity and duration dependent. The peak effect was generally observed at 2 h after exposure and subsided thereafter.

López-Martín, Jorge-Barreiro [118] exposed female Sprague Dawley rats (n=21 per group) for 30 min to 2.45 GHz EMF at a SAR of 0.1 or 0.4 W/kg to the thyroid and investigated parameters indicative of cellular stress. The intensity of immunomarking of calcitonin-positive cells was significantly higher in the thyroid tissue of exposed rats and cell hyperplasia appeared 90 min after exposure at both SAR levels. Co-localized expression of HSP-90 and calcitonin in parafollicular cells was significantly reduced 90 min after exposure and remained low 24 h after exposure.

Kim, Paik [119] exposed male Sprague Dawley rats (n=12 per group) to an RFID signal at 915 MHz for 8 h per day, 5 days per week for 2 weeks. The whole-body SAR was 2 W/kg. Tryptophan, 5-hydroxytryptophan, serotonin, 5-hydroxyindoleacetic acid, and 5-methoxyindole-3-acetic acid concentrations were examined in 24-h urine. Urinary levels of serotonin decreased by 20% and 40% in the sham and exposed groups, respectively. The level of 5-methoxyindole-3-acetic acid decreased by 30% in the exposed group only. The results indicate that the exposure can alter serotonin metabolism in rats.

de Jenlis, Del Vecchio [120] exposed young male Wistar rats (n=12 per group) for 5 weeks to continuous RF-EMF (900 MHz, SAR = 30 mW/kg) for 23 h per day. In the rest period the animals were exposed to high-level noise (87.5 dB, 50-20000 Hz). After the exposures, they measured more active wakefulness in the EMF-only group, but no differences in sleep duration. They conclude that RF EMF exposure has an effect on sleep, regardless of whether or not the animals were also exposed to noise.

Mai, Delanaud [121] investigated the effect of RF EMF exposure on body temperature in mice, measured by temperature loggers implanted in the abdomen. They exposed 3-months-old C57BL/6J mice (n=11 sham exposed, 12= RF EMF exposed, no sex provided) to a continuous RF signal at 900 MHz, 20 ± 5 V/m, for 7 consecutive days, twice per day for 1 h during the light phase. The average body temperature in the light phase in the exposed group was higher than in the control group. Administration of a TRPM8 antagonist induced a temperature decrease in sham-exposed controls, but not in real exposed mice. The TRPM8 receptor is the primary cold sensor in mammals, which was checked by a control group (n=6) housed at 5 °C.

4.3.7 Conclusions

As in previous years, there is again a variety of endpoints with varying results. This year, most included studies show effects of exposure, a few do not. The exposure parameters, such as frequency, duration and exposure level, again vary considerably between studies. It is therefore difficult to draw general conclusions other than that under certain circumstances some effects from RF EMF exposure are observed in experimental animals. However, there is too much variation to clearly state relevant exposure levels, biological relevance or effect magnitudes. The observations of increased oxidative stress reported in previous SSM reports continue to be found. It is of concern that no less than 30 out of the 54 retrieved studies had to be excluded from analysis because of various reasons as listed in the appendix. Analyses that include all studies regardless of these flawed studies will provide a biased picture. The systematic analyses performed as part of the WHO review of effects of RF EMF will take the study quality into consideration.

Table 4.3.1 Discussed studies

Endpoint	Reference	Species/ strain	Exposure and duration	Effect
Effects on brain	Kumar, Deshmukh [98]	Wistar rats	900, 1800, 2450 MHz; 2 h /d, 1, 3, 6 mo; SAR 5.84×10^{-4}, 5.94×10^{-4}, 6.4×10^{-4} W/kg	Decreased DNA methylation, increased histone methylation in hippocampus
	Lameth, Arnaud-Cormos [99]	Sprague Dawley rats, normal and with neuroinflammation	1800 MHz; 2 h; head SAR 3.22 W/kg	Gene up- and downregulation in cortex in animals with neuroinflammation
	Zhao, Sun [100]	Wistar rats	2.856 GHz; 15 min; 300 W/m^2	Increased escape latency at 7, 15 d, normal at 16+ d; synapse damage hippocampus, reduced acetylcholine
	Er, Basaranlar [101]	Wistar rats	900 MHz; 2h/d, 5d/wk, 1, 10 wk; brain SAR 0.66 W/kg	Latency auditory brain wave responses, oxidative stress increased at 1 wk, decreased at 10 wk
	Gao, Chen [102]	Sprague Dawley rats	UWB; 1 pulse; 50, 200. 400 kV/m	Permeability BBB increased 3-6 h after 200, 400 kV/m, then return to normal
	Kaprana, Vardiambasis [103]	Rabbit	1800 MHz; 1, 15, 30, 45, 60 min; 0.274 V/m	Increased latency auditory brain stem responses at 30, 45, 60 min
Effects on behaviour	Singh, Rohit [104]	Wistar rats	1966 MHz; 2 h/d, 16 wk; WBA SAR 0.36 W/kg	No effect fear memory; increased oxidative stress in hippocampus, IL-1β, IL-6 and TNF-α, adrenocorticotropic hormone, corticosterone in blood
	Jeong, Son [105]	C57BL/6 mice, young, adult	1950 MHz; 2 h/d, 5 d/wk, 8 mo; WBA SAR 5 W/kg	No effect memory in young, improved in adults; no effect genes in young, increased expression 2/15 neurogenesis genes in adults

