Research

Recent Research on EMF and Health Risk

Fifteenth report from SSM's Scientific Council on Electro-magnetic Fields, 2020

2021:08

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.

Objectives

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

The present report is number fifteen in the series and covers studies published from January 2019 up to and including December 2019. The report covers different areas of EMF (static, low frequency, intermediate, and radio frequency fields) and different types of studies such as biological, human and epidemiological studies.

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

New research on brain tumours and mobile phone use is in line with previous research suggesting mostly an absence of risk. The thyroid gland is potentially highly exposed during mobile phone calls but little research on thyroid cancer has been conducted so far. However, some suggestive elevated incidence of thyroid micro-carcinoma associated with long-term and more frequent mobile phone use have been observed. Recall bias of self-reported mobile phone use may be an alternative explanation for these results.

Associations between mobile phone use and non-specific symptoms such as headache, and mental health problems have been observed in epidemiological studies. However, several studies suggest that these associations may be attributed to other factors such as short sleep duration or stress. One factor that contradicts that radio wave exposure is a significant contributing element is that stronger correlations are often seen when the exposure level is expected to have been low.

The studies published in 2019 support that RF exposure does not change the concentration of biomarkers in human beings with symptoms attributed to electrohypersensitivity. However, the sample sizes of the studies were small, thereby limiting the statistical power to show absence of a risk with satisfactory certainty.

In line with previous reports, the animal study section reports observed increased oxidative stress due to weak radio wave exposure, some even

below the 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.

As previous years, there are reports of observed effects on behaviour and spermatozoa (without an effect on male fertility, however) in animal studies. However, there is not much consistency between the studies.

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. 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.

The 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 authorities´ recommendation to generally limit exposure to low frequency magnetic fields therefore still remains. It is the Swedish Environmental code[1] that applies when there is a need to assess precautionary measures in the area.

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.

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[1] Chapter 2 in the Swedish Environmental Code , see https://www.government.se/legal-documents/2000/08/ds-200061/ The English version is not completely up to date but the precautionary principle described in chapter 2 is valid. For an updated version, see the Swedish version https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/miljobalk-1998808_sfs-1998-808

The incidence time trends for thyroid cancer are increasing. There could be numerous different reasons for this. However, the newer mobile phone generations can potentially give relatively high radio wave exposure to the thyroid gland and therefore it is desirable to closely examine a possible causal relationship. So far, the research regarding this issue has been limited.

There is also a need to further investigate the observed effects on behaviour and spermatozoa observed in animal studies. Since consistency between the studies are lacking, it is important to emphasize that the next step here should be to develop high quality study designs. This step is necessary before these observations can contribute to the overall picture of knowledge.

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. Only about 100 in vivo and in vitro studies are available that have considered exposures to frequencies higher than about 6 GHz. 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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Recent Research on EMF and Health Risk
Fifteenth report from SSM's Scientific Council on Electromagnetic Fields, 2020

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

Recent Research on EMF and Health Risk

Fifteenth report from SSM's Scientific Council on Electromagnetic Fields, 2020

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 fifteen in the series and covers studies published from January 2019 up to and including December 2019.

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

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

Stockholm in November 2020

Leif Moberg
Chair

Executive Summary

This report reviews studies on electromagnetic fields (EMF) and health risks, published from January 2019 up to and including December 2019. The report is the fifteenth 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.

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)[1] are magnetic resonance imaging (MRI) devices for medical diagnostic purposes. 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
No epidemiological study on static fields has been identified during the reporting period.

Human studies
One study shows that some subjects unconsciously react by neural activity to Earth strength magnetic fields. This study needs replication by an independent group of researchers. In another study the application of a static magnetic field over the supplementary motor area with magnetic flux densities of 166 and 92 mT at a distance from the surface of 2 and 3 cm, respectively, led to increases in the time to initiate movements in correct trials in a choice-reaction time task while the number of errors decreased. At a functional level exposure led to an increased resting-state activity as observed by fMRI.

Animal studies
High-strength magnetic fields in the range of 2 to 23 T did not significantly affect general health, blood cell count or blood chemistry in mice. Hippocampal neurotransmitters, learning and memory in mice exposed to a 35 kV/m static electric field, a field strength in the range of the strength at ground level with high-voltage direct-current transmission lines, were not significantly affected. This is mostly in line with previous results. In fish exposed in the range of 2.5 to 200 mT, slight delays in some developmental parameters (growth of inner ear, yolk-sac absorption rate, hatching time) were observed. The reported effects of static fields on oxidative stress and metabolism in aphid and cockroach are hard to assess.

Cell studies
The results of the *in vitro* studies identified in this period suggest that static fields are able to induce slight variations in the biological endpoints considered, such as protein conformation, cell viability and chemically-induced oxidative stress.

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[1] These magnetic fields (>1 T) are about a thousand times stronger than magnetic fields used in animal and cell studies which are most often in the mT-range. The geomagnetic field at the Earth´s surface ranges from 25 to 65 microtesla (µT). For comparison a fridge magnet has a strength of about 0.005 tesla when measured at close distance.

Extremely low frequency (ELF) fields

The exposure of the general public to extremely low frequency (ELF) fields (>0 Hz-300 Hz) is primarily from 50 and 60 Hz electric power lines and from electric devices and wiring in buildings. Regarding the exposure to ELF magnetic fields and the development of childhood leukaemia 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. One study addressed the question whether occupational ELF-MF exposure or electrical shocks could underlie observed increased risks of amyotrophic lateral sclerosis, and found both to be associated. This is of interest as previous studies rather identified one or the other exposure as underlying observed associations. An Italian study addressing exposure from high voltage power lines and Alzheimer's and Parkinson's disease does not suggest associations. A large Canadian study reported very slightly increased risks of birth defects in children born to mothers exposed to high voltage power lines.

Human studies

The number of studies identified continues to be very low with just one study in the current reporting period. This study systematically analysed thresholds for phosphene perception and showed that independent from location of stimulation perception threshold is lowest for 16 Hz. However, the thresholds differ between stimulation locations.

Animal studies

Similar to the previous Council reports, studies used exposure levels mostly in the 0.5 to 2 mT range at 50 Hz. Two studies in mice showed improved learning and memory in exposed animals. Five reports on cytokines by an Iranian research group do not provide a clear conclusion regarding the immune response following ELF-MF exposure. It is not explained if all data originate from one single experiment or several similar studies were run between 2018 and 2020. In particular, a sound interpretation of the immunosuppressive effects after low-level exposure (1 to 100 µT) versus no effect after mid-level exposures (0.5 and 2 mT) is missing. Nevertheless, the repeatedly observed decreased numbers of $CD8^+$ T cells in exposed juvenile mice may indicate a biological effect of ELF-MF. In addition, a newly developed mouse specific model should be used for ELF-MF studies addressing the etiology of childhood B-cell acute lymphoblastic leukemia.

A study on honeybees showed that ELF-MF may be an environmental stressor for flying insects, having impact on their aversive learning and aggression level. The rainbow trout studies demonstrated some developmental retardation of the inner ear and of the yolk sac absorption. A report on altered weight and antioxidative markers in the gut of cockroach nymphs led to a speculation of a future use of cockroach nymphs as an indicator of increased environmental ELF-MF levels.

In conclusion, the very different reports of effects following ELF-MF exposure demonstrate again the absence of knowledge on biological-relevant mechanisms of ELF-MF in the range 1 mT and below.

Cell studies

The new *in vitro* studies confirm the previous Council conclusions. Several endpoints have been investigated and in most cases no effect of the exposure was detected. It is interesting to note that several studies deal with the evaluation of action mechanisms of interaction between ELF fields and cell proliferation.

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 because human exposure to such fields is increasing, for example from different kinds of electronic article surveillance systems and the increasing use of induction cooking. Studies on possible effects associated with chronic exposure at low levels are particularly relevant for confirming adequacy of international exposure limits.

Epidemiology
No epidemiological IF study was identified during the reporting period.

Human studies
No human experimental study on effects of IF exposure was identified in 2019. A systematic review was published on biological effects of electric, magnetic and electromagnetic fields in the intermediate frequency range (300 Hz to 1 MHz). Three of the 56 studies included in this review were human studies. All studies considered effects on visual and cognitive functions. Overall, the authors state that the evidence for adverse health effects of fields in the IF range is inadequate for drawing conclusions. This is specifically true for the human studies, based on the risk-of-bias rating, one of these studies showed an impaired quality. The other two showed conflicting results.

Animal studies
Within the kHz range, relevant for wireless power transfer systems, no significant differences in transcriptional expression of brain and liver in mice were observed. Importantly, a lack of carcinogenicity of exposure to a 20 kHz IF magnetic field in a specific mouse model was demonstrated.

Cell studies
The results of the studies considered are contrasting, although different cell types and different exposure conditions have been investigated.

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 health effects associated with exposure to radiofrequency fields. Measurements and exposure calculations have shown that a person's radiofrequency field exposure is dominated by personal mobile phone use. The exposure from environmental sources such as mobile phone base stations plays a minor role.

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 is on the intention to use 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 the higher data rates and faster connection, frequency bands of around 26 GHz will be used in a more distant 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

New research on brain tumours and mobile phone use is in line with previous research suggesting mostly an absence of risk. The thyroid gland is potentially highly exposed during mobile phone calls but little research on thyroid cancer has been conducted so far. A case-control study of 701 cases from the USA found no significant association between mobile phone use and thyroid cancer, although some suggestive elevated risk of thyroid micro-carcinoma associated with long-term and more frequent mobile phone use was observed. Recall bias of self-reported mobile phone use may be an alternative explanation for these results. A subsequent gene-environment analysis did not provide consistent evidence.

Associations between mobile phone use and non-specific symptoms such as headache, and mental health problems were observed. However, several studies suggest that these associations were mediated by other factors such as short sleep duration or stress. Noteworthy is the first paper from the COSMOS study. To date, this is the largest prospective study on headache, tinnitus and hearing loss using objective mobile phone usage data obtained from the network operators. No association with tinnitus and hearing loss were observed, but headache was developed slightly more often in participants with the longest call time. The association was mainly found for participants making calls in the UMTS network and not for those in the GSM network. This indicates that observed associations were unlikely to be caused by RF-EMF, because when making calls in the newer UMTS network, RF-EMF exposure is about 100 to 500 times lower than in the GSM network. Innovative approaches allowing differentiating between device usage and physical RF-EMF exposure are needed to better understand the causality of RF-EMF exposure for health.

Human studies

The studies published in 2019 support that RF exposure does not change the concentration of biomarkers in electrohypersensitive subjects. However, in the new studies sample sizes were small limiting the statistical power to prove absence of a risk. Three studies addressing brain effects during wake found physiological changes related to RF exposure, two of them with contradictory results. This underlines that effects which have been considered to be consistent in the past are less consistent than stated. Effects at the physiological level, however, do not necessarily translate into behavioural measures as shown by a lack of effects on cognitive performance outcome measures. A sleep study revealed no effects of UMTS exposure on symptoms, sleepiness, reaction time, subjective perception of sleep and sleep macrostructure. The observed decrease of the spectral power in the slow spindle frequency range during REM sleep does not confirm previous findings.

Animal studies

As in previous years, there is again a variety of endpoints with mixed and sometimes contradicting results. Some studies show effects of exposure, others do not. The exposure parameters, such as frequency, duration and exposure level, also 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 Council reports continue to be found, as are effects on behaviour and spermatozoa (without an effect on male fertility, however). But there is not much consistency between the studies. Indeed, the conclusion from last year's Council report that there is a need for systematic reviews of these studies before any conclusions concerning the possible implications for human health can be drawn is still valid. Such reviews are now underway as part of the major review on effects of RF EMF exposure that is performed by WHO.

Cell studies

The new *in vitro* studies confirm the previous Council conclusions: several endpoints have been investigated and in most cases no effect of the exposure was detected.

Sammanfattning

I rapporten granskas studier av elektromagnetiska fält och hälsorisker, publicerade från januari 2019 till och med december 2019. Det är den femtonde 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.

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)[2] 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

Ingen epidemiologisk studie rörande statiska fält har identifierats under rapporteringsperioden.

Studier på människa

En studie visar att några försökspersoner omedvetet reagerar genom neural aktivitet i hjärnan vid exponering för fält av samma storleksordning som det jordmagnetiska fältet. Denna studie behöver upprepas av andra forskare. I en annan studie användes statiska magnetfält med styrkorna 166 mT och 92 mT för att exponera ett område i hjärnan beläget på storhjärnans yta framför primärmotorbarken (supplementära motorområdet). Exponeringarna skedde på ett avstånd av 2 cm respektive 3 cm från ytan. Detta ledde till en ökning av den tid det tog för att initiera korrigeringar i en val-reaktionstidsuppgift medan antalet fel minskade. På funktionell nivå ledde exponering till en ökad aktivitet på vilonivå observerat med funktionell magnetresonanstomografi, fMRI (med denna teknik kan man se skillnad på syrerikt och syrefattigt blod, vilket ger information om hjärnans aktivitet lokalt).

Djurstudier

Exponering för mycket starka magnetfält, 2 till 23 T, påverkade inte påtagligt det allmänna hälsotillståndet, blodvärdet eller blodkemin hos möss. Ingen tydlig påverkan kunde ses på ämnen som överför nervsignaler i hippocampus, inlärning eller minnesfunktioner, hos möss som exponerats för ett statiskt elektriskt fält på 35 kV/m. Denna fältstyrka är i samma nivå som fältstyrkan vid marknivå under högspänningsledningar för likström. Detta ligger i linje med tidigare resultat. Hos fiskar som exponerats för fält mellan 2,5 och 200 mT har smärre förseningar observerats i några utvecklings-parametrar - innerörats tillväxt, gulesäckens absorptionstid, och kläckningstid. De effekter på oxidativ stress och metabolism som rapporterats hos bladlus och kackerlacka vid exponering för statiska fält är svåra att bedöma.

Cellstudier

Resultaten från de *in vitro*-studier som identifierats under rapporteringsperioden antyder att exponering för statiska fält kan orsaka smärre variationer hos de biologiska parametrar som studerats, som proteinkonformation, cellöverlevnad och kemiskt inducerad oxidativ stress.

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[2] De statiska magnetfälten i en magnetkamera är större än 1 T vilket är omkring tusen gånger starkare än de magnetfält som normalt används i djurstudier och cellstudier som oftast är i milliteslaområdet. Det geomagnetiska fältet vid jordytan varierar mellan 25 och 65 mikrotesla. En vanlig kylskåpsmagnet har en styrka på cirka 0,005 Tesla (5 millitesla) om man mäter alldeles intill.

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. En studie undersökte om yrkesexponering för lågfrekventa fält eller elektriska stötar skulle kunna vara orsak till en observerad ökad risk för ALS (amyotrofisk lateralskleros) och fann samband för båda exponeringarna. Detta är av intresse eftersom tidigare studier snarare tytt på att antingen den ena eller den andra exponeringen kunde ligga bakom observerade samband. I en italiensk studie rapporteras inte några samband mellan exponering från högspänningsledningar och Alzheimers sjukdom eller Parkinsons sjukdom. En stor kanadensisk studie rapporterar en mycket liten ökning av risken för fosterskador hos barn till mödrar som exponerats för fält från högspänningsledningar.

Studier på människa

Antalet studier som identifierats är fortfarande litet med endast en studie publicerad under rapporteringsperioden. Studien har systematiskt undersökt tröskelvärden för att uppfatta fosfener (signaler från näthinnans nervceller till syncentrum som tolkas av hjärnan som synupplevelser) och resultaten tyder på att tröskelvärdet är lägst vid 16 Hz. Tröskelvärdena varierar emellertid beroende på var stimuleringen ägt rum.

Djurstudier

Som rapporterats tidigare, använder de flesta identifierade studier exponeringsnivåer som oftast ligger i området 0,5 till 2 mT vid 50 Hz. Två studier på möss visade förbättrad inlärning och minnesfunktion hos exponerade djur. Fem rapporter rörande cytokines (den celldelning som följer omedelbart efter mitosen) av en forskargrupp från Iran ger inte något tydligt svar på vilken immunrespons som kan följa efter exponering för lågfrekventa fält. Det är oklart om alla data härrör från ett enda experiment eller från flera experiment som genomförts mellan 2018 och 2020. Framför allt saknas en rimlig förklaring till de effekter som verkar hämma immunförsvarets funktion efter exponering för låga fältnivåer (1 till 100 µT) jämfört med avsaknaden av påverkan från medelhöga nivåer (0,5 till 2 mT). Men de upprepade fynden av ett minskat antal CD8$^+$ T-celler hos unga möss skulle kunna tyda på en biologisk effekt av lågfrekventa elektromagnetiska fält. En nyligen utvecklad specifik musmodell bör användas vid studier av möjliga orsaker till akut lymfatisk leukemi av B-cellsursprung hos barn.

En studie på honungsbin visar att lågfrekventa fält skulle kunna vara en stressfaktor för flygande insekter med betydelse för deras aggressionsnivå och inlärning av ogynnsamma beteenden. Studier på regnbågsforell har visat på en viss försenad utveckling av innerörat och av gulesäckens absorption. En rapport om ändrad vikt och antioxidativa markörer i tarmkanalen hos kackerlackslarver har lett till spekulationer om en framtida användning av sådana larver som en indikator på ökande nivåer av lågfrekventa fält i miljön.

Sammanfattningsvis, de många olika rapporterna om påverkan efter exponering för lågfrekventa fält demonstrerar än en gång frånvaron av kunskap om relevanta biologiska mekanismer från exponering för lågfrekventa fält i området under 1 mT.

Cellstudier

De nya *in vitro*-studierna bekräftar Rådets tidigare slutsatser. Flera olika cellparametrar har studerats och i de flesta fall har ingen påverkan av exponering för lågfrekventa fält observerats. Det är intressant

att notera att ett flertal studier syftar till att utvärdera mekanismer för samverkan mellan lågfrekventa fält och celldelning.