	Gökçek-Saraç, Akçay [106]	Wistar rats	2100 MHz; 2 h/d, 1 wk; brain SAR 0.41, 1.3 W/kg	Highest SAR: impaired memory, decreased acetylcholinesterase, choline-acetyltransferase, vesicular acetylcholine transporters
Genotoxicity	Lerchl, Klose [107]	C57Bl/6N mice	1960 MHz; 8-12 d; WBA SAR 0.04, 0.4 W/kg	No effect DNA adducts brain, liver, lung
	Habauzit, Nugue [108]	CD hairless rats	94 GHz; 3 h/d, 3 d/wk, 5 mo; 100 W/m^2	No effects gene expression skin
	Li, Lu [109]	Wistar rats	2856 MHz; 10 min/ 2d, 3 d; 300 W/m^2	Downregulation presynaptic marker VGLUT1 at 1 d, normal at 7 d after exp. No changes postsynaptic marker PSD-95. Upregulation miR219 at 1 d, downregulated at 7 d after exp.
Cancer	de Seze, Poutriquet [110]	Sprague Dawley rats	3.7 GHz; 2.5 ns pulses, 14 min; SAR 22 W/kg 3.7 GHz; 2.5 ns pulses, 2x8 min; SAR 4.7 W/kg 3.7 GHz; 2.5 ns pulses, 2x8 min/d, 5d/wk, 8 wk; SAR 0.83 W/kg 10 GHz; 1 ns pulses, 10 s/5 min, 1 h; SAR 0.34 W/kg	Increased GFAP at 2 or 7 d post-exposure. Shorter survival, increased subcutaneous tumours with repeated 3.7 GHz exposures
Development	Dasgupta, Wang [111]	Zebrafish	3.5 GHz, 42 h; SAR 8.27 W/kg	No effect mortality, morphology, photomotor response, only modest inhibition of startle response
	Li, Zhang [112]	Wistar rats	1800 MHz; d1-21 pregnancy, 12 h/d; 10 W/m^2 2400 MHz, d1-21 pregnancy, 12 h/d; 1 W/m^2	Y maze @ 3wk: decreased searching 2400 and 1800+2400 MHz; open field @ 7wk: increased searching 1800+2400 MHz; down- and upregulation NMDARs hippocampus
Physiology	Furman, Komoshvili [113]	C57BL/6 mice	101 GHz; 5-10 µs pulses, 20-50 pulses; 0.5-1.5 kW	No changes in various physical, physiological and behavioral endpoints
	Misek, Veternik [114]	New Zealand white rabbits	1788, 1805-1870 MHz; 150 min; E field 160 V/m	Changes in HRV parameters, indicating lower heart rate

	Ouadah, Blazy [115]	Wistar rats	900 MHz GSM; 45 min/d, 5x/wk, 4 wk; brain SAR 1.5, 6 W/kg	Increased heat avoidance with 6 W/kg, counteracted by NMDA
	Fahmy and Mohammed [116]	Wistar rats	2.45 GHz Wi-Fi; continuous, 40 d; WBA SAR 0.01 W/kg	Increased oxidative stress liver
	Guo, Zhang [117]	Kunming mice	UWB; 2 ns pulses, 100 Hz, peak 98 kV/m, 30, 60 min; 168 kV/m, 10, 30 min; 344 kV/m, 10 min	Intensity and duration dependent increased levels of ALT and AST, increased oxidative stress, accumulation of lipid droplets in hepatocytes
	López-Martín, Jorge-Barreiro [118]	Sprague Dawley rats	2.45 GHz; 30 min; thyroid SAR 0.1, 0.4 W/kg	Immunomarkingintensity of icalcitonin-positive cells was stronger, increased cell hyperplasia, reduced HSP-90 and calcitonin in parafollicular cells
	Kim, Paik [119]	Sprague Dawley rats	915 MHz RFID; 8 h/d, 5 d/wk, 2 wk; WBA SAR 2 W/kg	Altered serotonin metabolism
	de Jenlis, Del Vecchio [120]	Wistar rats	900 MHz; 23 h/d, 5 wk; WBA SAR 0.03 W/kg + noise	Increased active wakefulness, no differences in sleep duration
	Mai, Delanaud [121]	C57BL/6J mice	900 MHz; 2x1 h/s, 7 d; 20 V/m	Increased body temperature

4.4 Cell studies

Eight studies have been recognized in the period of interest and, as for the previous Council report, in most cases no effects were detected. When differences with respect to unexposed samples were detected, they were related to the experimental conditions adopted.

4.4.1 DNA damage

Human peripheral blood lymphocytes from three donors were exposed by Gulati and co-workers to different frequencies (1923, 1947.47, or 1977 MHz) of UMTS, 40 mW/kg SAR, for 1 h and 3 h Gulati, Kosik [122]. Upon RF exposure, several endpoints were investigated, such as DNA damage, by alkaline comet assay, tumor suppressor gene TP53 (the most commonly mutated gene in human cancer) and chromosomal translocations in hematopoietic cells, resulting in so-called preleukemic fusion genes (PFG). In addition, the induction of reactive oxygen species (ROS) formation and apoptosis were measured by flow cytometry. A slight but statistically significant increase in DNA migration was detected following exposure to 1977 MHz when data from 1-h and 3-h exposures were pooled (p=0.04). Treatments with tert-Butyl Hydroperoxide served as positive control and worked properly. No mutations of TP53 gene were detected for all the conditions tested. ROS formation and apoptosis also resulted not altered by the exposure, while positive controls worked properly.

Choi and co-workers exposed for 72 h several human cell types to 1700 MHz, LTE, at 1 and 2 W/kg SAR. Choi, Min [123]. In particular, they used adipose tissue-derived stem cells (ASCs), liver cancer stem cell (CSC) populations of Huh7 and Hep3B, the neuroblastoma SH-SY5Y, the cervical cancer HeLa, and the normal fibroblast IMR-90 cells. The results of three independent experiments for each condition demonstrated that the exposure consistently decreased the proliferation of both cancer and normal cells regardless of their tissue of origin ($p<0.01$). Such a decrease varied from 30 to 88% compared to sham-exposed samples and was more pronounced at 2 W/kg SAR. In addition, they also investigated the effect of RF exposure on the induction of DNA double strand breaks (DSBs) and apoptosis in ASC and Huh7 cells in terms of expression of phospho-histone 2AX (γ-H2AX) and cleaved poly ADP-ribose polymerase (PARP), respectively. No effects were detected at both SAR values investigated. Cell cultures treated with UV or doxorubicin were used as positive controls for DNA DSBs and apoptosis and worked properly. To examine whether the decline of cell proliferation would be due to cell senescence, which slows cell cycle progression, they also evaluated β-galactosidase activity in ASC and Huh7 cells exposed to RF for 72 h. No effect was detected in cultures exposed at 1 W/kg SAR, while exposure at 2 W/kg resulted in a 42% increase in Huh7 cells. Treatments with hydrogen peroxide served as positive control and worked properly. In addition, the expression of molecular markers for cellular senescence (p21, phosphorylation of p53 at serine 15, and the phosphorylation of retinoblastoma (Rb) at serine 780) were examined and resulted modified by the exposure, suggesting induction of senescence. Cellular senescence was also confirmed by a delay in cell cycle progression, associated to an increased production of reactive oxygen species (ROS) that was negated in presence of a ROS-scavenger.

A multimethodological approach was employed by Regalbuto and co-workers to evaluate the effect of 2.45 GHz, 0,7 W/kg SAR, in human adult fibroblasts (HDF) Regalbuto, Anselmo [124]. Cell cultures were exposed in a wire patch cell for 2 h either to a CW or to the same carrier frequency modulated in amplitude with a square pulse 1 ms period and 50% duty cycle (pulsed wave, PW), representative of a Wi-Fi burst. The authors investigated the induction of genotoxic effects, evaluated as phosphorylation of H2AX histone and micronucleus formation, effects on cell cycle progression and gene expression profile through the RNA sequencing approach. The results of 3 to 4 independent experiments performed blinded indicated absence of effects for all the endpoints investigated (no positive controls were included in the study design).

Schuermann and co-workers applied classical (Comet and sister chromatid exchange assays) and novel *in vitro* approaches (live cell imaging) to assess the genotoxic potential of the wireless EMF modulations, such as UMTS, GSM, Wi-Fi and RFID, on cultured human cells. Continuous wave exposures were also included Schuermann, Ziemann [125]. Three independent experiments for each condition were carried out blinded on primary human lung fibroblast (MRC-5) and immortalized human trophoblast cell line (HTR-8/SVneo). Cell cultures were intermittently exposed (5/10 min on/off cycles) for 1, 4 and 24 h. Exposure to GSM signal was carried out at 2 W/kg SAR, while exposures to UMTS and Wi-Fi signals were at 4.92, 2 and 0.5 W/kg. Exposures to RFID were at 4.92 W/kg. Treatments with γ radiation and ethyl methane sulfonate served as positive controls and gave the expected DNA damage. Key experiments were independently performed in two laboratories, using identical cell lines, standardized experimental protocols, and the same exposure equipment. Since in the literature two studies in particular indicated that exposure to generic GSM signals (SAR 2 W/kg) can increase the level of DNA damage in primary human fibroblasts and in immortalized trophoblast cells, to validate the published data, the authors also included the conditions tested in such studies. On the whole, negative results were obtained, including the experimental conditions that previously reported positive findings. The authors discussed the underlying reasons for this discrepancy and identified cell culture conditions and the CA methodology as likely relevant variables.

4.4.2 Other cellular endpoints

Li and co-workers exposed intermittently (5 min on/10 min off) mouse embryonic fibroblasts NIH/3T3 to 1800 MHz, 2 W/kg SAR, for different periods of time (12, 24, 36, 48 h) and evaluated several parameters, such as viability, apoptosis, p53 expression and mitochondrial structure. For each parameter investigated at least three independent experiments were carried out Li, Song [126].