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 men eftersom det endast finns ett mycket begränsat antal studier tillgängliga kan inga slutsatser dras för närvarande. Fler studier skulle vara värdefulla eftersom människor exponeras för dessa fält i ökande grad, t.ex. från olika typer av utrustning för artikelövervakning och en ökande användning av induktionshällar för matlagning. Studier av möjliga effekter vid långvarig exponering för låga nivåer är särskilt betydelsefulla för att bekräfta tillförlitligheten i gällande rikt- och gränsvärden.

Epidemiologi
Ingen epidemiologisk studie inom området intermediära fält har identifierats under rapporteringsperioden.

Studier på människa
Under 2019 har inte någon experimentell studie på människa identifierats inom det intermediära frekvensområdet. En systematisk granskning har publicerats av biologiska effekter av exponering för elektriska, magnetiska och elektromagnetiska fält inom frekvensområdet. Tre av de 56 studier som ingick var studier på människa. De studierna behandlade visuella och kognitiva funktioner. Sammanfattningsvis menar författarna att underlaget är otillräckligt för att dra några slutsatser rörande skadliga hälsoeffekter från exponering för fält inom det intermediära området. Detta gäller särskilt för studier på människor på grund av risken för bedömningsfel. En av dessa studier var av dålig vetenskaplig kvalitet, de andra två uppvisade motsägande resultat.

Djurstudier
Inom kHz-området, som bl.a. utnyttjas i system för trådlös kraftöverföring, har inga tydliga skillnader i transkriptionsuttryck kunnat iakttas i hjärna eller lever hos möss (transkription, eller RNA-syntes, är den process varmed genetisk information i cellens DNA översätts till information i RNA). Frånvaro av cancerutveckling vid exponering för ett 20 kHz intermediärt magnetfält som demonstrerats i en specifik musmodell, bedöms som viktigt.

Cellstudier
Resultaten av de utvärderade studierna är motsägande, olika celltyper och olika exponeringsförhållanden har undersökts.

Radiofrekventa fält

Allmänheten exponeras för radiofrekventa fält (10 MHz-300 GHz) från en mängd olika källor som radio- och TV-sändare, trådlösa telefoner och mobiltelefoner och deras respektive basstationer samt från trådlösa datornätverk. Delar av allmänheten känner oro för möjliga hälsoeffekter som skulle kunna orsakas av exponering för radiofrekventa fält. Mätningar och beräkningar har visat att de högsta exponeringsnivåerna orsakas av användning av egen mobiltelefon. Omgivningskällor som basstationer för mobiltelefoni spelar endast en mindre roll.

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

Resultaten från ny forskning rörande eventuella samband mellan hjärntumörer och användning av mobiltelefon ligger i linje med tidigare forskningsresultat och tyder huvudsakligen på en avsaknad av risk. Sköldkörteln skulle kunna vara högexponerad vid mobiltelefonsamtal men inte mycket forskning rörande samband mellan sköldkörtelcancer och användning av mobiltelefon har genomförts hittills. En fall-kontroll-studie på 701 fall från USA fann inte något signifikant samband mellan användning av mobiltelefon och förekomst av sköldkörtelcancer, även om en möjlig förhöjd risk för småcellig cancer kunde observeras i samband med långvarig och frekvent användning av mobiltelefon. Minnesfel vid självrapporterad mobiltelefonanvändning kan vara en alternativ förklaring till resultaten. En uppföljande gen-miljöanalys gav inga klara bevis.

Samband mellan mobiltelefonanvändning och icke-specifika besvär som huvudvärk och mental ohälsa har observerats. Flera studier tyder dock på att dessa samband orsakades av andra faktorer som för lite sömn och stress. Noterbart är att den första artikeln från COSMOS-studien har publicerats. Detta är den hittills största framåtblickande studien av huvudvärk, tinnitus och hörselnedsättning som använder objektiva data på mobilanvändning från mobiloperatörerna. Inga samband med tinnitus eller hörselnedsättning kunde ses, men huvudvärk utvecklades något oftare hos deltagare med de längsta samtalstiderna. Sambandet fanns huvudsakligen hos deltagare som använde UMTS-nätverket och inte hos de som använde GSM-nätverket. Detta tyder på att det är osannolikt att de observerade sambanden skulle bero på exponering för radiofrekventa fält eftersom, när man ringer samtal i de nyare UMTS-nätverken så är exponeringen vanligen 100 till 500 gånger lägre än i GSM-nätverken. Innovativa tillvägagångssätt som möjliggör en uppdelning mellan besvär orsakade av apparatanvändning och besvär orsakade av exponering för radiofrekventa fält behövs för att förstå vilka orsakssamband som kan finnas mellan exponering och hälsa.

Studier på människa

De studier som publicerats under 2019 stödjer att exponering för radiofrekventa fält inte ändrar koncentrationen av biomarkörer hos elkänsliga personer. Antalet försökspersoner var dock relativt litet vilket begränsar den statistiska styrkan hos resultaten och därmed möjligheten att bevisa att risken är obetydlig. Tre studier som undersökt effekter i hjärnan hos vakna personer fann fysiologiska förändringar relaterade till exponering för radiofrekventa fält, två av dem med motsägande resultat. Detta understryker att effekter som tidigare har ansetts robusta inte är så pålitliga. Effekter på fysiologisk nivå behöver dock inte nödvändigtvis leda till beteendemässiga förändringar som kan avläsas i parametrar som beskriver den kognitiva förmågan. En sömnstudie med UMTS-exponering visade ingen påverkan på symtom som sömnighet, reaktionstid, subjektiv upplevelse av sömn och sömnens makrostruktur. Den observerade sänkningen av effekten av spektret i det långsamma spindelfrevensområdet under REM-sömn bekräftar inte tidigare resultat.

Djurstudier

Liksom tidigare år omfattar studierna en mängd olika variabler med varierande och ibland motsägande resultat. Några studier visar effekter av exponering, andra inte. Exponeringsparametrarna, som frekvens, exponeringstid och exponeringsnivå, varierar också kraftigt mellan olika studier. Därför är det svårt att dra några allmänna slutsatser annat än att man under speciella omständigheter kan observera en del effekter hos försöksdjur som exponerats för radiofrekventa fält. De fynd av ökad oxidativ stress som rapporterats i tidigare rapporter från Rådet fortsätter att observeras liksom beteendemässiga effekter och effekter på spermier, dock utan att man ser någon påverkan på hanars fortplantningsförmåga. Men det finns inte mycket samstämmighet mellan studierna. Slutsatsen från förra årets rapport, att det behövs en systematisk genomgång av dessa studier innan man kan dra några slutsatser angående möjliga konsekvenser för människors hälsa, gäller fortfarande. En sådan granskning pågår nu som en del av den stora genomgång av effekter av exponering för radiofrekventa fält som genomförs av WHO.

Cellstudier

De nya *in vitro*-studierna bekräftar Rådets tidigare slutsatser. Ett flertal olika parametrar har studerats och i de flesta fall har ingen påverkan av exponeringen iakttagits.

Preamble

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

As a general rule, only articles that are published in English language peer-reviewed scientific journals[3] since the previous report are considered by the Council. A main task is to evaluate and assess these articles and the scientific weight that is to be given to each of them. However, some of the studies are not included in the Council report either because the scope is not relevant, or because their scientific quality is insufficient. For example, poorly described exposures and missing unexposed (sham) controls are reasons for exclusion. Such studies are normally not commented upon in the annual Council reports (and not included in the reference list of the report)[4]. Systematic reviews and meta-analyses are mentioned and evaluated, whereas narrative and opinion reviews are generally not considered.

The Council considers it to be of importance to evaluate both positive and negative studies, i.e. studies indicating that exposure to electromagnetic fields has an effect and studies indicating a lack of an effect. In the case of positive studies the evaluation focuses on alternative factors that may explain the positive result. For instance, in epidemiological studies it is assessed with what degree of certainty it can be ruled out that an observed positive result is the result of bias, e.g. confounding or selection bias, or chance. In the case of negative studies it is assessed whether the lack of an observed effect might be the result of (masking) bias, e.g. because of too small exposure contrasts or too crude exposure measurements. It also has to be evaluated whether the lack of an observed effect is the result of chance, a possibility that is a particular problem in small studies with low statistical power. Obviously, the presence or absence of statistical significance is only one of many factors in this evaluation. Indeed, the evaluation considers a number of characteristics of the study. Some of these characteristics are rather general, such as study size, assessment of participation rate, level of exposure, and quality of exposure assessment. Particularly important aspects are the observed strength of the association and the internal consistency of the results including aspects such as exposure-response relation. Other characteristics are specific to the study in question and may involve aspects such as dosimetry, method for assessment of biological or health endpoint and the relevance of any experimental biological model used.[5]

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

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[3] 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.

[4] 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.

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

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

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

Previous Council reports concluded that epidemiological studies confirmed associations between magnetic resonance imaging (MRI) work and experiencing acute symptoms. Newer studies suggested possible risks of menometrorrhagia in women using intrauterine devices, accidents during commuting and high blood pressure. Underlying mechanisms are unclear. It was concluded that future studies should explore if these associations are true or if alternative explanations such as residual confounding, i.e. other factors related to MRI work and the outcomes under investigations, underlie the observed associations.

No epidemiological study on static fields has been identified during the reporting period.

1.2. Human studies

The number of experimental studies investigating the impact of static magnetic fields in humans continues to be very low. In 2019 two studies with sufficient quality were identified.

Based on the observation that various animals are sensitive to Earth's magnetic field, Wang et al. (2019a) investigated whether humans lost a shared, ancestral magnetosensory system or whether the system is modified so that there is no conscious component while effects on neural activity are still present. To test these options, Wang et al. (2019a) investigated possible brain reactions to different magnetic stimuli in 36 volunteers (24 male, 12 female), age range 18 to 68 years. A number of stimuli (constant and changing fields with various orientations and polarities) were designed to differentiate between three possible physical principles of reception: (1) electrical induction, (2) chemical reactions and (3) ferromagnetism. The authors observed specific and repeatable effects on oscillation of the electroencephalogram (EEG) in the alpha frequency range (8 – 13 Hz) in some volunteers resulting from two classes of rotations of Earth-strength magnetic fields (35 µT). Effects were observed in some subjects for 1) vertical (inclination) rotation of the field vector, 2) counter clockwise horizontal (declination) rotation with a downward oriented vertical field present while e.g. clockwise rotation did not lead to an effect. Since the neural response was sensitive to static components of the magnetic field, electrical induction was ruled out as a mechanism. Furthermore, a free-radical "quantum compass" was ruled out as a possible mechanism, since the neural response was also sensitive to the polarity of the field. The authors thus concluded that magnetite based ferromagnetism seems to be responsible for the underlying mechanism.
Although great effort was made to prevent artificial effects and non-magnetoreception transduction, it cannot be ruled out that subconsciously perceived cues of other quality (for example sound or vibrations) generated in delivering the different stimuli caused the observed effects. An attempt to independently replicate the results is needed.

Pineda-Pardo et al. (2019) analysed whether the transcranial focal application of a static magnetic field of a permanent magnet (tSMS) over the supplementary motor area (SMA) in healthy young subjects affects local changes in brain function. They performed two experiments, which included altogether 79 healthy volunteers. In the first one, which consisted of three sub-experiments, behavioural after-effects of 30 min tSMS stimulation were analysed in a double-blind sham-controlled design. In experiment (1a), which was performed with a parallel-group design, 20 subjects (14 females and 6 males, 31.9 ± 9.3 years) received tSMS stimulation of the SMA and 22 (14 females and 8 males, 31.2 ± 8.4 years) received sham exposure stimulation. In experiment (1b) a subgroup of 16 subjects from experiment (1a), 8 with real exposure and 8 with sham exposure (11 females and 5 males, 33.1 ± 8.1 years), received stimulation of the SMS in a cross-over design. Finally, in experiment (1c) 17 new subjects (12 females and 5 males, 29.4 ± 7.4 years) received stimulation of the primary motor cortex (M1) in a single-blind cross-over design. In experiment (2) functional after-effects were measured using resting-

state functional magnetic resonance imaging (fMRI) in a randomized, double-blind sham-controlled cross-over study. The sample consisted of 20 healthy volunteers (9 females and 11 males, 28.5 ± 5.2 years). The amplitude of the low frequency fluctuations, the regional homogeneity (ReHo) and the whole brain seed-based functional connectivity using regions of interest were investigated. A permanent magnet or an identically looking sham device (non-magnetic metal piece) was applied to the SMA or M1. The magnetic flux densities at 2 and 3 cm distance from the surface of the magnet were 166 and 92 mT, respectively. Behavioural outcome was measured by reaction times in three different tasks. Independently from the task, tSMS increased the time to initiate movements in correct trials while decreasing errors in choice reaction-time tasks. At a functional level exposure led to an increased resting-state activity as observed by functional magnetic resonance imaging (fMRI). Furthermore, an increased bilateral connectivity between the SMA and both the paracentral lobule and the lateral frontotemporal cortex have been observed. The authors conclude that "the results suggest that tSMS over the SMA can induce behavioural after-effects associated with modulation of both local and distant functionally-connected cortical circuits involved in the control of speed-accuracy trade-offs, thus offering a promising protocol for cognitive and clinical research." However, for all the experiments there was at least a tendency that subjects correctly guessed the exposure condition.

1.2.1. Conclusions on static field human studies

There is one study which shows that some subjects unconsciously react by neural activity to Earth strength magnetic fields. This study needs replication by an independent group of researchers. In another study a focal application of a static magnetic field led to effects at the behavioural and functional level.

1.3. Animal studies

For the reporting year 2019, nine experimental studies using non-mammalian species were identified, while only three described mouse experiments. In two mouse experiments strong magnetic fields up to 23 T were applied, while the third mouse study was run with a static electric field of 35 kV/m, which is in the range of field strengths at ground level beneath high voltage DC power lines.
Mostly studying larval development, the non-mammalians covered fish (rainbow trout, Northern pike, and zebra fish), aphid and cockroach. Except one zebra fish study with 9 T, the field intensities were in the range from 2.5 to 200 mT or 2 to 6 kV/m.

1.3.1. Brain and behaviour

Di et al. (2019) compared effects of 35 kV/m static electric field (0 Hz, SEF) and 35 kV/m ELF-EF (50 Hz) on cognition and hippocampal neurotransmitters in mice[6]. Groups of n=10 male 4-week old ICR mice were 24 h/d continuously exposed to SEF for 7, 14, 21, 35 and 49 days, another n=10 mice per time-point served as non-exposed controls. The exposure unit was the same as used by Wu et al. (2017). In addition, the first 3 time-points correspond to Di et al. (2018) (Council reports SSM 2019 and SSM 2010). Following 7, 14, 21, 35 or 49 days of SEF-exposure, the hippocampus was removed and the levels of the main excitatory neurotransmitter glutamate (Glu) as well as of the main inhibitory neurotransmitter γ-aminobutriy acid (GABA) were determined. Before humanely killing and hippocampal sampling, spatial learning and memory was tested by the use of Morris water maze on days 2-6, 9-13, 16-20, 30-34 and 44-48, respectively. Compared to non-exposed control mice, the exposure to 35 kV/m static electric field did not significantly change learning and memory ability. Also no significant differences in Glu and GABA levels were detected.

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[6] The ELF-EF part of the study is described in chapter 2.3.1.

1.3.2. Physiology, pathophysiology and oxidative stress

Tian et al. (2019) exposed male C57BL/6J mice at high SMF of 3.5, 6.7, 13.5, 21.9 and 23.0 T, respectively, for 2 h in non-magnetic stainless steel tubes. The water-cooled magnet provided a 23.0 T SMF in the center and descending SMF intensities with various gradient (B') off the center. As a result, mice in the upper part of the magnet were in 'hypogravity' whereas mice in the bottom part were in 'hypergravity' conditions. Therefore, for 6.7, 13.5 and 21.9 T two groups of n=6 mice each were used. Only one group was exposed at 3.5 T (low B' =27.7 T/m) and at 23.0 T (B' =0 T/m). A total of 8x6 mice were SMF-exposed, 8x6 mice were sham-exposed and further 16 mice were tube-restrained outside the magnet. Following the single 2h-treatment and conventional housing for another 3 weeks, all mice were humanely killed. Food consumption and body weight were slightly decreased for 23.0 T-exposed mice only. The 13.5 T field with the highest gradient (117.2 T/m) caused spleen weight increase, while white blood cell (WBC), neutrophils and lymphocytes were decreased. WBC was slightly, but significantly decreased by all SMF intensities, lymphocyte numbers by 13.5, 21.9 and 23.0 T. Total bilirubin, aspartate transaminase and platelet numbers were slightly affected by SMFs. Overall, SMF-exposure using strong magnetic fields for 2 h has no severe "long-term effects" on basic organ and blood parameters in mice.

Another Chinese research group (Wang et al., 2019b), continously exposed groups of n=12 male C57BL/6 mice at 3 different high static magnetic field (HiSMF) strengths (2–4 T, 6–8 T, and 10–12 T) for 28 days. A fourth group of 12 mice was sham-exposed. Body weight, hematology, blood chemistry, (relative) organ weights, and histomorphology of major organs were analyzed. The three HiSMF had no significant effect on body weight, relative organ weights, or histomorphology of major organs (heart, liver, spleen, lungs, brain, kidneys, testicles, duodenum and proximal femur). Also, there were no effects seen on most routine blood and biochemical parameters, but the value of the mean corpuscular hemoglobin was increased in the 2–4 T group compared with that of the other groups, and the uric acid level was decreased in all three HiSMF groups compared with that of the sham control group. Similar to the overall results of the above experiment (Tian et al., 2019), the C57BL/6 mice were not significantly affected when exposed to different HiSMF for 28 days.

1.3.3. Studies in Non-Mammalians

Fey et al. (2020) determined in rainbow trout the effect of a 10 mT SMF or a 50 Hz, 1 mT ELF-MF on the developmental instability of the inner ear organ, expressed by otolith size fluctuating asymmetry (FA) index[7]. Larval rainbow trout were reared and exposed to 10 mT for 37 days (13 days in egg stage and 24 days in larval stage (= days post hatching (dph)). Three subgroups (n=40, n=60 and n=60) were exposed to 10 mT SMF or sham-exposed to the geomagnetic field (GMF) for 5, 15 and 23 dph. Analysis of the FA-index demonstrated an increased otolith size FA in SMF-exposed rainbow trout, with the highest significance in youngest larvae of 5 dph (compared to larvae 15 and 23 dph). The data indicate that underwater constructions and cables which emit a SMF of 10 mT or higher can affect the functioning of the hearing and balance organ of nearby living fish larvae.

In a second experiment with rainbow trout and using the very same exposures, Fey et al. (2019b) tested further parameters of early development, like embryonic and larval mortality, hatching time, and larval growth. Eggs and larvae were exposed to a SMF of 10 mT (and a 50 Hz, 1 mT ELF-MF)[8] for a period of 36 days (i.e., from eyed egg stage to approximately 26 dph). Three replications of 500 eggs each were 10 mT SMF- or (sham-) exposed for 6, 11, 16, 21 dph (n≈40 per subgroup) and 24 dph (n=100 live larvae each). SMF had no significant effect on embryonic or larval mortality, hatching time, larval growth, and the time of larvae swim-up from the bottom. However, SMF enhanced the yolk-sac absorption rate.

In a third experiment, Fey et al. (2019a) exposed eggs and larvae of Northern pike for 6 dph to a 10 mT SMF or to the GMF (sham control). The exposures were replicated once. Per group and replication

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[7] The ELF-EF part of the study is described in chapter 2.3.6.
[8] The ELF-EF part of the study is described in chapter 2.3.6.

n=50 pike were used. Comparing SMF- and sham-exposed pike, hatching success, larvae mortality, size of larvae at hatching and their growth rate during the first 6 days of life were almost the same. But compared to sham control, a significant SMF-effect was observed on the time of hatching (one day earlier), on yolk-sac size (smaller) at 1 dph, and yolk-sac absorption time (faster in SMF-exposed larvae). Faster yolk-sac absorption time in a MF was interpreted as an indication of increased metabolic rate. Nonetheless, the researchers assess the actual risk for increased Northern pike larvae mortality due to the above factors as negligible.

Ge et al. (2019) exposed zebra fish eggs, just after fertilization, for 24 h to a 9.0 T SMF. Developmental effects were studied until 6 days post fertilization. The applied 9 T SMF was neither lethal nor teratogenic. But slower hatching, pharyngeal development and body growth, altered gene expression and inferior performance in behavioural tests, compared to control, demonstrated some delayed development. Finally, the authors used a computational simulation explaining the developmental delay by the interference of SMF in microtubule and spindle positioning during mitosis.

Under controlled greenhouse conditions, Luo et al. (2019b) examined the activities of anti-oxidative enzymes and the metabolic rate of the aphid *Sitobion avenae* over multiple (2nd, 6th, 11th, 16th, and 21st) generations in response to direct and host-seed exposure to a high-voltage electrostatic field (HVEF) of varying strength (0, 2, 4, 6 kV/cm, 20 min) for different durations (20, 40, 60 min at 4 kV/cm). Relative to the control activities, 20-min exposure of *S. avenae* and wheat seeds to a 2- or 4-kV/cm HVEF resulted in increased activity of superoxide dismutase (SOD) in the 6th, 11th, 16th, and 21st generations, whereas SOD activity was decreased in the 2nd generation. Catalase (CAT) and peroxidase (POD) activities decreased over all tested generations. The lowest values of CAT and POD were found with the 20-min 4 kV/cm treatment, longer durations did not show further decreases. Similarly, the 4-kV/cm HVEF for 20 min decreased also the metabolic rates of *S. avenae*, as demonstrated by CO_2 production rate. According to the authors, these findings increase the understanding of plant-pest interactions under HVEF environments and may lead to an improvement of integrated management strategies for *S. avenae*.

Sedigh et al. (2019) investigated stress and reproductive parameters of acute (one-week) and sub-acute (three-week) exposure of 3 different SMF on adult zebra fish by assaying glucose, cortisol, E2 (estradiol), 17-OHP (17α-hydroxyprogesterone) and fecundity. Groups of 10 zebra fish (5 female + 5 male) were one-week and three-week exposed for 1 h/d at 0 (control), 2.5, 5.0 and 7.5 mT SMF, respectively. Each treatment (one-and three-week) was replicated three times. Immediately after exposure, the zebra fish were frozen (-70°C) for later analysis. Following acute and sub-acute exposures, whole body concentrations of cortisol, glucose increased almost SMF-'dose'-dependently, while in females E2 and 17-OHP was most decreased at 7.5 mT SMF. Finally and especially after three-week exposure, fecundity revealed a significant 'dose'-dependent decrease – with no spawning at 7.5 mT SMF. Summarizing, higher SMF-levels (5.0 and 7.5 mT) demonstrated some harmful effects on stress and reproductive parameters.

Sun et al. (2019a) exposed Medaka fish embryos over the whole period of the embryo development, i.e. 15 days, at a SMF of 80 to 98 mT. Subgroups of n=15 were exposed for 1, 3, 6, 10 and 15 days, respectively. Further 3 subgroups were sham exposed. Swimming behaviour of adult male Medaka fish was tested under exposure of approximately 70 to 200 mT. Embryo development, i.e., the embryo malformation rate, did not alter. Differences of growth cycle were not observed. But in adults the swimming behaviour, average swimming velocity, and swimming positions were different between SMF- and sham-exposed fish. SMF-exposed fish tended to dwell.

Todorović et al. (2019) examined effects of chronic exposure of orange-spotted cockroach (*Blaptica dubia*) nymphs to a SMF or 50 Hz magnetic field on gut mass and antioxidant markers[9]. One month-old cockroach nymphs (n=10 per group) were exposed for 5 months each: (1) 110 mT SF, (2) 50 Hz, 10 mT ELF-MF, (3) control. The exposure of cockroach nymphs (groups 1 and 2) led to a

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[9] The results following exposure to 50 Hz, 10 mT ELF-MF are described in chapter 2.3.6.

significantly reduced gut weight compared to controls. Analysis of antioxidative markers in homogenates from individual *B. dubia* guts demonstrated that the enzyme activities of the antioxidative markers SOD and CAT were significantly increased in exposed nymphs of groups 1 and 2, while the activities of glutathione reductase and glutathione S-transferase were significantly reduced. SMF had no effect on total glutathione. Summarizing their results, the authors speculate about the use of cockroach as an indicator of increased environmental levels of MF.

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

High MF in the range of 2 to 23 T did not significantly affect general health, blood cell count and blood chemistry in mice. Hippocampal neurotransmitters, learning and memory in mice exposed to 35 kV/m SEF, a field-strength in the range of the ground level of high-voltage direct-current transmission lines, were not significantly affected. This is mostly in line with previous reports.
In fish exposed in the range of 2.5 to 200 mT, slight delays in some developmental parameters (growth of inner ear, yolk-sac absorption rate, hatching time) were observed. The effects of static fields on oxidative stress and metabolism in aphids and cockroach are hard to assess.

Table 1.3.1. Animal studies on exposure to static magnetic fields

Endpoints	Reference	Exposure SMF / SEF	Exposure Duration and Species	Effect
Rodent studies				
Brain and behaviour	Di et al. (2019)	35 kV/m	7, 14, 21, 35, 49 d 24 h/d Mouse	No significant effects on learning & memory, Glu and GABA levels in hippocampus.
(Patho)Physiology	Tian et al. (2019b)	3.5, 6.7, 13.5, 21.9, 23.0 T	2 h Mouse	Strong SMF has no severe long-term effects.
	Wang et al. (2018b)	2-4, 6-8, 10-12 T	28 d Mouse	No significant effects on bw, organ weights, hematology, blood biochemistry and histomorphology.
Studies in Non-Mammalians				
	Fey et al. (2019a)	10 mT	37 d (13 d egg + 24 dph) Rainbow trout	Increased otolith fluctuating asymmetry may affect hearing & balance.
	Fey et al. (2019b)	10 mT	19 d (13d egg + 6dph) Northern pike	Hatching 1 d earlier, yolk-sac size smaller, yolk-sac absorption faster.
	Fey et al. (2019c)	10 mT	36 d (12 d egg + 24 dph) Rainbow trout	No effect on embryonic & larval mortality, hatching time & larval growth. Increased yolk-sac absorption rate.
	Ge et al. (2019)	9 T	24 h 6 d dpf observation Zebrafish (eggs)	Developmental delay
	Luo, Luo et al. (2019)	2, 4, 6 kV/cm	20, 40, 60 min Aphid	Increased SOD, decreased CAT, POD, and metabolic rate
	Sedigh et al. (2019)	2.5, 5.0, 7.5 mT	1 wk, 3 wk 1 h/d Zebrafish (adult)	'Dose'-dependent a) increase of cortisol & glucose (m+f), b) decrease of E2 & 17-OHP, and c) decrease of fecundity.
	Sun et al. (2019a)	80-200 mT	1, 3, 6, 10,15 d *24h/d?* Medaka fish	No disturbed embryo development. Swimming movement of adults "more static" compared to sham.

Todorovic et al. (2019)	110 mT	5 mo	Gut weight, SOD, CAT increased;
		Cockroach	GR, GST decreased;
		B. dubia	Total GSH unaffected.

1.4. Cell studies

In this period six studies have been recognized, but three of them have not been included in the analysis due to scanty quality of the research. The three studies considered addressed the effect of exposure on protein conformation, cell viability and the effect of combined exposures on chemically-induced oxidative stress.

Calabrò and Magazù (2019) employed SH-SY5Y neuronal-like cells as cell model to study separately the effects of exposure to static and to low-frequency (50 Hz) magnetic field on unfolding and aggregation processes of proteins[10]. To this purpose Fourier transform infrared (FTIR) spectroscopy, a technique to monitor protein structure, was used to monitor the unfolding and aggregation processes. Among the polypeptide and protein repeat units, amide I and II bands are the two most prominent vibrational bands used as indicator of such processes. In four independent experiments a significant increase in intensity of the Amide I band and of methylene group (CH2) stretching vibrations was detected after 6 h exposure at 1 mT RMS. In particular, a statistically significant increase in intensity of the Amide I band and of CH2 stretching vibrations was recorded after 6 h exposure compared to sham exposed cultures (p<0.01). The authors explained these results as a consequence of an increase of ions flux across cellular membrane channels after exposure.

In a study conducted by Lin et al. (2019) the potential for enhancing the killing ability of natural killer (NK) cells under a static magnetic field was investigated by measuring viability. To this purpose, a human NK92-MI cell line was cultured in the presence of a 0.4 T SMF for 4 h and a significantly higher viability was detected compared to sham-exposed cells after 48 h and 72 h after exposure (p<0.05), as evaluated by applying the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) test To evaluate cell membrane fluidity, a fluorescence technique was employed by using two fluorescent probes: 1–6-diphenyl-1,3,5-hexatriene (DPH) and 1-(4-trimethylammonium) phenyl)-6-phenylhexa-1,3,5-triene (TMA-DPH). An increased fluorescence of the DPH probe was detected in exposed cultures compared to sham samples up to 1 h after exposure (p<0.05). No variation was recorded for the TMA-DPH probe. To investigate the possible signaling pathway as its putative mechanism of the observed SMF-induced increase in cell viability, the effect of several inhibitors of the pathways involved in proliferation were tested. In particular, the SMF-induced viability was not negated by treating cell cultures with W7 or AG490, two inhibitors of DAG/IP3 and STAT3 signal pathways, respectively. In contrast, when three inhibitors of MAPK pathways were tested, a suppression of SMF-induced proliferation was found (p<0.05 vs. sham exposed cultures), indicating that the exposure induces an activation of MAPK pathway. The killing activity of NK92-MI cells was investigated using K562 leukemia cell lines as the target. Exposure to SMF for 4 h had no effect on K562 cells. When K562 cells were co-cultured with NK92-MI cells, an enhanced killing activity against K562 cells was detected, but only if the exposure to the SMF was 48 h before co-culturing (p<0.05). For each condition at least 4 independent experiments were performed.

Kimsa-Dudek et al. (2019) investigated the effect of the simultaneous exposure to fluoride and SMFs (0.45, 0.55 and 0.65 T flux density) for 24 h on viability and antioxidant status of normal human fibroblasts (NHDF). In the present investigation, treatments with fluoride, given alone or in

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[10] The results of exposure to ELF-MF are reported in section 2.4.

combination with SMF, did not induce effects on cell viability, as assessed by applying the MTT test (three independent experiments).

To investigate the effect of combined exposures on oxidative stress, the intracellular reactive oxygen species (ROS) production, lipid peroxidation (evaluated by measuring malondialdehyde (MDA) levels, and the activities of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) were measured. To compare treatments to fluoride alone with combined exposure to SMF, cultures with fluoride were sham-exposed. Fluoride induced oxidative stress was evident by a significant increase of ROS formation ($p<0.05$) and MDA levels, and a significant decrease in antioxidant enzymes activities ($p<0.05$). When the effect of combined exposures was evaluated, treatments with fluoride and a SMF with a 0.65 T flux density significantly reduced the fluoride-induced ROS production ($p<0.05$). No ROS decrease was recorded when lower flux densities were tested. MDA levels did not change following co-exposures at 0.45 T while 0.55 and 0.65 T reduced the fluoride-induced MDA levels ($p<0.05$). The fluoride-induced decrease in SOD activity was also detected in cultures co-exposed to SMF at 0.45 T, while at the higher flux densities tested a statistically significant increase was induced ($p<0.05$), restoring the basal levels. Increased GPx activity was also detected for all the flux densities tested ($p<0.05$). On the whole, the results of this study indicate a protective effect of SMF at 0.55 and 0.65 T against the oxidative stress induced by treatments with fluoride. The authors stated that SMF exposures alone did not induce variation in the parameters investigated with respect to sham controls, but the results are not shown.

1.4.1. Conclusions on static field cell studies

The results of the studies considered confirm that static fields are able to induce slight variations in the biological endpoints considered.

Table 1.4.1. Cell studies on exposure to static magnetic fields

Cell type	Endpoint	Exposure conditions	Effect	References
Human neuroblastoma (SH-SY5Y) cells n=4	Proteins unfolding and aggregation	1 mT 6 h	Increased intensity of the Amide I and II bands and of CH2 group stretching vibrations	Calabrò and Magazù (2019)
Human NK92-MI cells n=4	Killing activity	0.4 T 4 h	Higher viability after 48 and 72 h from the exposure; increased cell membrane fluidity; activation of MAPK pathway. Increased NK killing activity against K562 leukemia cells. No effect of SMF on K562 leukemia cells	Lin et al (2019)
Normal human fibroblasts (NHDF) n=6-8	Cell viability, antioxidant status	0.45, 0.55 and 0.65 T 24 h Co-exposure: fluoride	Decreased fluoride-induce ROS at 0.65 T; reduced fluoride-induced MDA levels at 0.55 and 0.65 T; increased fluoride-induced SOD activity reduction at 0.55 and 0.65 T; increased fluoride-induced GPx activity reduction for all the flux densities tested.	Kimsa-Dudek et al (2019)

Abbreviations: CH2: methylene group; GPx: glutathione peroxidase; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; NK: natural killer; ROS: reactive oxygen species; SOD: superoxide dismutase.

2. Extremely low frequency (ELF) fields

2.1. Epidemiological studies

In the previous Council reports it was concluded that little progress had been made to resolve whether the consistently observed association between ELF magnetic field (ELF-MF) exposure and childhood leukaemia in epidemiology is causal or not. Another open question relates to occupational ELF-MF exposure and/or electric shocks as a risk factor for amyotrophic lateral sclerosis (ALS). Although associations are often reported, there is no consistent pattern that suggests either ELF-MF or electric shock as the cause. Studies evaluating occupational ELF-MF exposure and risk of Alzheimer disease (AD) have reported heterogeneous results. Occupational ELF-MF studies on adult cancer are inconsistent and no firm conclusions can be made on this subject.

2.1.1. Childhood cancer

Swanson et al. (2019) examined time trends in 41 studies on childhood leukaemia in relation to ELF-MF by means of a cumulative meta-analysis. They found a decreasing trend of relative risks from a maximum of 2.44 in 1997 to 1.58 in 2017. However, this linear trend was not statistically significant. They found suggestions of higher risks in studies with higher exposure levels and in studies with better quality exposure assessment. They concluded that the decline in reported risk from the mid-1990s to now is unlikely to be solely explained by improving study quality. A somewhat elevated risk remained in the most recent studies.

The Childhood Leukaemia International Consortium (CLIC) combined 11 pre-existing case-control studies in Europe, USA and New Zealand yielding 9723 cases of childhood leukaemia (age<15 yrs.) with 17 099 controls. Cases diagnosed between 1989 and 2011 were identified from cancer registries, hospitals or clinical trial. Controls were recruited from population registers, hospitals or by random digit dialling. Participants with Down syndrome were excluded (1.8% cases and 0.1% controls). Using these data, Talibov et al. (2019) investigated parental occupational exposure to ELF-MF during pregnancy and risk of leukaemia. Information on parental occupation and child characteristics where obtained from questionnaire interviews of both parents (Finland used census data). Paternal ELF exposure was assessed at time of conception and maternal exposure during the entire pregnancy. Exposure was assessed by means of the INTEROCC ELF-MF JEM (Turner et al., 2014) and dichotomized (above or below 0.2 µT). Using exposure <0.1 µT as reference exposures, >1 µT and >0.2 µT were investigated in fathers and mothers respectively. In pooled analyses, there was no evidence of associations between maternal or paternal occupation and total leukaemia, acute lymphoblasic leukemia (ALL) or acute myeloid leukaemia (AML). For ALL, ORs were 1.04 (95% CI: 0.96-1.13) for paternal exposure (>0.2 µT) at conception and 1.00 (95% CI: 0.89-1.12) for maternal exposure during pregnancy. Conclusions did not change in sensitivity analyses or when combining studies by meta-analysis methods (enabling adjustment for information not available in all studies). In a meta-analysis including four additional studies not part of CLIC, the OR for any leukaemia was 1.11 (95% CI: 1.00-1.22) for paternal exposure and 1.04 (95% CI: 0.92-1.17) for maternal exposure. The definition of exposure differed between the studies not part of CLIC. There was evidence of small study effects when also including non-CLIC studies. The authors conclude that they did not observe associations between parental ELF-MF exposure during pregnancy and leukaemia in the offspring. Some degree of exposure misclassification is inevitable due to using JEMs and may have driven risk estimates towards the null, potentially masking weak associations. Regarding the elevated risk for paternal exposure in meta-analysis including also other studies, this appears to be driven by a few studies reporting elevated risk whereas most studies as well as the individual studies forming CLIC are compatible with the null association. Particularly for maternal exposure, it was a limitation that it was not possible to include women with higher exposures in the CLIC data. The authors interpret funnel plot asymmetry (small study effects) as due to publication bias. However, this is counter-intuitive, as the effects indicate different directions for studies analysing paternal as compared to maternal

exposure. Underlying reasons for funnel plot asymmetry therefore remain unclear. Overall, this is an informative study that does not strengthen the hypothesis that parental exposure to ELF-MF is underlying childhood leukaemia risk.