Cell viability was decreased in cultures exposed for 48 h ($p < 0.05$), compared to the sham-exposed ones. Such an effect was not detected for shorter exposure durations. Similar results were obtained when apoptosis was evaluated: after 48 h exposure the percentage of late apoptotic cells and the total percentage of apoptotic cells in the exposure groups were higher than those in the sham groups and such an increase resulted statistically significant for late apoptotic cells ($p < 0.05$). The expression of p53 at the mRNA level increased significantly by 1.4-fold following 48 h exposure compared with the sham group ($p < 0.05$). Immunofluorescence and confocal microscopy confirmed such an increase at both 24 and 48 h. On the contrary, western blot analysis did not show differences compared to sham-exposed samples. Immunofluorescence and confocal microscopy were also employed to evaluate the number of intact mitochondria. The results indicate a slight but not statistically significant decrease following the exposure.

The effect of 935 MHz RF-EMF, GSM signal, on apoptosis, autophagy, oxidative stress and electron exchange was investigated by Zielinski, Ducray [127] in murine microglial cells (N9) and human neuroblastoma cells (SH-SY5Y). The exposure/sham exposure was carried out for 2 and 24 h (2 min on/2 min off cycles) at 4 W/kg SAR. For each cell type and experimental condition three independent experiments, performed double blinded, were carried out. The results indicated that apoptosis, evaluated by flow cytometry and by measuring the expression of the apoptosis markers AIF, Bcl-2 and Bax, was not affected by the exposure. Treatments with Staurosporine were used as positive control and induced apoptosis, as expected. Autophagy (an intracellular machinery for degrading damaged and aggregated proteins and organelles, involved in the pathology of neurodegenerative disorders) was evaluated by measuring several markers, including ATG5 and LC3B-I and II and pERK. For some experimental conditions an increase was measured in RF-exposed samples, but it was not statistically significant, except for ATG5 protein levels in SH-SY5Y exposed for 24 h ($p \leq 0.05$). To evaluate oxidative stress, GSH levels and H2O2 production was measured. No differences were detected with respect to sham controls, except for GSH that resulted higher in SH-SY5Y cells exposed for 6 h. Cytochrome c oxidase activity, measured in N9 cells only, resulted decreased after 2 h exposure ($p \leq 0.05$), but no 24 h, compared to sham-exposed controls.

In a study carried out by Szilágyi and co-workers the effect of combined exposure to solar UV radiation and 1950 MHz, UMTS modulation, on inflammation processes was investigated Szilagyi, Nemeth [128]. A 3D full thickness human skin model was employed, and RF exposure was given before or after UV irradiation. The inflammation process was examined by evaluating cytokines (IL-1α, IL-6, and IL-8) and Matrix Metalloproteinase-1 (MMP-1) enzyme secretion to check whether the combined exposure enhances the adverse effect of exposure to UV radiation (UV + RF; Protocol#1) or if prevent the skin from adverse effects of UV radiation (RF + UV; Protocol#2). The UV exposure was realized by using a solar simulator lamp and the exposure was at 2 (Protocol#1) and 4 SED (Protocol#2) for 30 and 60 min, respectively. For Protocol #1, immediately after 30 min UV exposure, RF was given (20 min on/20 min off) for 24 h at a 4 W/kg, while for Protocol #2 a continuous exposure of 24 h was performed at 1.5 W/kg and after 4 h UV was given for 1 h. The sham-exposed groups served as negative control. For both protocols, cells were incubated for 24 h and cytokines and MMP-1 concentration were evaluated by ELISA and the results were expressed as mean of three independent experiments. The results of experiments performed under Protocol#1 showed no significant changes in the IL-1 α and IL-6 concentration, while a significant increase in the IL-8 concentration was found in UV-treated samples. The concentration of the MMP-1 enzyme in the samples treated with UV alone was significantly higher than that in the samples treated by sham exposure or UV + RF. The samples treated with RF alone did not show differences compared to sham samples. In the experiments performed under Protocol#2, all the parameters investigated were increased by the UV treatment, while a slight, not significant decrease in UV-induced damage was detected in samples pre-exposed to RF.

One study was carried out at higher frequencies:
Human keratinocytes were employed by Martin and co-workers to investigate whether the gene regulation observed in a previous paper Habauzit, Le Quement [129] was specific to the type of cell used or whether it reflected a more general regulation that could be found regardless of the cell type

studied Martin, Percevault [130]. For this purpose, four cell types were used, three pools of primary human keratinocytes isolated from neonatal foreskins (HEK_3N, HEK_1N and NHEK_3N) and a derived keratinocyte cell line (HaCaT). Cell cultures were exposed in the same experimental conditions applied in the previous study, such as for 3 h to 60.4 GHz at a peak SAR value of 1.233 W/kg. By comparing exposed and sham-exposed samples, the results of 3 to 6 experiments did not confirm the ability of RF exposure to modify the regulation of the three protein-encoding genes investigated: ADAMTS6, IL7R and NOG. Since the experiments were conducted at the same frequency, in the same exposure system, and for the same exposure duration, the authors concluded that the biological model exerts a strong influence on the data obtained, which may at least partly explain the heterogeneity of the reported results in bioelectromagnetic research.

4.4.3 Summary and conclusions for cell studies

The new *in vitro* studies evaluated several biological endpoints, including DNA damage, gene and protein expression, proliferation, apoptosis and oxidative stress. The results are not univocal, with increase, decrease or no difference compared to sham controls. It is interesting to note that two of them are replication studies and the results previously reported have not been confirmed.

Unfortunately, as in previous years, a number of studies had to be excluded from the analysis, mainly due to the lack of dosimetric information or of sham-exposed cultures to be used as control. 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.

Table 4.4.1. Cell studies on exposure to radiofrequency fields

Cell type	Endpoint	Exposure conditions	Effect	References
Human peripheral blood lymphocytes n=3	SB, gene mutation, apoptosis, ROS formation	923, 1947.47, 1977 MHz, UMTS 40 mW/kg 1 h and 3 h	Slight increase in SB at 1977 MHz (pooled data at 1 and 3 h) No effects for the other endpoints investigated.	Gulati, Kosik [122]
ASC, Huh7, Hep3B, SH-SY5Y, HeLa, and IMR-90 cells. n=3	Proliferation, cell cycle, DSB, apoptosis, senescence, ROS	1700 MHz, LTE 1 and 2 W/kg 72 h	Decreased proliferation in all cell types and for all the conditions tested. ASC and Huh7 cells: no effect on DSB and apoptosis. Induction of senescence in Huh7 cells exposed at 2 W/kg	Choi, Min [123]
Human adult fibroblasts (HDF) n = 3-4	γ-H2AX foci, MN, cell cycle, gene expression	2.45 GHz SAR 0.7 W/kg 2 h	No effects.	Regalbuto, Anselmo [124]
Primary human lung fibroblasts (MRC-5) Human trophoblasts (HTR-8/SVneo) n = 3	SB, SCE	900 MHz, GSM, CW SAR 2 W/kg 1, 4, 24 h 1950 MHz, UMTS SAR 0.5, 2, 4.92 W/kg 1, 4, 24 h Wi-Fi SAR 0.5, 2, 4.92 W/kg 1, 4, 24 h 866 MHz, RFID SAR 0.5, 2, 4.92 W/kg 24 h (5 min on/10 min off)	No effects. Replication study of Diem, Schwarz [131] and Franzellitti, Valbonesi [132]	Schuermann, Ziemann [125]
Mouse embryonic fibroblasts NIH/3T3 n = 3	viability, apoptosis, p53 expression and mitochondrial structure	1800 MHz 2 W/kg 12, 24, 36, 48 h 5 min on/10 min off	Decreased viability and increased apoptosis after 48h exposure; Increased expression of P53 at mRNA level and by confocal microscopy, not confirmed by WB analysis; No effects on mitochondrial structure	Li, Song [126]

Murine microglial cells (N9) Human neuroblastoma cells (SH-SY5Y) n = 3	apoptosis, autophagy, oxidative stress, electron chain transport	935 MHz, GSM 4 W/kg 2 and 24 h 2 min on/2 min off	Increased ATG5 protein levels in both cell types exposed for 24 h. Decreases cytochrome c oxidase activity in N9 cells exposed for 2 h.	Zielinski, Ducray [127]

3D human skin model n = 3	IL-1α, IL-6, IL-8; MMP-1	1950 MHz, UMTS 1.5 and 4 W/kg 24 h, continuous or 20 min on/20 min off UV before or after RF	UV+RF: no effect of RF alone; no combined effects RF+UV: no effect of RF alone; no combined effects	Szilagyi, Nemeth [128]
Primary human keratinocytes (HEK_3N, HEK_1N and NHEK_3N) HaCaT cell line n = 3-6	Expression of three protein-encoding genes	60.4 GHz 1.233 W/kg 3 h	No effects. Results reported in Habauzit et al., 2014 not confirmed.	Martin, Percevault [130]

Abbreviations: CW: Continuous Wave; DSB: double strand breaks; GSM: Global System for Mobile Communication; IL: interleukin; LTE: long term evolution; MMP-1: Matrix Metalloproteinase-1; MN: micronuclei; RFID: Radio-frequency identification; ROS: reactive oxygen species; SAR: specific absorption rate; SB: strand breaks SCE: sister chromatid exchanges; UMTS: universal mobile telecommunications system; UV: ultraviolet; WB: western blot; Wi-Fi: Wireless Fidelity.

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. 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, the excluded studies[12] are listed and the reasons for exclusion are indicated. The list is divided into epidemiological studies, human studies, animal studies and cell studies.

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).

Further, the following exclusion criteria were applied after screening the abstracts:

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.
N) Studies on self-reported quality of life outcomes/psychological outcomes and media use if they do not explicitly mention EMF

Reference	Reason for exclusion
Akkam, A Al-Taani [133]	I
Alexias, Kiouvrekis [134]	B
Amoon Amoon, Swanson [31]	B
Alexias, Kiouvrekis [135]	B
Bagheri Hosseinabadi, Khanjani [136]	B
Bagheri Hosseinabadi, Khanjani [44]	B
Bektas, Dasdag [137]	I
Birks, van Wel [138]	B
Boehmert, Witthöft [139]	B
Bottauscio, Arduino [140]	B

[12] 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.