Auger et al. (2019b) investigated in a retrospective cohort of 784 944 new-borns between 2006 and 2016 in Quebec, Canada, whether exposure to electromagnetic fields during pregnancy increased the risk of childhood cancer. Children were followed from birth until the first hospitalization for cancer, death or the end of study on March 31, 2017 using hospitalization data. Residential exposure to ELF-MF was estimated by calculating the distance between centroids of six-digit postal codes and the nearest transformer station or high voltage transmission line (≥120 kV). Data were analysed using Cox proportional hazards regression models adjusted for maternal age, maternal comorbidity, infant sex, multiple birth, macrosomia, congenital anomaly, material deprivation, and rural residence. Exposure-response relationship was modelled using splines and a dichotomized variable. In total, 1114 incident cases of cancer were observed during 4 647 472 person-years of follow-up. Twenty-six cases occurred within 200 m of transformer station and 181 cases within 100 m of a high voltage transmission line. A distance of 80 m from a transformer station was associated with a hazard ratio of 1.08 (95% CI: 0.98-1.20) for any cancer, 1.04 (95% CI: 0.88-1.23) for hematopoietic cancer, and 1.11 (95% CI: 0.99-1.25) for solid tumours compared with a distance of 200 m. There was no association with transmission lines.

The sample size is relatively large and the retrospective design allowed including virtually all children in the study area. Potential loss to follow up and the quality of the linking for case ascertainment are not reported. A limitation of the study is exposure misclassification. The coordinates for residency are inaccurate (six digital postal code) and underground cables were not excluded from the analysis, although ELF-MF levels are rapidly decreasing with distance from these cables. Also, only exposure of the address as birth could be taken into account. Due to the absence of ELF-MF exposure data, it remains unknown whether children within 200 m of transformer stations are exposed to higher ELF-MF levels than children within 100 m of high voltage line. Typically, ELF-MF exposure is mostly increased within a distance of 50 m of highest voltage overhead transmission line (≥220 kV). Such an analysis was not done.

Risk for childhood leukaemia has repeatedly been associated with overhead power-lines. To elucidate if magnetic fields or some other factor associated with living close to power line is the most likely explanation, Crespi et al. (2019) conducted an exploratory analysis of a pre-existing register-based Californian case-control study. The original study (described in SSM 2018 and SSM 2019) included 5788 childhood leukaemia cases diagnosed between 1988 and 2008 and an equal number of matched controls. For birth addresses of all participants, distance to nearest overhead power line was determined from GIS data and aerial photographs. For addresses estimated to potentially have magnet fields ≥0.1 µT, distance was determined from site visits. These visits also formed the basis for calculating the total magnetic field strength from all neighbouring power lines >100 kV and some lower voltage lines. For all other residences, field strength was assumed to be <0.1 µT. For the present study, some cases (n=909) and controls (n=953) were excluded because of imprecisions in birth address location. The OR for leukaemia among children living <50m from a power line with >0.4 µT was 4.06 (95% CI: 1.16-14.3, 13 cases, 3 controls) when compared to children living >600 m away with <0.1 µT magnetic fields. The ORs associated with living within 50 m with <0.4 µT was 0.81 (95% CI: 0.35-1.88, 10 cases, 12 controls). For those living >50 m way with ≥0.4 µT the OR was 0.50 (95%CI: 0.15-1.67, 4 cases, 8 controls). In analyses looking at those with high exposure, elevated ORs was only observed near the >200 kV lines, but again the number of cases and controls was extremely small and confidence intervals overlapped between the different groups. The authors concluded that neither distance nor magnetic field strength alone predicted risk and that their "findings argue against magnetic fields as a sole explanation for the association between distance and childhood leukaemia". They recommend, however, cautious interpretation as the analysis was exploratory in nature and numbers were often small. The authors also mention the possibility that magnetic fields may be better modelled near higher voltage power lines, which could have driven the results.

Although this is a large sample size, number of exposed cases and controls is small. It is unclear whether researchers who performed the site visit were blinded towards case - control status. If not, this

may have biased the exposure calculations. Finally, the study disregards any exposure changes that may have occurred if families moved address after the birth of the child.

Using simulated datasets based on the study described above, and the mobility pattern of cases, Amoon et al. (2019) investigated the sensitivity of the observed association to unmeasured confounding due to residential mobility. Even when assuming a strong correlation between exposure, outcome and residential mobility, the resulting bias was not sufficient to fully explain the associations observed in this dataset.

2.1.2. Neurodegenerative diseases

A previous systematic review and meta-analysis by Gunnarsson and Bodin (2019) was updated with a few additional studies. Small increased risks for ALS and for Alzheimer's disease, but not for Parkinson's disease were observed in workers with occupational exposure to ELF-MF.
Several more recent publications are either missing or were omitted for unclear reasons. Also, the authors combined results of studies addressing ALS and Alzheimer's disease and subsequently interpreted funnel plot asymmetry as publication bias. Such an interpretation overlooks potential real differences between the two diseases. Variations in accuracy of the exposure assessment due to different study designs may also have impacted the funnel plots. For example, smaller studies with higher standard errors but more accurate exposure assessment may be more likely to detect associations than larger studies with lower standard errors but more exposure misclassification. If that was the case, then funnel plot asymmetry would be present as well. Otherwise, the report is in line with previous reviews.

The aim of the population-based case-control study by Gervasi et al. (2019) was to investigate a potential association between exposure to ELF-MF from high-voltage overhead power lines and the occurrence of neurodegenerative diseases such as Alzheimer's and Parkinson's Disease in the Milan metropolitan area (Italy). The distance of the residential address to the nearest high-voltage overhead power line (>30 kV) was used as a proxy for exposure to ELF-MF. The study included cases diagnosed between 2011 and 2016 (Alzheimer: n = 9835, Parkinson: n = 6810), and four control subjects per patient. The authors found slightly elevated but non-significantly increased risks for persons living within 50 m from a high-voltage power line compared to persons whose residential address was at least 600 m away from a high-voltage power line for Alzheimer's Disease (OR=1.11, 95% CI: 0.95-1.30) and Parkinson's Disease (OR=1.09, 95% CI: 0.92-1.30).
The strengths of the study are the large sample size, and the fact that the authors accounted for important confounding factors including a deprivation index. Interesting is the result of a validation analysis done with regard to diabetes mellitus (positive control outcome). As expected, this disease was associated with proximity to high-traffic roads, but not with proximity to high-voltage power lines. It would have been interesting to see an analysis restricted to higher-voltage lines (>200 kV), which may have been possible given the relatively high number of cases living within 50 m of a power line (n=241), which was defined here as at least 30 kV.

In a pooled case-control study of data from Ireland, Italy and the Netherlands, Peters et al. (2019) investigated whether occupational exposure to extremely low-frequency magnetic fields (ELF-MF) or electric shocks increases the risk of amyotrophic lateral sclerosis (ALS). Lifetime occupational histories were obtained using questionnaires. Job exposure matrices were used for assigning occupational exposure levels to ELF-MF and likelihood for electric shocks. The clinical diagnosis was verified on the basis of hospital records. A total of 1323 ALS cases, diagnosed between 2010 and 2015, and 2704 randomly selected population controls of the same age, sex and geographic location were included in the analysis. The statistical analysis was adjusted for age, sex, study centre, education, smoking, and alcohol consumption. Both ever having had exposure to ELF-MF above the background level (OR = 1.16, 95% CI: 1.01-1.33) and ever having had potential exposure above background for electric shocks (OR = 1.23, 95% CI: 1.05-1.43) were associated with ALS. However, the results were not consistent between the three study centres/countries, and showed no dose-response

relationship with respect to cumulative exposure. Exclusion of cases with a genetic predisposition to ALS resulted in the same findings.

The results of this study suggest that both occupational ELF-MF exposure and electric shocks independently increase the risk of ALS. Previous studies have often found an increased risk for one of the two factors, but not for both at the same time. Strengths of the study include the relatively large number of cases for this rare disease, as well as the thoroughly conducted process of data collection. Nevertheless, it is unclear whether a control selection bias occurred, as there is no information on how the controls were selected, and the participation rate is not reported. The authors state that control subjects on average had a higher education level than cases, which might be an indication of selection bias. If controls have been chosen selectively with a lower probability of electric shocks and/or exposure to ELF-MF, this would lead to an overestimation of ALS risk in this study.

Sorahan (2019) evaluated a UK cohort of 83 284 electricity workers (72 352 male, 10 932 female). All employees had employment durations of at least 6 months between 1973 and 1982. Employees were categorised based on the first known job into different groups (e.g. transmission or substation site, non-operational site). Workers were followed up until 31st December 2015. After excluding for example untraced workers, a total of 81 616 workers remained in the cohort. Cancer incidence (via linkage to registry data) in the cohort was compared with expected values based on incidence rates for England and Wales, taking sex, age and calendar period into account. Higher risks were observed for several cancers, e.g. non-melanoma skin cancer in transmission workers. No increased risks were observed for leukaemia or brain cancers, cancer types previously discussed as possibly related to magnetic field exposure (which would be expected to be elevated in electricity workers).
Strengths of the study include the large size and rather complete follow-up for a long period of time and the linkage to registry-based incidence data. Weaknesses include that no EMF exposure was directly assessed, the lack of information regarding relevant lifestyle factors such as smoking or alcohol consumption, and that possible job changes within and outside of the electric utility companies could not be taken into account. All in all, the paper is in line with a series of previous publications from the same cohort indicating no increased risk of malignant neoplasms in ELF-MF exposed workers. The observed increased risk for skin cancer is most likely owed to UV exposure for transmission line operators working outdoors.

2.1.3. Reproduction

In a large-scale study conducted in Canada, Auger et al. (2019a) investigated births registered in hospitals in the province of Quebec between 1989 and 2016 with regard to maternal low-frequency magnetic field exposure. Residential proximity to the nearest high-voltage transmission line (≥120 kV) or transformer station was used as a proxy for ELF-MF exposure. A total of 2 164 246 children were included in the analysis. In total, 123 575 birth defects were observed, the most common being clubfeet (29 192), noncritical heart defects (19 718) and disorders of the urogenital system (15 853). The analyses were adjusted for age and diseases of the mother, sex of the infant, number of siblings of the infant, multiple birth, urbanity, socio-economic status and time period. Mothers who lived within 200 meters from a transmission line or transformer station at the time of birth had a very slightly increased risk for a child with a birth defect (Risk ratio of 1.02 (95% CI: 1.00–1.03) and 1.05 (95% CI: 1.00–1.09), respectively). However, the risk within a distance of 50 m from a transmission line was not increased.

This is a very large study on a topic that has hardly been investigated so far. Strengths of the study are that virtually all births in Quebec were included and that objective data from hospital discharge reports were used. However, distance to a high-voltage transmission line or transformer station is a suboptimal proxy for exposure. ELF-MF exposure is mainly increased within a distance of 50 m of highest voltage transmission lines (≥220 kV). The fact that the risk was not increased within a radius of 50 m of a transmission line compared to a radius of 200 m may indicate that other factors than ELF-MF are relevant. The slightly increased individual risks within 200 m could thus be attributable to confounders that were not taken into account. The authors also have not described whether the analysis included underground transmission lines. If this was done (as indicated in their study on

childhood cancer (Auger et al., 2019b)), this would result in exposure misclassification, as ELF-MF near underground transmission lines are relatively small even in close proximity.

Ren et al. (2019) evaluated maternal extremely low frequency MF (ELF-MF) exposure during the 3rd trimester of pregnancy in relation to foetal growth. 250 participants of an ongoing birth cohort study in Shanghai, China, were invited to participate and 140 agreed (56%). In the final analysis, 128 pregnant women were included who carried an EMDEX Lite meter for 24 h. Foetal growth was measured at the time of birth. After adjustment for family income, gestational age, parity, parental age at childbirth, parental BMI before pregnancy, and maternal passive smoking during pregnancy, time-weighted average ELF-MF above median was associated with statistically lower birth weight, triceps skinfold thickness, back skinfold thickness, upper arm circumference, and abdominal circumference. These inverse associations between ELF-MF and foetal growth were mainly seen in girls.
The prospective exposure measurements are a strength of this study. A concern remains, however, in how far one 24 h measurement is representative for ELF-MF exposure during the whole pregnancy period. Maternal physical activity levels during pregnancy have been shown to be associated to ELF-MF exposure levels. Associations of maternal physical activity levels with foetal growth exist but are complex. Such associations were not accounted for in this analysis. The small sample size is a limitation of this study. Previous large scale studies on this subject are inconclusive.

Esmailzadeh et al. (2019) published a case-control study performed in Babol, North-Iran. Between 2014 and 2016, of "nearly 500" infertile women visiting the Fatehmazahra infertility clinic, 475 signed informed consents and 462 could be included into the study. Controls were selected from the birth registry from the Rohani hospital. The 371 control-women were described to be matched. Addresses were geolocated based on postal codes and grids. The closest distance to the nearest 63-400 kV overhead power line or cable was assessed and categorised into living within 500 m, 500-1000 m or further away (the reference group). 19% of cases and 6% of controls lived within 500 m of an exposure source, the adjusted (age, urban/rural residence, type of occupation, educational level) OR for infertility was 4.4 (95%CI: 2.8-7.1).
In this study, the authors tried to account for several potential confounders, which is a plus. The authors describe that cases and controls were matched, but it was not explained on what information matching was performed. While addresses were geolocated based on postal codes and grids, no information was provided about the spatial accuracy of this measure. Usually no elevated exposure is observed beyond a distance of about 200 m even from very high voltage level power lines, which raises the question if other factors may explain the observed strong effects. In fact, the selection of the control population from a different hospital is a considerable weakness, because the control population is not representative of the case population.

2.1.4. Other outcomes

In a small volunteer study in Paris, France, Touitou et al. (2020) compared chromogranin A (CgA) profiles, as a marker of neuroendocrine tumours and stress, between 15 high and 15 low exposed men around 40 years of age. The 15 exposed individuals lived close to substations with high-voltage lines overhanging and they worked as high voltage power line (225 kV and 400 kV) operators. Their weekly geometric mean exposures ranged from 0.1 to 2.6 µT. Exposure of controls was <0.1 µT, these were white collar workers. Blood sampling were carried out hourly between 20:00 h and 08:00 h and lights were turned off from 22:00 h to 08:00 h. Volunteers were recumbent for the nocturnal samplings and seated for 15 min before the samples were taken at 20:00 and 21:00 h. In this study, profile and serum concentrations of CgA did not differ between the exposure groups.
It is unclear how this extensive sampling during night has affected the CgA profiles of the study participants. No confounders were considered in the analysis. The small sample size does not allow for firm conclusions regarding absence of associations.

Zendehdel et al. (2019) analysed single-strand DNA breaks in 29 male utility workers from Teheran, Iran. Exposed workers were matched to 28 male support personnel in terms of age, work experience

and smoking level. DNA percent in tails, tail length, olive length, and tail moment was determined using the comet assay. ELF-MF exposure was measured based on a protocol from NIOSH. The median exposure of utility workers was 11.0 µT and for support personnel 0.85 µT. Tail length, olive moment, percentage DNA in tail and tail moment were significantly increased in exposed workers compared to unexposed personnel.

This study does not discuss how comparable exposed and unexposed workers were in terms of other potential risk factors and occupational exposures. Apart from matching, no confounders were considered in the analysis. Thus, it remains unclear whether observed differences are caused by ELF-MF exposure or if they are due to some other factor.

Hosseinabadi et al. (2019) conducted a cross-sectional study among all employees of an Iranian power plant who had worked at the plant full time for ≥2 years and who were 20-50 years of age. Participants were 112 exposed workers (engineers, operators and technicians and some office workers) and 138 unexposed office workers. Average magnetic and electric field exposure was calculated from self-reported daily routines and spot measurements at workstations. Haematological parameters and pro-inflammatory cytokines were measured in blood. Among unexposed, average magnetic and electric field exposure was 1.5 (SD: 0.5) µT and 2.6 (SD: 0.8) V/m, respectively. For exposed workers, the corresponding numbers were 29.5 (SD: 16.8) µT and 25.5 (SD: 12.09) V/m. Exposure differed strongly across the included occupational groups. A number of blood parameters including interleukin-1β (IL-1β) and interleukin-6 (IL-6) were significantly higher among exposed workers and exhibited a significant positive trend across exposed jobs as a function of increasing average exposure. For IL-6 and IL-1β, linear analysis found significant positive correlation with magnetic field levels. The authors conclude that long-term ELF-EMF exposure probably affects immune response.

No participation rate is provided which hampers interpretation and the study is limited by its small size increasing the risk of chance results. The major concern is the high correlation between exposure and occupational groups. The unexposed were office workers and the highly exposed were technicians and it appears that observed significant trend tests and linear analysis are largely driven by this factor. It can therefore not be determined if the observed results relate to ELF-EMF or to other differences between men in the different jobs because no confounders were considered in the data analysis.

Using the same basic dataset as above, Bagheri Hosseinabadi et al. (2019) also analysed DNA damage by means of comet assays. In this study, they included 102 workers from the exposed group and 136 from the unexposed group. For all comet assay indices, the levels were higher in the exposed group, significantly so for tail DNA percent, tail factor (%) and damage index. Exposed were grouped into three levels of exposure, low (<11.3 µT), medium (11.3-18.9 µT) and high (>18.9 µT). In this analysis, the high exposed appeared to display higher levels of DNA damage in nearly all analysed indices. The authors conclude that long-term exposure to ELF-EMFs can probably cause genotoxic effects.