Brascher, Schulz [95]	F*
Bueno-Lopez, Eggert [91]	F*
Almirall [141]	B
Christopher, Mary [142]	H
Dasdag, Adalier [143]	K
de Andrade, de Figuêiredo [144]	B
De Giudici, Genier [145]	B
Dergham, Alayli [146]	F
Dieudonné [147]	K
Eggert, Dorn [94]	B
Gao, Zheng [148]	B
Górski, Kotwicka [149]	F
Gupta, Sharma [150]	K
Haanes, Nordin [151]	B
Hardell and Carlberg [152]	B
Hardell, Carlberg [153]	E
Hardell and Nyberg [154]	B
Hosseinabadi, Khanjani [155]	C
Hosseinabadi, Khanjani [156]	C
Huang, Li [157]	N
International Commission on Non-Ionizing Radiation Protection [158]	B
Khan, Juutilainen [159]	B
Koh, Choi [160]	B
Kurnaz and Aygun [161]	B
Kurnaz and Mutlu [162]	B
Li, Chen [163]	L
Liu, Luo [164]	A
Luo, Li [165]	H
Magiera and Solecka [166]	K
Moon [167]	B
Okechukwu [168]	B
Pareja-Peña, Burgos-Molina [169]	K
Park, Jeong [170]	B
Rahban and Nef [171]	C
Ramirez-Vazquez, Arabasi [172]	B
Regrain, Caudeville [173]	B
Selmaoui and Touitou [174]	K
Seo, Choi [175]	B
Shih, O'brien [176]	Retracted study
Stege, Bolte [177]	B
Stein and Udasin [178]	B
Suri, Dehghan [179]	B
Tyrakis, Gourzoulidis [180]	B
Wang and Wiart [181]	B

* Included in the human study chapter

Human studies

Static fields (SF) and extremely low frequency (ELF) fields

Reference	Reason for exclusion
Grant, Metzger [182]	No sham condition

Radiofrequency fields (RF)

Reference	Reason for exclusion
Alassiri, Alanazi [183]	No sham exposure condition, different verum exposures applied in a fixed order
Azmy, Shamloul [184]	no sham and exposure condition, all subjects received 15 min sham prior to 30 min exposure, and 15 min sham post exposure, commercial mobile phone, no detailed exposure characterisation, no double-blinding, no information about electromagnetic interference with the EEG recording device, no information on handling of EEG artefacts.
Kacprzyk, Kocoń [185]	No exposure control
Shokoohi-Rad, Ansari [186]	non exposure non exposure comparison

Animal studies

Static fields (SF) and extremely low frequency (ELF) fields

Reference	Reason for exclusion
Ahn, Jung [187]	Treatment-related. HD-tDCS and functional improvement in ischemic stroke mice.
Albert, Deschamps [188]	Review. Magneto- and electrosensitivity in marine invertebrates.
Barnes and Greenebaum [189]	Theoretical paper. Mechanism(s) of weak static and slowly varying MF on animals' nerve cells and orientation.
Barnes and Greenebaum [190]	Non-experimental. Discussion of research needs and how weak field exposure guidelines for long- term exposures might be set.
Batool, Bibi [191]	Review of benefits and hazards of electromagnetic waves.
Bhattacharyya, Sahu [192]	Treatment related (spinal cord contusion). No sham exposure.
Bukia, Jojua [193]	Treatment-related (depression). Imprecise description of animal model.
Burns, Kamykowski [194]	Electroshock weapon/TASER and spinal injury in a porcine model.
Cai, Shao [195]	Treatment-related (osteogenesis in rats). Co-exposure of PEMF & mechanical vibration. No real sham.
Cai, Shao [196]	Treatment-related. Glucocorticoid therapy, bone fragility & PEMF treatment in rabbits.
Caspar, Moldenhauer [197]	GMF. Eyes are essential for magnetoreception in mole-rats.
Charles James and Funke [198]	Treatment-related. (TMS & excitability of visual cortex). rTMS improves the visual performance in dark reared Long-Evans rats.
Cheng, Wu [199]	Treatment-related. Spinal cord injury & electro-acupuncture.
Chernetsov, Pakhomov [200]	GMF. Adult (experienced) night-migratory songbirds use magnetic declination for long-range navigation.
Chicas- Mosier, Radi [201]	GMF. In foraging honeybees small fluctuations in GMF are less important than other stimuli.
Dong, Li [202]	Treatment-related. *Ex-vivo* epilepsy model using the brain slices of rats exposed by 0.5 Hz MF.
Driessen, Bodewein [203]	Review of biological and health-related effects of weak static magnetic fields (≤ 1 mT) in humans and vertebrates.
Duncan and Dinev [204]	Treatment-related. Non-invasive induction of muscle growth in pigs by HIFEM (pulses of up to 1.8 T). Exposure description weak.
Ernst, Fitak [205]	GMF, magnetoreception of lobsters. Influence of 5 ms magnetic pulses of max. 85 mT on gene expression. Duration of exposure nebulous.
Fitak, Wheeler [206]	GMF. Magnetite-based magnetoreception in rainbow trout.
Fredericks, Petersen [207]	Treatment-related. PEMF & combined MF effects on healing of a rabbit tibial osteotomy.
Gellner, Reis [208]	DCS and induction of synaptic plasticity in the sensorimotor cortex. Exploratory study in transgenic mice.
Halaas and Bernardy [209]	Treatment-related (reduction of adipose tissue). Pilot study in 2 pigs testing effects of HIFEM (alternating dynamic MF of up to 1.8 T).
Hong, Liu [210]	Treatment-related (ischemic stroke). rTMS in ischemic rats.
Jung, Ahn [211]	Treatment-related (ADHD). Therapeutic effects of HD-tDCS on recovery from cognitive symptoms in a rat model of ADHD.
Kobylkov, Schwarze [212]	GMF & magnetoreception in night-migratory birds.

Krylov, Papchenkova [213]	GMF. Diurnal geomagnetic variation is an additional zeitgeber for biological circadian rhythms in Daphnia magna.
Li, Shang [214]	Treatment-related (cerebral ischemia). rTMS "alleviates neurological deficits".
Lin, Chang [215]	Treatment-related (bone restoration). SPEMF restores bone mass and microarchitecture.
Liu, Bi [216]	Treatment-related (osteoporosis). PEMF & disuse osteoporosis in rats.
Liu, Xiong [217]	Treatment-related (spinal cord injury). rTSMS & axonal regeneration in the spinal cord.
Luukkonen, Naarala [218]	Treatment-related (cancer). Pilot study. Effects of Rf-MF, SMF, HMF on growth of implanted tumors in mice.
Margalef, Bosque [219]	Treatment-related (MPS). Percutaneous EF (4 x 0.4 mA, 3 x 1.5 mA for 5 s each) in a mouse and rat model.
Matsuda, Takikawa [220]	Pilot-tests using a new and simple electrostatic-based experimental system to enable investigations of insect behavior (rice weevils and cigarette beetles)
Mert, Sahin [221]	Treatment-related. Combination of a) antiLy6G monoclonal antibody or b) minocycline and PMF exposure using the CG inflammation rat model.
Mikaelyan, Eloyan [222]	Treatment-related (cancer). 4 Hz 0.2 mT PMF treatment of tumor inoculated mice.
Murris, Arsenault [223]	Treatment-related. DBS targeting the ventral tegmental area (i.e., midbrain structure) in 2 macaques.
Naisbett-Jones, Putman [224]	GMF & magnetoreception in fish (salmon).
Nuccitelli, McDaniel [225]	Treatment-related (cancer). NPS & implanted hepatocellular carcinoma in rats.
Ogneva, Usik [226]	GMF, also other exposures without EMF of fruit flies.
Oh, Kwon [227]	GMF. Geomagnetic imprinting / transgenerational inheritance in fruit flies.
Orlov, Gurieva [228]	GMF. HMF influence on the embryogenesis of Japanese quail.
Ouyang, Zhang [229]	Treatment-related (arthritis). Antiinflammatory effects of PEMF in mouse synovitis.
Peng, Fu [230]	Treatment-related. PEMF after myocardial ischemia in mice.
Perucca Orfei, Lovati [231]	Treatment-related. PEMF & healing process in a rat model of Achilles tendinopathy. Pilot study.
Putman, Williams [232]	GMF. Magnetic displacement experiments in pink salmon.
Qian, Liu [233]	Treatment related: Liver regeneration in mice after nsPEF ablation.
Qian, Wang [234]	Treatment-related. PEMF & sclerostin monoclonal antibody in rabbits with ovariectomy-induced osteoporosis.
Ryu, Paulk [235]	Treatment related. Optimization of intracortical micro-magnetic stimulation using implanted micro-coils in mice.
Sefton, Iwasa [236]	Treatment-related. Electrical (cortical) stimulation *in vivo* (mouse) *and in vitro* expanded the size of the neural stem cell pool and enhanced neurogenesis.
Sun, Dhamne [237]	Treatment-related (epilepsy, depression). cDCS *in vitro* in mouse motor cortex and in human postoperative neocortex, *in vivo* in mouse somatosensory cortex, and in a mouse kainic acid-seizure model.
Takikawa, Takami [238]	Body water loss and conductivity in (dehydrated, rehydrated, refrigerated, and frozen) houseflies.
Topal, Çina Aksoy [239]	Treatment related. PEMF & bone healing in rats with heparin-induced osteoporosis.

Turner, Degan [240]	Treatment related (e.g., stroke). TES & cerebral blood flow. Linear correlation between TES dose and peak blood flow increase.
Uzun, Erdal [241]	Treatment-related. Comparison of PEMF and extracorporeal shockwave therapy in a rabbit model of Achilles tendon injury.
Vale and Acosta- Avalos [242]	GMF & magnetosensitivity: Magnetic inclination & departure angle from the nest of stingless bees.
Wan, Liu [243]	GMF. 45 µT vs. 50µT migration-related traits of insects.
Wan, Jiang [244]	GMF. Near-zero MF reduces bw via affecting insect feeding behavior and underlying regulatory processes
Winarni, Husen [245]	Treatment-related (diabetes). EF, MF & IR ray combination in mice.
Xue, Yang [246]	Treatment-related. Hypomagnetic field inhibits recovery of bone loss in mice.
Ye, Chen [247]	Treatment-related (epilepsy). PMF stimulation using of hippocampus in mice using a miniature coil system.
Ye, Guo [248]	Treatment-related. PEMF & knee osteoarthritis in mice.
Zhang and Tian [249]	Review. HMF & ROS
Zhu, Liu [250]	Tumor treatment in mice using moderate SMFs (0.3 & 0.6 T) which enhances antitumor CD8+ T cell function.