The concerns regarding interpretation of this study are the same as the ones listed for the previous study.

The same cross sectional study as above was also used to investigate ELF-MF exposure in relation to muscoskeletal disorders (MSD) and oxidative stress (Hosseinabadi and Khanjani, 2019). In total 152 workers were included. The most common MSD was back pain. There was no significant difference in magnetic or electric field strength between those with and without self-reported MSD.

The same concerns as discussed above apply. However, given the null result of the present study a major concern is the small sample size and the likelihood that exposure levels in this study are likely to correlate with other factors that can influence why workers experience musculoskeletal pain. In total, four papers were published from this dataset, each with different number of participants. In the present study, 152 workers were described as always exposed. In the two studies summarized above the number exposed workers was 102 and 112, and in a study on the same dataset summarized in the Council report from last year (SSM 2019) the number of exposed workers was 132. No justification is given for the variation in study population between studies.

2.1.5 Conclusions on ELF epidemiological studies

Also the current reports do not resolve whether the consistently observed association between ELF magnetic field (ELF-MF) exposure and childhood leukaemia in epidemiology is causal or not. One study addressed the question whether occupational ELF-MF exposure or electrical shocks could underlie observed increased risks of amyotrophic lateral sclerosis, and found both to be possible risk factors. This is of interest as previous studies rather identified one or the other exposure as underlying observed associations. An Italian study addressing exposure from high voltage power lines and Alzheimer's and Parkinson's disease did not provide strong support for associations. A large Canadian study reported very slightly increased risks of birth defects in children born to mothers exposed to high voltage power lines.

2.2. Human studies

As in the previous years, the number of human experimental studies on effects of extremely low frequency (ELF) fields continues to be very low. In 2019 just one new study was identified. This study addresses phosphene perception thresholds.

Transcranial alternating current stimulation (tACS) can induce phosphenes (visual perceptions of flashing or shimmering light in the absence of accompanying visual input). Evans et al. (2019) investigated systematically and thoroughly the relationship between electric currents and phosphene perception in a sample of 24 healthy participants (12 females and 12 males, mean age 27.9 years). A cross-over study design (test sessions scheduled on different days, usually within a week, at the same time of the day) was used to apply either a stimulation with a frontal site (Fpz) as cathode or a stimulation with an occipital site (Oz) as cathode. For both stimulations, which were presented randomized and counterbalanced across subjects, the central location Cz served as anode. Subjects were familiarized with the perception of phosphenes under standardized conditions (10 s of tACS at 1000 µA, first at 12 Hz and then at 22 Hz) to show that perception of phosphenes can vary just by changing the frequency of stimulation. All experiments were conducted with eyes open under controlled dim light conditions and sufficient time (20-30 min) to adapt to the lighting condition. At each experimental session tACS was conducted at various frequencies (2-30 Hz in steps of 2 Hz). Thresholds for phosphene perception (in µA) were determined for each frequency by a Bayesian adaptive staircasing procedure starting with 700 µA for an overall interval between 25 µA and 1500 µA. Results showed that independent from location of the stimulation phosphene perception threshold was lowest at 16 Hz stimulation with small interindividual variation of thresholds. This threshold is consistent with the view that phosphenes could be either generated by the cortex or by the retina. With regard to the location of stimulation perception thresholds were consistently lower for the Fpz-Cz stimulation (412.36 µA) as compared to Oz-Cz stimulation (944.10 µA), a result, which confirms earlier observations.

2.2.1. Conclusions on human studies

The number of studies continued to be very low with just one study in the current reporting period. This study systematically analysed thresholds for phosphene perception and showed that, independent from location of stimulation, perception threshold is lowest for 16 Hz. But the thresholds differ between stimulation locations.

2.3. Animal studies

Twelve studies on brain and behaviour, oxidative stress, cytokines, physiology and cancer were identified in rodents. In addition, five studies in non-mammalians describe effects of ELF-MF on fish, honeybees, round worm (*C. elegans*) and cockroach.

2.3.1. Brain and behaviour

To evaluate anxiety-like behaviour, spatial and passive learning and memory, and to measure oxidative stress markers, Karimi et al. (2019) exposed groups of n=12 male adult Wistar rats to 50 Hz ELF-MF: (1) control group, (2) sham exposure group, (3) 1 µT, (4) 100 µT, (5) 500 µT and (6) 2000 µT MF. Exposure (2 h/d) lasted 60 days. Behaviour (elevated plus maze) was tested immediately the day after the 2 months of exposure, followed by six days training and testing spatial learning in the Morris water maze (MWM). After a further week of recovery the passive avoidance test was conducted. At study end blood was collected. For all test parameters no significant differences were found between the control group 1 and the sham exposure group 2 (data were not shown). Thus the exposure groups were compared only with the control group. Lipid peroxidation (groups 4 and 5), total antioxidant capacity (groups 3 and 5), total thiol molecules (groups 3, 4, 5 and 6) and total oxidant status (group 5) were significantly increased compared to controls. In MWM rats of groups 4 and 6 spent significantly more time in the target zone than controls. The passive avoidance test demonstrated that the latency to step into the dark box was significantly increased in ELF-MF-exposed rats (groups 4, 5, and 6), and all exposed rats (groups 2, 3, 4, 5, 6) spent significantly less time in the dark box compared to controls. In the elevated plus maze, exposed rats of groups 5 and 6 entered open arms significantly to a lesser extent and spent less time in there (groups 3, 4, 5 and 6) compared to controls. From these data the authors conclude that ELF-EMF exposure may "improve" memory retention - but not acquisition.

Di et al. (2019) compared effects of 35 kV/m static electric field (0 Hz, SEF) and 35 kV/m ELF-EF (50 Hz) on cognition and hippocampal neurotransmitters in mice[11]. Groups of n=10 male 4-week old ICR mice were 24 h/d continuously exposed to ELF-EF for 7, 14, 21, 35 and 49 days, another n=10 mice per time-point served as non-exposed controls. The exposure unit was the same as used by Wu et al. (2017). In addition, the first 3 time-points correspond to Di et al. (2018) (compare Council reports SSM 2019 and SSM 2010). Following 7, 14, 21, 35 or 49 days of SEF-exposure, the hippocampus was removed and the levels of the main excitatory neurotransmitter glutamate (Glu) as well as of the main inhibitory neurotransmitter γ-aminobutriy acid (GABA) were determined. Before humanely killing and hippocampal sampling, spatial learning and memory was tested by the use of MWM on days 2-6, 9-13, 16-20, 30-34 and 44-48, respectively. Compared to non-exposed control mice, the exposure to 50 Hz, 35 kV/m ELF-MF significantly improved learning and memory ability on day 33. Correspondingly Glu and GABA levels were increased on days 21 and 35. The different effects of SEF vs. ELF-EF on hippocampal neurotransmitters, learning and memory may be, according to the authors, due to a different "degree of molecular polarization and ion migration in organisms" under exposure of two electric fields.

In continuation of previous research, Rauš Balind et al. (2020) reported effects of ELF-MF and/or cerebral ischemia on pituitary cells of 3-month-old male gerbils. The study comprised the following groups: (1) Intact - no surgical procedure or ELF-MF (n = 3); (2) Sham-operated, no occlusion of both carotid arteries (n = 6); (3) Sham-exposed (n = 6); (4) ELF-MF (50 Hz, 0.5 mT) for 7 days (n = 11); (5) ischemia (occlusion of both common carotid arteries for 10 min (n = 11); (6) combination of 10 min-ischemia followed by ELF-MF-exposure for 7 days (n = 11). For testing of immediate and delayed EMF-MF effects, one half of the gerbils per group (except intact) were sacrificed 7 days and the other half 14 days after study start. ELF-MF (50 Hz, 0.5 mT) and 10 min ischemia decreased the volume density of adrenocorticotrophic (ACTH) cells, while only the combination resulted in increased intracellular ACTH content and plasma ACTH on day 7. Furthermore, ELF-MF elevated serum thyrotrophic (TSH) concentration on day 7 and intracellular TSHβ content on day 14. Also on day 14, 10 min ischemia alone increased serum TSH, whereas intracellular TSHβ was increased by the combination (ischemia + ELF-MF) after 14 days. Summarizing, ELF-MF exposure and/or 10 min cerebral ischemia can induce immediate and delayed stimulation of ACTH and TSH synthesis and secretion in gerbils. The lack of data about the influence of the two stressors (ELF-MF and/or ischemia) on circulating levels of hypothalamic CRH (corticotropin releasing hormone) and TRH (thyrotropin releasing hormone), corticosterone and thyroid hormones is addressed as a study

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[11] The SEF part of the study is described in chapter 1.3.1.

limitation. Nevertheless, the author argue that ELF-MF may be useful for (additional) treatment of stroke.

2.3.2. Cytokines

Mahaki et al. (2019) tested - in an identical experimental setting (or in the same animals?) as reported in the previous Council report SSM 2019 (Mahdavinejad et al. (2018) and Sobhanifard et al. (2019)) - the effects of four different ELF-MF (50 Hz; 1, 100, 500 µT and 2 mT) on gene expression of the transcription factors c-Maf, STAT6 and RORα (which are important for differentiation into T-helper cell types Th2 and Th17) in spleen and thymus of rats. Four groups (n=16 per group) of 8-week-old male Wistar rats were exposed to the above ELF-MF for up to 60 days (2 h/d), a fifth group was sham-exposed. For stimulation of the immune system, all rats were immunized by human serum albumin (HSA) on days 31, 44 and 58 of ELF-MF-exposure. After termination of the of 2-month-exposure period, spleen and thymus were collected. Compared to sham controls, the expression levels of c-Maf, STAT6 and RORα genes in thymus were not significantly changed following exposure to different intensities of ELF-MFs. But the expression levels of c-Maf and RORα in the spleen were significantly downregulated at intensities of 1 and 100 µT, and of STAT6 at 100 µT only. Compared to (sham) controls, expression of c-Maf, STAT6 and RORα at 0,5 and 2 mT did not significantly differ, but exhibited a trend to lower levels. Summarizing, low intensities of ELF-EMF (50 Hz, 1 and 100 µT) reduced the expression of c-Maf, STAT6 and RORα in spleen. As a result, Th2 and Th17 functions may be suppressed.

Molaei et al. (2019) described in a second paper using the same study (design) serum levels of inflammatory cytokines/interleukins IL-1β and IL-23 and in spleen the expression of immune system related genes (B lymphocyte-induced maturation protein-1 (BLIMP-1), X-box-binding protein-1 (XBP-1) and interferon regulatory factor-4 (IRF-4)). 80 rats formed five ELF (50 Hz)-MF-groups (n=16 per group): (1) 1 µT, (2) 100 µT, (3) 500 µT, (4) 2000 µT and (5) sham control. Blood was obtained after the first month of exposure (pre-immunization phase). Then animals were injected with HSA three times over the course of the second month (days 31, 44, and 58) to stimulate the immune system. At the end of exposure (after 2 months; post-immunization phase), all animals were killed, the second blood sample was drawn and spleens were removed. Serum level of IL-1β significantly decreased after 1 µT and 100 µT MF at pre-immunization phase compared to the control group, whereas IL-23 level was significantly increased after 100 µT at post-immunization phase compared to the control group. In addition, a trend towards slightly lower IL-1β levels (1 month, 0,5 and 2 mT) and towards slightly higher IL-23 levels (2 month, 1 µT, 0,5 and 2mT) was seen. In spleen the expression of BLIMP-1, XBP-1 and IRF-4 genes significantly decreased following 2-month 100 µT MF-exposure. The authors point out that exposure to weak ELF-MF (50 Hz,100 µT) may decrease inflammation after short exposure durations and increase inflammation and immune response after longer durations.

Mahaki et al. (2020) tested in a further similar experimental setting the effects of the above four ELF-MF (50 Hz; 1, 100, 500 µT and 2 mT) on serum levels of interleukin 9 (IL-9), IL-10 and tumor necrosis factor α (TNF-α). Four groups (n=16 per group) of 8-week-old male Wistar rats were exposed to the above ELF-MF for 2 months (2 h/d), a fifth group was sham-exposed. After a 1-month exposure, blood serum of all rats was separated for cytokine measurements. For stimulation of the immune system, all rats were were immunized by HSA on days 31, 44, and 58. At study termination after 2 months of exposure, again blood sera were collected. After 1 month (preimmunization phase), the serum levels of proinflammatory cytokines IL-9 and TNF-α were decreased at ≥100 µT as compared to sham. After two months (postimmunization phase), IL-9 and TNF-α levels were significantly increased at ≥100 µT as compared to the corresponding groups of the preimmunization phase. The antiinflammatry cytokine IL-10 was not clearly affected at both testing points.

Taken together, the five reports of the Iranian research group (Mahdavinejad et al. (2018), Sobhanifard et al. (2019), Mahaki et al. (2019a, 2020), and Molaei et al. (2019)) do not explain if all data originate

from one single experiment or if several similar studies were run. Nevertheless, no clear conclusion can be drawn regarding the immune response following ELF-MF exposure, especially a sound interpretation of the immunosuppressive effects after low dose-exposures (1 to 100 µT) versus mid dose-exposures (0.5 and 2 mT) is missing.

2.3.3. Physiology

Alekperov et al. (2019) studied the effects of 30 Hz, 4 kA/m (≈5 mT) ELF-MF on rat ovaries. Parental Wistar rats were ELF-MF or sham-exposed for 2 h/d. Thirty females per group were mated over two oestrus cycles. During pregnancy and after birth, F1 progeny was exposed for 2 h/d for a total of 11 weeks. Following exposure, alltogether 40 female F1 per ELF-MF and sham-exposed group each were monitored for effects on estrus cycle, sexual hormones and ovaries. The average duration of the estrus cycle, the mean serum concentrations of luteinizing hormone (LH) and estradiol (E2), mean weight and histomorphology of ovaries did not significantly differ between the ELF-MF and sham-exposed groups. Lower levels of follicle stimulating hormone (FSH) in the proestrus and progesterone in the estrus phase were found in the ELF-MF group; in the ovaries, the number of primordial follicles was slightly lower than in the sham controls. In conclusion, the exposure to ELF-MF in the selected mode (30 Hz, 4 kA/m) caused no significant defects in the structure and function of rat ovaries.

Harakawa et al. (2020) reported a subsequent complex follow-up experiment to Hori et al. (2017), Hori et al. (2018) and Harakawa et al. (2017) (described in SSM 2018 and SSM 2019). Again, plasma glucocorticoid (GC) levels as an indicator for stress response were determined in 50 Hz EF-exposed male, intact female and ovariectomized female BALB/c mice. In addition, red and white blood cell counts (RBC, WBC), hemoglobin and hematocrit levels were analyzed. Groups of n=6 mice were exposed to 10 kV/m for 60 min, and tube-immobilized (stressed) for 30 min between minute 30 to 60. Immediately after (EF)treatment blood samples were collected.
Test 1 aimed to investigate the effect of EF exposure with or without immobilization stress on plasma GC level. Groups of 10-week old male, female, and ovariectomized female BALB/c mice were divided into four groups (n = 6 each): 1) control [Stress(−)/EF(−)], 2) EF-alone [Stress(−)/EF(+)], 3) stress alone [Stress(+)/EF(−)], and 4) co-treatment [Stress(+)/EF(+)].
Test 2 addressed the influence of age and/or EF on stress-induced plasma GC-levels. Again, four groups (n=6 per group; 1) control, 2) EF-alone, 3) stress-alone, 4) co-treatment) were built for each age group of male BALB/c mice: 15 (young adult), 25 (adult), and 55 (older adult) week-old.
In all tests and compared to (sham) control group(s), plasma GC levels in restraint [Stress] mice were increased. But GC-levels were lower in the stress-EF co-treated groups compared to stress-alone groups. Overall, GC levels were highest in intact females followed by ovariectomized females and lowest in males. A significant age correlation was not seen. No difference in WBC count between male and female mice in each group, whereas RBC count, HGB and HCT levels were higher in males than in females, and were lower in controls of both sexes than in the corresponding treatment groups. All tested blood parameters did not show any age correlation. The study demonstrated that ELF-EF (50 Hz,10 kV/m) suppresses the stress response of restrained mice, regardless of gender or age.

Lundberg et al. (2019) studied the effects of 50 Hz 580 µT fields on circadian rhythm control in mice. Groups of n=6 male C57BL/6J mice were exposed once for 30 min starting at zeitgeber time 14 (ZT14, 2 h into the dark period of the day) to 50 Hz 580 µT ELF-MF using a pair of Helmholtz coils and/or to blue LED light at 700 lux or neither. An acute adrenal response to blue light was demonstrated by increased adrenal *per1* gene expression, increased serum corticosterone levels, increased time spent sleeping, and decreased locomotor activity compared to an unexposed controls. (*per 1* belongs to the PERIOD gene family which is important in circadian rhythm control.) The 580 µT MF did not modulate the response to light, and there was also no effect of the ELF-MF alone except for a decrease in locomotor activity. Furthermore, gene expression of the cryptochromes cry1 and cry2 in the adrenals, liver, and hippocampus was not affected by light and/or ELF-MF exposures. That means that 50 Hz, 580 µT ELF-MF did not modulate the acute adrenal light response.

Vallejo et al. (2019) exposed transgenerationally OF1 mice to 50 Hz, 15 µT ELF-MF and examined blood coagulation parameters in 31-35 month-old offspring. Exposure of parental mice (10 females, 5 males) started two weeks prior mating. Controls (11 females, 6 males) were "treated in the same way"; i.e., a real sham exposure may be questionable. Gestation, birth, lactation, weaning, development and housing of the F1 offspring all took place within the MF, generated by a Helmhotz coil system. After cardiac puncture, the blood was analysed of 53 female, 53 male 15 µT-exposed F1 and of 37 female and 38 male F1 non-exposed controls. White blood cells (WBC) were counted, the activated partial thromboplastin time (APPT) and prothrombin time (PT), plasma fibrinogen, reptilase time (RT), and factor VIII activity determined. Differences in the studied coagulation parameters were largely sex-dependent. However, compared to control the APPT and PT were significantly shorter in ELF-MF exposed female OF1 mice. RT was significantly reduced in exposed mice of both sexes. The authors conclude that a chronic 50 Hz, 15 µT ELF-MF exposure increased coagulability in female OF1 mice.

Wang et al. (2019c) tested whether ELF-MF-exposure induced DNA damage *in vitro*[12] and *in vivo*. Ten male, 8-week old Sprague-Dawley rats were exposed to 50 Hz, 100 µT ELF-MF for 15 h/d and 7 days continously. Another 10 rats were sham-exposed. After humanely killing on day 8, samples of heart tissue were obtained. Protein levels of (the cell division controlling) p53 and of (the stress responding heat shock protein) Hsp70 were analysed by western blot. No significant differences were detected in p53 and Hsp70 expression levels of ELF-MF exposed compared to sham-exposed rats. Combining the *in vitro* and *in vivo* data, 50 Hz exposure at 100 µT did not result in primary DNA damage in cardiomyocytes.

2.3.4. Cancer / Leukaemia

Campos-Sanchez et al. (2019) in a pilot study tested the effects of exposure to a 50 Hz magnetic field on the occurrence of leukemia in a specific mouse model. They used mice carrying the *ETV6-RUNX1* fusion gene, the most common chromosomal alteration detected in childhood B-cell acute lymphoblastic leukemia (B-ALL). Sca1-ETV6-RUNX1 mice are genetically predisposed to B-ALL, making subjects susceptible to subsequent exposure to exogenous agents, such as infection or ELF-EMF etc., as a secondary step what finally may result in a full-blown leukemia.
Mice were divided into two groups: an exposure group (n=34, 22 females, 12 males) and a cage control group (n=27, 12 females, 15 males). The 34 mice were exposed age to 50 Hz, 1.5 mT ELF-MF (10 min/5 min on/off cycle) for 20 hours/day from conception until 3 months of age. Animals' blood was examined every 1-2 months until 2 years of age in order to detect the development of B-ALL. Total B cells (B220+, CD19+), CD4+ T cells and CD8+ T cells in peripheral blood were analyzed by flow cytometry. One mouse of the exposure group developed B-ALL while none of the animals in the control group did. This result is statistically non-significant due to the limited number of mice used, while significantly decreased numbers of CD8+ T cells in exposed mice at 2 months of age correlate to previous findings in ELF-MF exposed CD1 mice (Schüz et al. (2016)) and may be used as biomarker indicating a biological effect of ELF-MF in mice.
Summarizing, the results demonstrate that the newly developed *ETV6-RUNX1* mouse model should be used for ELF-MF studies addressing the etiology of childhood B-ALL.

2.3.5. Studies in non-mammalians

Fey et al. (2020) determined in rainbow trout the effect of a 50 Hz, 1 mT ELF-MF (or a 10 mT SMF)[13] on the developmental instability of the inner ear organ, expressed by otolith size fluctuating asymmetry (FA) index. Larval rainbow trout were reared and exposed to 50 Hz, 1 mT ELF-MF for 37 days (13 days in egg stage and 24 days in larval stage (days post hatching (dph)). Three subgroups (n=40, n=60 and n=60) were exposed to 10 mT SMF or sham-exposed to the geomagnetic field (GMF) for 5, 15 and 23 dph. Analysis of the FA index demonstrated only a trend to, but not

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[12] For *in vitro* results see chapter 2.4.3
[13] The SMF part of the study is described in chapter 1.3.3.

significantly increased otolith size FA in ELF-MF-exposed larvae. According to the authors, the FA index values confirm earlier data and revealed a significant effect of 10 mT SMF (compare chapter 1.3.3.), but not of 50 Hz, 1 mT ELF-MF.

In a second experiment using rainbow trout, Fey et al. (2019b) tested again with the very same exposures further parameters of early development, like embryonic and larval mortality, hatching time, and larval growth. Eggs and larvae were exposed to a 50 Hz, 1 mT ELF-MF (and a 10 mT SMF)[14] for a period of 36 days (i.e., from eyed egg stage to approximately 26 dph). Three replications of 500 eggs each were ELF-MF- or (sham-)exposed for 5, 10, 14, 21 dph (n≈40 per subgroup) and 25 dph (n=100 live larvae each). ELF-MF had no significant effect on embryonic or larval mortality, hatching time, larval growth, and the time of larvae swim-up from the bottom. Similar to the results for 10 mT SMF, 50 Hz, 1 mT ELF-MF enhanced the yolk-sac absorption rate. The authors point out, if larvae use the yolk-sac too early, they can be less efficient at first feeding and subsquent growth rates will be short.

Shepherd et al. (2019) investigated in 50 Hz ELF-MF exposed bees the effects on aversive learning and aggression levels, as they are critical factors for bees to maintain colony strength. Honey bees were divided into three groups and exposed for 17 h to the following MF: (1) 0.1 mT, n=118, (2) 1 mT, n=120, and (3) sham, n=119. Immediately after exposure termination, the sting extension response assay was performed. For testing the aggression level (using intruder assay), 100 bees were collected from 5 different hives in groups of 20 bees. Each group of 20 was split into two paired subgroups of 10. For 17 h overnight, one subgroup was exposed to the 0.1 mT MF, the other sham exposed. (For this test, no exposure to the 1 mT MF was run.) Exposure to both 0.1 mT and 1 mT MF significantly reduced the aversive learning performance. Moreover, exposure to the 0.1 mT MF resulted in significantly increased aggression scores. In conclusion, reduced aversive learning and increased the aggression level following short-term exposure of honey bees to a 50 Hz MF might have ecological implications for bees in nature.

Sun et al. (2019b) examined in the nematode *C. elegans* changes of the lipid metabolism, as well as gene and protein expression following (1) 50 Hz, 3 mT ELF-MF and (2) sham exposure. The exposure duration was reported with circa 48 hours (from egg to the fourth larval stage). For the protein analysis, 40 000 worms were utilized. No numbers were reported for the other analyses. After 3 mT exposure, 64 lipids were significantly decreased or increased compared to sham. Within the glycero-lipids, the level of triacylglycerols was significantly increased, while diacylglycerols were decreased. On the proteomic level, in total 82 proteins were up-regulated and 72 proteins were down-regulated in exposed worms compared to sham controls. Transcriptomic analysis demonstrated that 172 genes were up-regulated and 284 genes were down-regulated. In further analyses, the altered gene expression was found to be related to alteration in the lipd composition, mitochondrial dysfunction and the stress defense. The authors conclude that exposure to a 50 Hz magnetic field can affect the nematode *C. elegans* mainly through disturbing lipid metabolism and eliciting stress defense responses.

Todorović et al. (2019) examined effects of chronic exposure of orange-spotted cockroach (*Blaptica dubia*) nymphs to a static magnetic field or 50 Hz magnetic field on gut mass and antioxidant markers[15]. One month old cockroach nymphs (n=10 per group) were exposed for a period of 5 months: (1) 110 mT SF, (2) 50 Hz, 10 mT ELF-MF, (3) control. Following 5 months of exposure, the average weight of the gut was significantly reduced in exposed nymphs (groups 1 and 2) compared to the controls. In gut homogenates, the enzyme activities of the antioxidative markers superoxide dismutase (SOD) and catalase (CAT) were significantly increased in exposed nymphs of groups 1 and 2, while the activities of glutathione reductase (GR) and glutathione S-transferase were significantly reduced. In addition, the enzyme activities SOD and GR in group 2 (exposure to 50 Hz, 3 mT) were significantly increased compared to group 1 (exposure to 110 mT SMF). The total glutathione content showed no significant differences between the groups. Summarizing, chronic exposure of cockroach nymphs to MF alters the weight of the gut and the antioxidative markers SOD and CAT. Finally, the authors speculate about the use of cochroach as an indicator of increased environmental levels of MF.

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[14] The SMF part of the study is described in chapter 1.3.3.
[15] The SF part is described in chapter 1.3.3.

2.3.6. Summary and conclusions on ELF animal studies

Similar to the previous Council reports, studies used exposure levels mostly in the 0.5 to 2 mT range at 50 Hz. Two mouse studies showed an improved learning and memory. The total five reports on cytokines etc. of an Iranian research group do not provide a clear conclusion regarding the immune response following ELF-MF exposure, especially a sound interpretation of the immunosuppressive effects after low dose- (1 to 100 µT) versus no effect after mid dose-exposures (0.5 and 2 mT) is missing.

On the other hand, the repeatedly observed decreased numbers of CD8$^+$ T cells in exposed juvenile CD1 and *ETV6-RUNX1* mice may indicate a biological effect of ELF-MF. In addition, the newly developed *ETV6-RUNX1* mouse model should be used for ELF-MF studies addressing the etiology of childhood B-ALL.

A further study on honey bees showed that ELF-MF may be an environmental stressor for flying insects, having impact on their aversive learning and aggression level. The rainbow trout studies demonstrated some developmental retardation of the inner ear and of the yolk sac absorption. Finally, a future use of cockroach nymphs as an indicator of increased environmental ELF-MF levels is speculative. In conclusion, the very different reports of effects following ELF-MF exposure demonstrate again the absence of knowledge on biological-relevant mechanisms of ELF-MF in the 1 mT range and below.

Table 2.3.1. Animal studies on exposure to ELF magnetic fields

Endpoint	Reference	Exposure ELF - MF	Exposure Duration and Species	Effect
Rodent studies				
Brain & behaviour	Karimi et al. (2019)	50 Hz, 1, 100, 500, 2000 µT	60 d 2 h/d Rat	Improved memory retention, but no effect on spatial and avoid-ance learning.
	Di et al. (2019)	35 kV/m	7, 14, 21, 35, 49 d 24 h/d Mouse	Learning & memory improved after 33 days, hippocampal Glu and GABA levels increased after 21&35 days.
	Raus Balind et al. (2019)	50 Hz, 0.5 mT and/or cerebral ischemia (10 min)	7, 14 d 24 h/d Gerbil	D7: density↓ of ACTH cells, ACTH levels↑, D7+D14: TSHβ↑
Cytokines	Mahaki et al. (2019a)	50 Hz 1,100, 500, 2000 µT + HSA immunization (100 µg/rat on days 31, 44, 55)	2 mo 2 h/d Rat	Thymus: No change of c-Maf, STAT6, RORα. Spleen: Reduced expression of c-Maf & RORα at 1 & 100µT, of STAT at 100 µT only.
	Molaei et al. (2019)	50 Hz 1,100, 500, 2000 µT + HSA immunization (100 µg/rat on days 31, 44, 55)	2 mo 2 h/d Rat	1 mo.,1&100µT:IL-1β↓ 2 mo., 100µT: IL-23↑ 2 mo., spleen, 100 µT: BLIMP-1↓, XBP-1↓, IRF-4↓
	Mahaki et al. (2020)	50 Hz 1,100, 500, 2000 µT + HSA immunization (100 µg/rat on days 31, 44, 55)	2 mo 2 h/d Rat	1 mo., ≥100µT: IL-9↓ & TNF-α↓ 2 mo., ≥100µT: IL-9↑ & TNF-α↑
Physiology	Alekperov et al. (2019)	30 Hz 4 kA/m (≈ 5 mT)	11 wk 2 h/d Rat	No significant effect on structure and function of ovaries.
	Harakawa et al. (2019)	50 Hz 10 kV/m	60 min (incl. 30 min tube-restraint) Mouse	Suppression of stress. response (GC↓) in both sexes and 3 different ages (15, 25, and 55 wk).
	Lundberg et al. (2019)	50 Hz, 580 µT	30 min	No MF effect on the

		+/- blue light LED (700 lux)	Mouse	acute adrenal light response.
	Vallejo et al. (2019)	50 Hz 15 µT	35 wk 24 h/d Mouse	Increased coagulability in females.
	Wang et al. (2019a)	50 Hz 100 µT	7d, 15 h/d Rat	Protein levels of p53 and Hsp not affected.
Cancer / Leukemia	Campos-Sanchez et al. (2019)	50 Hz 1.5 mT	3 mo 20h/d(10'on/5' off) +18 mo observation	Decreased CD8^{+} T cell-number at 2 mo. B-ALL in 1/34 mice.
			Sca1-ETV6-RUNX1 mouse	Childhood B-ALL mimicking mouse model
Studies in non-Mammalians				
Inner ear develop-ment	Fey et al. (2019a)	50 Hz 1 mT	37 d (13 d egg + 24 dph) Rainbow trout	Trend to increased otolith fluctuating asymmetry in larvae.
Early development	Fey et al. (2019c)	50 Hz 1 mT	36 d (12 d egg + 24 dph) Rainbow trout	Enhanced yolk-sac absorption rate.
Cognitive & motor abilities	Shepherd et al. (2019)	50 Hz, 0.1, 1 mT	Short-term (17 h) Honey bee	Reduced aversive learning; increased aggression.
Lipid metabolism	Sun et al. (2019b)	50 Hz 3 mT	≈ 48 h C. elegans	Lipid concentrations & corresponding gene expression altered.
Antioxidative biomar-kers	Todorovic et al. (2019)	50 Hz 10 mT	5 mo Cockroach *Blaptia dubia*	Gut weight, SOD, CAT increased; GR, GST decreased; Total GSH unaffected.

Abbreviations: ↑=increase(d); ↓=decrease(d); ACTH: adrenocorticotropic hormone; B-ALL: B-cell (dependent) acute lympho-blastic leukaemia; BLIMP-1: B lymphocyte-induced maturation protein-1; bw: body weight; CAT: catalase; c-Maf: musculo-aponeurotic fibrosarcoma (MAF) protooncogene; DIFF: differential blood count; d or D: day(s); dpf: day(s) post fertilization; EF: electric field; ELF-MF: extremely low frequency magnetic field(s); GABA: γ-aminobutyric acid; GC: glucocorticoid(s); Glu: glutamate; GR: glutathione reductase; GSH: glutathione; GST: glutathione S-transferase; h: hours; IL: interleukin; IRF-4: interferon regulatory factor-4; mo: month(s); POD: peroxidase; RBC: red blood cell count; RORα: Retinoid-related orphan receptor alpha; ROS: reactive oxygen species; SMF: static magnetic field; SOD: superoxide dismutase; STAT6: Signal transducer and activator of transcription 6; TNF-α: tumour necrosis factor- α; w: week(s); WBC: white blood cell count; XBP-1: X-box-binding protein-1.

2.4. Cell studies

The new *in vitro* studies confirm the previous Council conclusions: several endpoints have been investigated and in most cases no effect of the exposure was detected. It is interesting to note that several studies deal with the evaluation of action mechanisms of interaction between ELF fields and cell proliferation. As for the past years, a large number of studies have been recognized but not considered, due to the scanty quality of the experimental methods employed. In addition, a review paper has been published on the oxidative stress (Lai, 2019).

2.4.1. Cell viability

The mouse glioma cell line CT2A was employed by Garcia-Minguillan and co-workers to investigate the effect of short and long term exposure to ELF-EMF at different frequencies and field intensities on cell viability (García-Minguillán et al., 2019). In particular, cell cultures were exposed a) for 24 h to 30 µT at 7.8, 14, 20, 26, 33, 39, 45, and 51 Hz and b) for 7 days intermittently (12 h on/12 off) to 100 µT at 20, 30, and 50 Hz. The results of four independent experiments indicated that for short exposure durations a frequency dependent decrease in cell viability was induced, that was statistically significant at frequencies up to 20 Hz ($p < 0.01$). Longer exposures also resulted in a decrease in cell viability, statistically significant only at 30 Hz ($p < 0.001$). In addition, to evaluate if a health effect was produced by the exposure, cell cultures were exposed for 24 h at 20, 30 and 50 Hz, 100 µT and the

cytoplasmatic expression of heath shock protein 90 was measured. No differences were detected between exposed and sham exposed cultures in any of the frequencies analyzed.

Kakikawa et al investigated the combined effect of 60 Hz, 50 mT magnetic fields and anticancer drugs (cisplatin, mitomycin C, or doxorubicin) on human hepatoma HepG2 cells, measuring cell viability by means of a colony forming assay. The results obtained from 6 to 8 experiments indicated that exposures from 0.5 to 4 h did not induce differences compared to sham exposed cultures. When the magnetic field was given in combination with drugs, the number of viable cells was decreased with respect to treatments with drugs alone. Such a decrease was detected for all the drugs tested, although the time associated with the greatest enhancement of the drug's efficacy achieved by magnetic fields differed among drugs. In particular, the combined treatment was more effective for cisplatin (p<0.01). [In this study experiments to compare the effect of sham exposures and controls were performed in a first step. Therefore, sham exposure was not concurrent to magnetic field exposure].

2.4.2. Cell proliferation

In previous studies Martinez and co-workers showed an increase in proliferation of NB69 cells, a human neuroblastoma cell line, following exposure to a 50 Hz, 100 µT magnetic field. In a new study Martínez et al. (2019) investigated the potential involvement of the epidermal growth factor receptor (EGFR) in the field-induced cell proliferation and the involvement of MAPK pathways activation. To this purpose, NB69 cells were exposed for short periods (from 5 to 30 min) or intermittently for 63 h (3 h on/3 h off) in the same conditions and in a blind fashion. The comparison between exposed and sham exposed cultures (four independent experiments) showed a statistically significant increase in cell proliferation (p<0.01) in exposed samples and the antiproliferative effect of erlotinib, an inhibitor of EGFR phosphorylation, was cancelled by the MF exposure. The expression of the active form of the EGFR was analysed at the end of short intervals of MF exposure (5, 10, 15, 20 min) and an increased rate of p-EGFR positive cells was detected after 10 and 15 min of exposure (p<0.05), but not after 5 or 20 min, consistently with the protein expression levels. Such an overexpression was blocked by erlotinib. It is known that the EGFR and its signalling pathways, including MAPK, are involved in the modulation of proliferation, both in normal physiological processes and in tumour development. In addition, there are also indications that matrix metalloproteinases (MMP) could mediate the cell-proliferation response to MF. Exposures of 20 and 30 min resulted in a statistically significant increase of several proteins involved in MAPK pathways (p<0.05) and the immunocytochemical results revealed a significant increase in the rate of cells expressing MMP at 5 minutes of MF exposure (p<0.05), but not at longer exposure intervals.
Taken together, the results of this study suggest an early signalling mechanism that is triggered by intermittent exposure MF, and is potentially involved in the field-induced proliferative response of NB69 human neuroblastoma cells.