ADHD: attention-deficit hyperactivity disorder; bw: body weight; DBS: deep brain stimulation; c: cathodal & (t)DCS: (transcranial) direct current stimulation; CG: carrageen; EF: electric field; GMF: geomagnetic field, HD-tDCS: high definition tDCS; HIFEM: High-intensity focused electromagnetic field, HMF: hypomagnetic magnetic field; IR: infrared; MF: magnetic field; MPS: myofascial pain syndrome; NPS: nano-pulse stimulation; nsPEF: nanosecond pulsed electric field; PEMF: pulsed electromagnetic field(s); P(E)MF: pulsed (electro)magnetic field; rf: radiofrequency; ROS: reactive oxygen species; rTMS: repetitive transcranial magnetic stimulation; rTSMS: repetitive trans-spinal magnetic stimulation; SPEMF: single pulsed electromagnetic field; TES: transcranial electrical stimulation

Intermediate frequency fields (IF)

Reference	**Reason for exclusion**
Son, Park [251]	Treatment-related. Effect of single IF radiation (2 MHz, 10 W, for 100 ms) on UVB-induced mouse model of rosacea *in vitro* and *in vivo*.
Wu, Wang [252]	Treatment-related. Tumor electric field (200 kHz, 0.84 V/cm) treatment system in a rat model of glioma.

Radiofrequency (RF) fields

Reference	**Reason for exclusion**
Asl, Goudarzi [253]	No sham, incomplete exposure description, no dosimetry
Aghajari, Mortazavi [254]	No sham exposed group, no description of dosimetry
Azimzadeh and Jelodar [255]	No sham RF exposed group
Azimzadeh and Jelodar [256]	No sham RF exposed group
Azimzadeh and Jelodar [257]	No RF sham exposed group, unclear dosimetry
Borzoueisileh, Monfared [258]	No dosimetry, lateral exposure of cages, so inhomogeneous field

Borzoueisileh, Monfared [259]	No dosimetry, lateral exposure of cages, so inhomogeneous field
Brasil, Marroni [260]	Intramuscular delivery, no RF frequency given
Dondoladze, Nikolaishvili [261]	Bad dosimetry (elektrosmog meter), exposure animals unknown
Haghani, Pouladvand [262]	No dosimetry
Hong, Huang [263]	No dosimetry
Hussien, Mousa [264]	No dosimetry, mob phone under cage
Keleş [265]	No sham control group
Pardhiya, Gaharwar [266]	No sham exposed group
Sharma, Shrivastava [267]	Incomplete / incorrect dosimetry
Sharma and Shukla [268]	Incomplete / incorrect dosimetry
Shokri, Shamsaei [269]	Mobile phone on cage, no dosimetry
Su, Zhu [270]	Culture medium but not zebrafish embryos directly exposed.
Sultangaliyeva, Beisenova [271]	No dosimetry, inadequate description of exposure setup
Tafakori, Farrokhi [272]	No sham control group
Tohidi, Sadr-Nabavi [273]	No dosimetry, no sham exposed group
Usman, Isyaku [274]	No dosimetry, exposure unknown
Sabri í–zen, Ateş [275]	No sham, no dosimetry
Vafaei, Kavari [276]	Incorrect dosimetry
Vafaei, Motejaded [277]	No sham, no dosimetry
Yahyazadeh and Altunkaynak [278]	No sham exposed group
Yahyazadeh and Altunkaynak [279]	No sham exposed group
Yu, Tang [280]	No dosimetry, exposure levels not clear
Zhang, Guo [281]	No dosimetry
Zymantiene, Juozaitiene [282]	Mobile phone as source, no dosimetry, not clear whether controls are sham

Cell studies

Static Magnetic Felds (SMF)

Reference	Reason for exclusion
Ben Yakir-Blumkin, Loboda [10]	No sham-control
Ashta, Motalleb [283]	No sham-control
Medeiros, Assumpcao [284]	No sham-control; number of independent experiments not reported
Yang, Li [285]	No sham-control
Zhu, Liu [250]	No sham-control

Extremely low Frequencies (ELF)

Reference	Reason for exclusion
Ki, Kim [286]	No sham-control
Koziorowska, Depciuch [58]	No sham-control
Lekovic, Drekovic [287]	No sham-control
Li, Liu [288]	No sham-control
Li, Liu [289]	No sham-control
Vinhas, Rodrigues [290]	No description of the exposure system
Górski, Kotwicka [149]	No sham-control
Naghibzadeh, Gholampour [291]	No sham-control
Ji, Teng [292]	No sham-control
Ashta, Motalleb [283]	No sham-control

Radiofrequency fields (RF)

Reference	Reason for exclusion
Azimipour, Zavareh [293]	No dosimetry. Exposure performed with a commercial device
Grasso, Pellitteri [294]	No dosimetry. Exposure performed with a commercial device
Özsobacı, Ergün [295]	No sham-control
Panagopoulos [296]	No dosimetry. Exposure performed with a commercial device
Szymański, Sobiczewska [297]	No sham-control
Kim, Lee [298]	No sham-control
Darvishi, Mashati [299]	Narrative review
Leszczynski [300]	Narrative review
Poque, Arnaud-Cormos [301]	Outside of area of expertise
Poque, Ruigrok [302]	Outside of area of expertise

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