In a study conducted by Qiu and co-workers the effect of a 50 Hz at 0.4 mT was investigated on cell proliferation, including the possible mechanisms implicated in the proliferative processes. In the literature it has been reported that metabolites of sphingolipids, such as ceramide, sphingosine, and sphingosine-1-phosphate (S1P) regulate cell behaviour and function, including cell growth, differentiation, senescence, and apoptosis. Ceramide and sphingosine activate cell death pathways, whereas S1P primarily regulates cell growth and suppresses apoptosis (Qiu et al., 2019). The authors exposed/sham-exposed human amniotic (FL) cells for 1 h and in 4 experiments carried out blinded an enhancement of ceramide metabolism and S1P production was recorded (p<0.05), while sphingosine was unaffected. When the effect of MF exposure on cell proliferation was investigated, an enhancement was detected after culturing for 24 h (p<0.01) and 36 h (p<0.05), as detected in 8 independent experiments. Pre-treatment with SKI II, an inhibitor of sphingosine kinase 1 (SK1), completely inhibited MF-induced cell proliferation with respect to the sham group (p<0.01).
In addition, the possible role of extracellular signal-regulated kinases (ERK1/2) in MF-induced cell proliferation was investigated in 6 independent experiments. ERK1/2 is a member of the Mitogen-Activated Protein Kinases (MAPK) family and plays a pivotal role in many cellular processes

including regulation of cell proliferation. The level of ERK1/2 phosphorylation increased (p<0.05) after MF exposure and its activation was blocked (p<0.01) when the cells were pretreated with U0126, an inhibitor of ERK kinases. In addition, pre-treatment with U0126 also inhibited the cell proliferation induced by MF exposure (p<0.01). These results suggested that MF-induced cell proliferation depended on activation of ERK1/2 signalling pathways.

In a further study, the same research group, by using the same cell type and the same exposure conditions, investigated the possible mechanisms of MF-induced SK1 activation, the relationships of intracellular Ca^{++} and its related signalling molecules (ERK and protein kinase Cα, PKCα) with SK1 (Yang et al., 2019). In three independent experiments FL cells were exposed from 5 to 60 min. MF exposure for 5 and 10 min increased intracellular Ca^{++} (p<0.05) which returned to basal values at 15 min, while no effects were detected for exposures of 30 min or 60. Treatments with Nifedipine (NIF), an inhibitor of L-type calcium channel, negated the increase of intracellular Ca^{++} induced by 10 min MF exposure. In addition, NIF inhibited the MF-induced phosphorylation of SK1 and ERK (p<0.05) and treatment with U0126, the inhibitor of ERK, also decreased SK1 phosphorylation induced by MF exposure, as shown in 6 independent experiments. Moreover, 60 min MF exposure increased the expression of both PKCα and its phosphorylated form (p<0.05), which was inhibited by treatments with NIF. To further investigate the relationships among SK1, ERK, and PKCα cell cultures were treated with SKI II, an inhibitor of SK1, and no effect was detected I PKCα phosphorylation, but the MF-induced increase in phosphorylated-PKCα was eliminated, while treatments with U0126 had no effect on MF-induced phosphorylation of PKCα. Taken together the results of this study suggest that ERK participate in the process of MF-induced SK1 phosphorylation which is dependent on the L-type calcium channel.

2.4.3. Other cellular endpoints

Consales et al. (2019) investigated several biological endpoints in SH-SY5Y human neuroblastoma cells following exposure to 50 Hz ELF-MF (1 mT) up to 72 h. They tested either SH-SY5Y wild type or two clones expressing two mutant SOD1 (superoxide dismutase), such as the G93A or the H46R and evaluated viability, proliferation, apoptosis, reactive oxygen species (ROS) formation and iron metabolism. By comparing exposed and sham exposed samples, no differences were detected except for the expression of some iron-related genes. In particular, in at least three independent experiments performed blinded, 72 h exposure induced a slight but statistically significant decrease in the expression of IRP1, MFRN1 and TfR1, three iron-regulating genes (p=0.0512). Such an effect was detected only SOD1G93A cells after 72 h exposure.

A cell line of human ventricular cardiomyocytes (AC16 cells) was exposed to 50 Hz ELF-MF at 100 µT for 1 h continuously or 75 min intermittently (15 min on/15 min off) by Wang et al. (2019c) and the effects of the treatments were evaluated in terms of DNA damage, redox status changes and relative signal molecular expression. By comparing exposed and sham exposed cultures no effects were detected for all the parameters investigated and for all the experimental conditions tested. In particular, in three independent experiments no significant variations were recorded between exposed and sham exposed samples in terms of DNA damage (alkaline comet assay), cell cycle distribution (flow cytometric analysis), redox status changes (reactive oxygen species formation and ratio of reduced/total glutathione) and expression of p53 and Hsp70 proteins. Positive controls were provided for DNA damage, redox status changes (hydrogen peroxide) and cell cycle distribution (nocodazole) and a statistically significant variation was recorded with respect to control cultures, as expected.

Calabrò and Magazù (2019) employed SH-SY5Y neuronal-like cells as cell model to study separately the effects of exposure to static and to low-frequency (50 Hz) magnetic field on unfolding and aggregation processes of proteins[16]. To this purpose Fourier transform infrared (FTIR) spectroscopy, a technique to monitor protein structure, was used to monitor the unfolding and aggregation processes. Among the polypeptide and protein repeat units, amide I and II bands are the two most prominent

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[16] The results of exposure to SMF are reported in section 1.4.

vibrational bands used as indicator of such processes. In four independent experiments a significant increase in intensity of the Amide I and II bands and of methylene group (CH2) stretching vibrations was detected after 6 h exposure. In particular, when 50 Hz EMF was tested at 50 µT (RMS), a low but statistically significant increase in intensity of the Amide I and Amide II bands and of CH2 stretching vibrations was recorded (p<0.05). The authors explained these results as a consequence of an increase of ions flux across cellular membrane channels after exposure.

In a study conducted by Yao et al. (2019) the effect of low frequency pulsed electromagnetic field on the differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes (OLs), which induce myelination, was investigated. The biochemical process involved in differentiation of OPCs into mature OLs involves the regulation of some miRNA expression. miRNAs are non-coding RNA molecules that bind to target mRNA sequences to induce mRNA degradation to regulate biological processes. In particular, miRNA 219 and Lingo1 are involved in this process. Primary OPCs obtained from the cerebral cortex of Sprague-Dawley rat pups were exposed to a pulsed square signal of 50 Hz and 1.8 mT for 3, 7, 14, and 21 days. In three experiments OLs stage-specific markers were examined at early (3 days and 7 days) and late stages (14 days and 21 days) after exposure and a significant difference in the expression levels of relative expression of stage-specific markers NG2, Galc, and MBP was found compared to sham exposed cultures (p<0.05). This effect was also validated by western blot analysis, indicating that PEMF promoted the differentiation of OPCs. When the expression profiles of miRNAs associated with OPCs differentiation was examined, an increase in miRNA219 expression was measured at early (7 days) and late (14 days) stages (p<0.01). Moreover, MF exposure also induced a decrease in the expression of Lingo1, a gene which negatively regulated OPCs differentiation (p<0.01). Thus, the authors speculated that PEMF promoted OPCs differentiation by regulating miR-219 activity.

2.4.4. Summary and conclusions for cell studies

The new *in vitro* studies confirm the previous Council conclusions: several endpoints have been investigated and in most cases no effect of the exposure was detected. As for the past years, several studies have been recognized but not considered due to the scanty quality of the experimental method. These are reported in the Appendix

Table 2.4.1. Cell studies on exposure to Extremely low frequency Electromagnetic fields

Cell type	Endpoint	Exposure conditions	Effect	References
Mouse glioma cell line CT2A n=4	Cell viability, HSP90 expression	7.8, 14, 20, 26, 33, 39, 45, and 51 Hz, 30 µT 24 h 20, 30, and 50 Hz, 100 µT 7 days (12 h on/12 off)	Significant decrease in cell viability up to 20 Hz for 24 h exposure and at 30 Hz for 7 days exposures No effect in HSP90 expression	Garcia-Minguillan et al (2019)
Human hepatoma HepG2 cells n=6-8	Cell viability	60 Hz, 50 mT 0,5 to 4 h Co-exposure: cisplatin, MMC, doxorubicin	No effect of ELF-EMF alone. Decreased cell proliferation in co-exposed cultures with respect to treatments with drugs alone	Kakikawa et al (2019)
Human neuroblastoma NB69 cells n=4	Cell proliferation	50 Hz, 100 µT 5 - 30 min 63 h (3h on/3h off)	Increase in proliferation; increase in EGFR for 5 and 10 min exposure, blocked by erlotinib; increase in proteins involved in MAPK pathways and MMP for 5 and 10 min exposure	Martinez et al (2019)
Human amniotic FL cells n=4-8	Cell proliferation	50 Hz, 0.4 mT 1 h	enhancement of ceramide metabolism and S1P production; enhanced proliferation after 24 and 36 h; increased level of ERK1/2 phosphorylation	Qiu et al (2019)

Human amniotic FL cells n=3-6	Cell proliferation	50 Hz, 0.4 mT 5 – 60 min	increased intracellular Ca++ after 5 and 10 min exposure; no effects for longer exposure durations; induction of SK1 and ERK phosphorylation; increased expression of both PKC-α and its phosphorylated form after 1h exposure.	Yang et al (2019)
Human neuroblastoma (SH-SY5Y) cells, wild type and G93A or H46R clones n=3	viability, proliferation, apoptosis, ROS formation and iron metabolism	50 Hz, 1 mT Up to 72 h	Decrease in the expression of three iron-regulating genes only in G93A clone after 72 h exposure.	Consales et al. (2019)
Human ventricular cardiomyocytes (AC16 cells) n=3	DNA damage, cell cycle, oxidative stress, expression of p53 and Hsp70 proteins	50 Hz, 100 µT 1 h continuously, 75 min (15 min on/15 min off)	No effects.	Wang et al. (2019)
Human neuroblastoma (SH-SY5Y) cells n=4	Proteins unfolding and aggregation	50 Hz, 50 µT 6 h	Increased intensity of the Amide I and II bands and of CH2 group stretching vibrations	Calabrò and Magazù (2019)
Rat Oligodendrocyte precursor cells (OPCs) n=3	Differentiation	50 Hz pulsed square signal, 1.8 mT 3, 7, 14, and 21 days	Differences in the expression levels of NG2, Galc, and MBP; Increase in miRNA219 expression and decreased expression of Lingo1	Yao et al. (2019)

Abbreviations: CH2: methylene group; miRNA: microRNA; EGFR: epidermal growth factor receptor; ERK1/2: extracellular signal-regulated kinases; Hsp: heath shock protein; MAPK: mitogen-activated protein kinase; MMC: mitomycin-C; MMP: matrix metalloproteinases; PKCα:protein kinase-Cα; ROS: reactive oxygen species; S1P: sphingosine-1-phosphate; SK1: sphingosine kinase 1; SOD: superoxide dismutase.

3. Intermediate frequency (IF) fields

Last years' reports observed that despite increasing use of intermediate frequency magnetic field (IF-MF) emitting sources (for example induction cooking, anti-theft devices, wireless power transfer systems), scientific evaluation of potential health risks was scarce – in fact, in the last report, two cell studies, two animal studies, no human study and no epidemiological study were identified. It should be stressed again that exposure assessment, especially of induced internal (electric) fields, remained challenging.

3.1. Epidemiological studies

No epidemiological study was identified during the reporting period.

3.2. Human studies

Like in the previous years no human experimental study on effects of IF exposure was identified in 2019. Overall, the number of human provocation studies is very low. Bodewein et al. (2019) published a systematic review on biological effects of electric, magnetic and electromagnetic fields in the intermediate frequency range (300 Hz to 1 MHz). Three of the 56 studies included in this review were human studies (de Vocht et al. (2007), Glover et al. (2007), and Navarro et al. (2016)). All studies considered effects on visual and cognitive functions. Overall, the authors state that the evidence for adverse health effects of fields in the IF range is inadequate for drawing conclusion. This is specifically true for the human studies, based on the risk-of-bias rating; one of these studies (Glover et al. 2007) showed an impaired quality. The other two showed conflicting results.

3.3. Animal studies

Two animal studies were identified dealing with transcriptional expression and cancer in mice.

3.3.1. Transcriptional Expression

Ohtani et al. (2019) analysed in whole brain and liver of male C57BL/6N mice the transcriptional expression after a 2-wk, 5 d/wk., 1 h/d lasting IF-MF exposure. An IF-MF was chosen which is relevant for wireless power transfer systems for charging electrical vehicles. Five mice were exposed to IF-MF at 82 kHz, 19.7 mT, another 10 mice to 82 kHz, 25.3 mT. Further, 15 mice were used for the corresponding sham exposures. Analysis of microarray data from both the brain and liver did not show significant differences in transcriptional expression.

3.3.2. Cancer

Nishimura et al. (2019) evaluated the carcinogenicity of a 20 kHz IF-MF, a typical frequency produced by induction-heating cookers, in an approved short-term bioassay using the transgenic rasH2 mouse model. Two independent and identical cancer studies were conducted. For each, 25 male and female CByB6F1-Tg(HRAS)2Jic mice (rasH2 mice) were exposed to a 20 kHz, 0.20 mT IF-MF (22 h/day) or sham-exposed for 26 weeks. Ten male and female rasH2 mice were administered a single intraperitoneal injection of 75 mg/kg N-methyl-N-nitrosourea (MNU) and served as positive controls. A blinded histopathological examination showed that ≥8 mice in each MNU group exhibited malignant lymphoma. The incidence of the neoplastic lesions did not significantly differ between IF-MF and sham-exposed groups and were consistent between duplicated experiments. Furthermore, incidences of (spontaneous) neoplastic and non-neoplastic lesions in the sham-exposed mice were similar to those reported in literature of control rasH2 mice. The same holds true for the MNU-treated

mice. Overall, the study indicates a lack of carcinogenicity of 20 kHz IF-MF in the rasH2 mouse model, and is in line with previous 'negative' genotoxicity studies on IF-MF (e.g., Herrala et al. (2018), see SSM 2019) providing evidence for lack of tumorigenic activity.

3.3.3. Summary and conclusions on IF animal studies

Within the 85 kHz range, relevant for wireless power transfer systems, no significant differences in transcriptional expression of brain and liver in mice were observed. Importantly, a lack of carcinogenicity of 20 kHz IF-MF in the rasH2 mouse model was demonstrated.

Table 3.3.1. Animal studies on exposure to intermediate frequency fields

Endpoint in rodents	Reference	Exposure IF - MF	Duration	Effect
Transcriptional expression	Ohtani et al. (2019)	82 kHz, 19.7, 25.3 mT	1 h/d, 5 d/wk, 2wk Mouse	No differences in transcriptional expression in brain and liver
Carcinogenicity	Nishimura et al. (2019a)	20 kHz, 0.2 mT	22 h/d, 26 wk rasH2 mouse	No carcinogenicity

Abbreviations: IF: intermediate frequency, MF: magnetic field; MN: micronucleus.

3.4. Cell studies

Two new studies have been published on the effect of IF-MF exposure on primary cell cultures, and both investigated the effect of exposure on DNA integrity. The results are contrasting, although different cell type and different exposure conditions have been investigated. In addition, a systematic review has been published (Bodewein et al., 2019).

Rat primary astrocyte cell cultures derived from the brains of one-day to three-day-old RccHan:WIST rats were employed by Herrala et al. (2019) to test if 24 h exposure to a vertical or horizontal 7.5 kHz, 300 µT magnetic field was able to induce or enhance genomic instability. To this purpose cell cultures were exposed/sham exposed to the field alone or in combination with two well-known genotoxic agents. In particular, they employed menadione (an agent that induces mitochondrial superoxide production and DNA damage, acting via ROS formation) and methyl methanesulfonate (an alkylating agent), given for 3 h after the MF treatment. Induced genomic instability was evaluated 36 days after exposures using the Comet assay and flow cytometric scoring of micronuclei. The results of three independent experiments evaluated in terms of DNA migration (comet assay) and micronucleus frequency did not support the hypothesis that IF exposure alone and in combination with the two chemicals tested induced genomic instability. Interestingly, micronucleus frequency was almost always lower in the MF-exposed group compared to the corresponding (same chemical treatment) sham-exposed group (p<0.05), suggesting decreased rather than increased genomic instability. In this paper, the results obtained by applying the comet assay are discussed but are not shown.

In a study conducted by Brech et al. (2019), peripheral blood lymphocyte from dogs and humans were exposed to 123.90 kHz (0.79 mT) and/or 250.8 kHz (0.1 mT) for different times from 1 to 24 h. The effect on DNA integrity was evaluated by applying the alkaline comet assay. Cell cultures were exposed in a 55 mm Petri dish divided cylindrically into three parts by concentric rings. Therefore, at the same magnetic flux density different induced electric fields (E) were achieved in the samples within the three concentric rings of the divided Petri dish. Three sets of experiments were performed and for each set three independent experiments were carried out. In all cases positive controls were set up by treating cell cultures with 4 Gy x-ray and they worked properly. In the first set dog peripheral blood lymphocytes were exposed/sham exposed to 123.9 kHz for 1, 2, 3, 4, 5, 20 and 24 h and a statistically significant increase in the %DNA in the tail was recorded following 20 h exposure

(p<0.05) in cultures exposed in the outer (E = 1.53 V/m) and in the inner (E = 5.75 V/m) portion of the Petri dishes. In a second set of experiments dog peripheral blood lymphocytes were exposed/sham exposed to 250.8 kHz for 20. In this case a significant increase in the %DNA in the tail was recorded only in samples exposed in the outer part of the Petri dishes (E = 1.45 V/m), with a p value lower than 0.05. In a third set of experiments cultures of human peripheral blood lymphocytes were exposed for 20 h at 123.9 and 250.8 kHz. For both frequencies investigated a statistically significant increase in %DNA in the tail was detected in samples exposed in the inner portion of the Petri dishes (1.53 and 0.38 V/m for 123.9 and 250.8 kHz, respectively).

3.4.1 Summary and conclusions on cell studies

The results of the studies considered are contrasting, although different cell type and different exposure conditions have been investigated.

Table 3.4.1. Cell studies on exposure to Intermediate Frequencies

Cell type	Endpoint	Exposure conditions	Effect	References
Rat primary astrocytes n=3	Genomic instability (MN and comet assay)	7.5 kHz 300 µT 24 h Co-exposure: MD and MMS	No effect of MF alone. No effect of combined exposure with MMS Decreased genomic instability in cultures co-exposed with MD	Herrala et al (2019)
Canine and Human peripheral blood lymphocytes n=3	DNA migration	123.90 kHz, 0.79 mT 250.8 kHz, 0.1 mT 1, 2, 3, 4, 5, 20, 24 h	Increased % DNA in both cell types for both frequencies, depending on the induced electric field	Brech et al (2019)

Abbreviations: MD: menadione; MMS: methyl methanesulfonate; MN: micronuclei.

4. Radiofrequency (RF) fields

4.1. Epidemiological studies

Last year's report concluded that various analyses of cancer incidence time trends did not observe patterns supporting the hypothesis of increasing incidence rates following, with some latency, the time period of mobile phone uptake. Critical evaluation of changes between diagnostic or topographic classification over time is, however, required, if observed temporal incidence trends are restricted to specific subgroups of diagnoses with overall stable cancer rates. Several studies have observed mobile phone and electronic media use to be associated with health-related quality of life, cognitive function and behavioural problems of children and adolescents. However, some studies indicate that other exposures than RF-EMF may be the underlying cause. It is methodologically challenging to separate RF-EMF effects from other aspects of mobile phone and electronic media use such as being woken up during night, blue light exposure or addictive behaviour. Thus, studies dealing with outcomes like health-related quality of life, cognitive functions or behaviour need innovative approaches to estimate effectively absorbed RF-EMF dose instead of device usage patterns to be informative for assessing possible health risks of RF-EMF.

4.1.1. Adult cancer

Safari Variani et al. (2019) conducted a systematic review and meta-analysis on occupational exposure to radar radiation and the risk to develop cancer. Six studies published between 1993 and 2016 with a total sample size of 53,008 workers fulfilled the inclusion criteria. Pooled random effects estimates for exposed workers were significantly below unity (cancer incidence=0.87, 95%CI: 0.75-0.99; mortality rate =0.81, 95%CI: 0.78, 0.83) with moderate heterogeneity between the selected studies (I^2=25-42%). One study provided more than 80% of cases, not all studies investigated the same cancer endpoints and it was not possible to perform analyses for different cancer entities. Healthy worker effect may be a plausible explanation for these seemingly protective effects of radar radiation.

Luo et al. (2019a) investigated mobile phone use and risk of thyroid cancer in a case-control study set in Connecticut, USA. In the period 2010-2011, 701 cases (age 21-84) of histologically confirmed incident thyroid cancer where identified in a central database. Of these cases, 462 (65.9%) participated. Controls where recruited by random digit dialling, 498 persons participated, corresponding to 61.5%. Controls were frequency matched by age (±5 years). Both cases and controls completed an administered questionnaire that included questions on use of mobile phones. Cell phone users were those who had "used a cell phone at least once a week for 6 months prior to one year before diagnosis". Unconditional logistic regression was used to calculate Odds Ratios (OR) for all tumours and for tumour size and histological groups with adjustment for age, sex, and educational level, family history of thyroid cancer, alcohol consumption, BMI, previous thyroid disease, occupation radiation exposure, and radiation treatment. Cases where on average 3 years younger than controls and more likely to be female, of lower educational level, occupationally exposed to radiation, had lower education level and a higher BMI. Cases were also more likely to have previous thyroid disease or a family history of thyroid cancer. There was no association between use of mobile phones and risk of thyroid cancer (OR= 1.05, 95%CI: 0.74-1.48). The authors reported suggestive evidence of increased risk in those speaking for more than 2 hours per day (OR= 1.40, 95% CI: 0.83-2.35), those having used a mobile phone for more than 15 years (OR= 1.29, 95%CI: 0.83-2.00) and those with cumulative use >9490 hours (OR 1.58, 95% CI: 0.98-2.54). These associations were not consistent between men and women. When grouping well-differentiated tumours by size, similar results were seen for tumours ≤10 mm whereas ORs where closer to the null for larger tumours. The authors conclude, "This study found no significant association between cell phone use and thyroids cancer. A suggestive elevated risk of thyroid micro-carcinoma associated with long-term and more frequent use warrants further investigation".
The suggestive evidence seen by the authors should be interpreted with caution. Recall bias is a

potential concern, particularly since it is unclear how long after diagnosis the interview was conducted. Cases had to recall past use and not be influenced by their usage pattern in the year preceding diagnosis. It is not stated when controls where interviewed and if they also reported on exposures some time before their interview. Another issue is that the relatively few persons in the various categories of high exposure are likely to be the same individuals meaning that any bias or random effects affecting this group will affect many of the analyses. Finally, it is known that increased screening has increased the detection rate of thyroid cancer, particularly so for small tumours (Liu et al., 2017). The suggestive associations seen by Luo et al. were largely restricted to tumours <10 mm whereas the ORs for larger tumours were much closer to the null. Although the authors state that the observed association did not differ by educational level or family income, stratified analyses could be a potential source of bias if mobile phone usage patterns were for some reason associated with the likelihood of screening.

In the same dataset as described above, Luo et al. (2020) investigated if an association between thyroid cancer and use of mobile phones might exist in genetic subpopulations. Blood samples where successfully genotyped for 440 cases and 465 controls, and 878 SNPs in 177 genes involved in DNA-repair were analysed in a Golden Gate assay. Fifty-five SNPs not in Hardy-Weinberg equilibrium were subsequently excluded. Each SNP was dichotomized into common group (common homozygote) and variant group (rare homozygote and heterozygote). SNPs with significant associations with mobile phone use were identified from unconditional logistic regression. This step identified 10 SNPs, all within introns, with p-values between 0.0008 and 0.0084. For these, the association with mobile phone use was evaluated in analyses stratified by SNP-variant. Mobile phone use was associated with increased risk for thyroid cancer for the variant genotypes of SNP rs11070256, rs1695147, rs6732673, rs396746, rs12204529 and rs3800537 with ORs in the range 1.59 (95%CI: 1.01-2.49) to 2.64 (95% CI: 1.30-5.36). In analysis of small (<10 mm) and large tumours separately, the authors note some differences in significant associations between the two types. Overall, the results were however similar to the combined analysis although numbers, particularly of non-user cases become very small. Additional analyses by amount and duration of mobile phone use found some positive associations for the variant genotypes. The authors conclude that genetic susceptibility modifies associations of mobile phone use and thyroid cancer and call for further studies to confirm their findings.
Several things are noteworthy: Firstly, the number of unexposed cases of the variant genotype was small for the SNPs where significant associations were observed. This increases the susceptibility to random effects or bias a risk that is possibly augmented by the fact that users where around 10 years younger than non-users. Secondly, wherever mobile phone use displayed elevated OR in the variant genotype, it showed a non-significant decreased OR in the common genotype. This suggests that other factors may have influenced the results, or that it may be a chance finding. Thirdly, exposure was assessed from questionnaires with potential for recall bias, especially if cases reported on exposures one year before their diagnosis and even longer before the interview and controls did not have similar lag period. Finally, a total of 1646 statistical tests on 823 SNPs were conducted, and thus 10 significant associations (p<0.01) is less than expected by chance. The observed associations may thus represent false positive results although the researchers tried to reduce false positive findings by applying Q-values. The observed associations need to be confirmed in an independent dataset before firm conclusions can be made.

Gao et al. (2019) investigated use of personal TETRA (terrestrial trunked radio) radios and risk of all cancer, and head and neck cancer in the British police in the Airwave Health Monitoring Study. TETRA is a telecommunication system adopted by police and other emergency workers that operates between 380-395 MHz. This is a cohort recruited between 2004 and 2015, consisting of 53 114 police personnel. For the present study, 3828 persons were excluded due to missing information about radio usage and 768 due to cancer prior to enrolment. Average monthly call duration from use of personal radios in the year prior to enrolment was calculated based on self-reports and objective network operator data. Self-reported non-users for whom no operator data were found were set to zero use, and for a remaining group of about 12 000 persons (users without objective data), imputation was used to calculate exposure data, based on a model that used objective data and participant characteristics (Vergnaud et al., 2018). Participants were followed in national registries until cancer, death or until

2016/2013 (England and Wales/Scotland). The study had a median duration of follow-up of 5.9 years. HRs were calculated from Cox-regression with age as underlying timescale and adjusting for sex, region, education, salary, rank, job satisfaction, BMI, smoking and alcohol. Compared to non-users, the HR of radio users for all cancer, and head and neck cancer was 1.10 (95% CI: 0.84-1.44; 373 cases) and 0.72 (95% CI: 0.30-1.70; 48 cases). For neither endpoint was there evidence of increasing risk with increasing exposure among users. The authors concluded that the study did not provide evidence of TETRA being associated with an increased cancer risk.
The study benefits from objective exposure data for a large proportion of participants and the large number of participants. It is however limited by the short follow-up time, low number of cases and exposure assessment relating only to the year before baseline. Unfortunately, the study did not consider other sources of exposure such as own mobile phone use.

Sato et al. (2019) simulated the impact of mobile phone usage on incidence trends of malignant brain tumours in three Japanese birth cohorts, namely those born in the 1960s, 1970s and 1980s. They simulated a range of scenarios based on RR for glioma as reported in the existing literature. They took the brain tumour incidence in 1990 as the baseline and simulated the incidence development until 2020. They assumed 30% of malignant tumours to be glioma and assed mobile phone ownership and usage in the cohorts from questionnaire data. By 2020, the simulated incidence of malignant brain tumours in the no-risk scenario was 4.98, 2.84 and 2.10 per 100 000, for those born in the 1960s, 1970s and 1980s respectively. Assuming carcinogenic effects of mobile phones gave rise to incidence rates per 100 000 in 2020 of 5.05-5.55 for the 60's cohort, 2.88-3.17 for the 70s cohort and 2.10-2.35 for the 1980s cohort. The authors concluded that the simulated incidence under scenarios of mobile phone effect started to deviate noticeably from the no-effect incidence risk around 2015 showing a clear increase from 2020. The actual incidence in Japan was available until 2010 and was lower than the simulated one even under the null risk scenario for the 1960s and 1970s cohort. For the 1980s cohort the actual incidence was higher than any simulated incidence. The authors suggest chance as a likely explanation due to the very low incidence in this age group.
The level of assumptions in the study is a concern. The development in mobile phone ownership and usage in the Japanese population was estimated from self-reported information from 1322 eligible persons (person or students) from a total of 7550 respondents recruited by distributing 700 000 flyers at Japanese schools and colleges. It is therefore a concern whether this sample is representative of the full cohorts. In addition, changes in diagnostic and classification practice over the course of the study are not accounted for by this method and may impede comparison with real world incidence developments.

Based on national data Natukka et al. (2019) investigated incidence trends of different types of adult malignant brain tumours in Finland over the years 1990-2016. The overall age standardized incidence rate of all glioma was 7.7 and 7.3 per 100 000 in the periods 1990-2006 and 2007-2016 respectively, with increases only observed for ages 80+. In both time intervals, the incidence of glioblastoma was found slightly increasing whereas unspecified tumours decreased. In the early period astrocytoma decreased and malignant glioma, oligoastrocytoma and anaplastic oligodendroglioma increased. Brain stem and frontal lobe tumour incidence increased 1990-2006, as did tumours of unspecified location. In the same period, there was a decrease of tumours in the parietal lobes, cerebrum and ventricles. The authors ascribe the observed changes to improved diagnostics and increased use of scanning. With regard to mobile phones they find it reassuring that neither malignant glioma nor tumours of the temporal lobe increased over the study period.

In Sweden Nilsson et al. (2019) investigated incidence trends of glioma and meningioma in the period 1980 to 2012 with data from the Swedish National Brain Tumour Registry. A slight increase in incidence rate of meningioma was observed for all under age 75. For those aged 75 or up, there was a decreasing trend and overall the incidence rate of meningioma was constant over the period. For low-grade glioma (LGG), the overall incidence rate trend was negative, this was apparent for all ages >39, whereas the incidence for those below this age was constant over the period. The authors suggested increased surveillance leading to earlier detection of tumours as a possible explanation for the observed incidence pattern for both LGG and meningioma. For LGG it was also suggested that the

decreasing trend could result from an elevated incidence in the late eighties/early nineties due to improved imaging technology. For high-grade glioma, the overall trend was constant, with slight decrease among the young (<40 yrs.) and a slight increase among those aged 60-74.

4.1.2. Reproduction

Using data from four cohort studies from Denmark (1996-2002), the Netherlands (2003-2004), Spain (2003-2008), and South Korea (2006-2011), Tsarna et al. (2019) investigated whether maternal mobile phone use during pregnancy was associated with pregnancy duration and foetal growth. The study included data from a total of 55 507 pregnant women. In their analysis, the authors compared 'no mobile phone use' (30 433 mothers), 'low use' with a maximum of one call per day (12 930), 'intermediate use' with 1-3 calls per day (8270) and 'high use' with at least 4 calls per day (3874). The analyses were adjusted for age, height, weight and marital status of the mother, alcohol consumption, active and passive smoking and number of pregnancies. Statistically significant exposure-response relationships were found for shorter duration of pregnancy and preterm birth, defined as birth before the 36th completed week of pregnancy. No associations were found regarding foetal growth and birth weight. The authors state that mobile phone use during pregnancy could be an indicator for the stress of the mother, and therefore the observed associations might also be due to this rather than mobile phone radiation.

Strengths of this study are the large number of mothers included, and the multitude of factors adjusted for in the analysis. A limitation of the study is that for 94% of mothers, the number of mobile phone calls per day was reported retrospectively, seven years after birth. Foetal exposure during a phone call of the mother is very low and it is unclear how such low levels of mobile phone radiation can affect the foetus. Regarding direct exposure of the foetus, it is probably more relevant how long and how frequently a mobile phone is carried near the belly. However, these data were not available. Nevertheless, it cannot be excluded that maternal mobile phone use affects the foetus in an indirect manner, e.g. via exposure of the placenta, or via the mother.

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

The first paper of the prospective international COSMOS cohort study on mobile phone use, which started in 2007, addressed headache, tinnitus and hearing loss using data from more than 24 000 participants from Sweden and Finland (Auvinen et al., 2019). Data on mobile phone use were collected at the beginning of the study using a written questionnaire. In addition, objective data on call duration using the GSM (2G) and UMTS (3G) network were collected from the mobile phone providers for a period of three months. After four years, the study participants answered follow-up questionnaires investigating whether they suffered from symptoms such as headaches, tinnitus or hearing loss. With regard to tinnitus and hearing loss, the study did not find any associations with mobile phone use. The group of participants with the longest call times (>276 min/week) reported new onset of headache 13% more frequently than the group with the lowest amount of weekly call time. The exposure-response relationship was close to being statistically significant (p=0.06). The association tended to be more pronounced for UMTS use (OR=1.16, 95% CI: 0.93-1.46) than for GSM use (1.06, 95% CI: 0.89-1.26).

In addition to the prospective study approach, major strengths of this study are the large number of study participants and the use of objective data from mobile phone operators including information about 2G and 3G. When making calls in the older GSM network, exposure is about 100 to 500 times higher than in the UMTS network. The fact that the association with headaches was mainly found for the participants making calls in the UMTS network and not for those in the GSM network indicates that observed associations were not caused by RF-EMF. Thus, it seems more likely that other (unknown) factors associated with intensive mobile phone use play a role regarding new onset of headache.

In the Netherlands, Bolte et al. (2019) followed 57 volunteers perceiving themselves as sensitive to electromagnetic fields. For five days, participants carried an exposimeter (Satimo: EME Spy 121) logging 12 RF-EMF bands. At random intervals (about eight times a day), they were cued to provide information on the most important health complaint and nine nonspecific physical symptoms at that specific moment. They analysed correlation between a range of exposure metrics and sum score of all symptoms as well severity of self-reported primary complaint. Most exposure/outcome correlations had r<0.1 and none exceed 0.2. In linear mixed effects models with random intercept for participants and adjusting for sex, age, education, season and hour of day there was no associations with the primary reported complaint that the participant attributed to RF-EMF exposure. For total nonspecific physical symptoms, there were statistically significant associations with most exposures. These associations, however, never explained more than 1% of variance and were dismissed by the authors. The authors also undertook individual analysis of 36 participants that ascribed their primary complaint to sources within the measuring range of the exposimeter. The relationship between exposure and self-reported symptoms were modelled with 0-1 hour and 1-4 hour exposure lags, in both cases adjusting for hour of day and type of location. For four individuals some significant associations appeared in unadjusted analysis. After adjustment, a significant association remained for one person where Wi-Fi exposure (rate of change and time above cut point) was associated with the sum of non-specific symptoms and with the self-reported most important complaint. The authors conclude that there were no relevant associations at group level but some at individual level. They also concluded that it may be relevant to analyse data on individual level and that other metrics than time weighted average may be of relevance.

The study is novel and interesting but has several limitations. The main concern is lack of control for nocebo effects in this study design because it cannot be ruled out that participants were aware of their exposure status (e.g. close to a Wi-Fi), which then may have triggered a symptom report. In addition, the RF-EMF meter used in this study was relatively insensitive which meant that in some cases metrics correlated with at-home versus out-of-home exposures. For example, the rate-of-change metric appeared zero for some persons when they were at home which could be the case if home exposure was relatively low. Such location-effects were not accounted for in the analysis. The sample was small and they were only able to investigate a limited number of exposure bands sampled every 36th second meaning that exposure peaks may have been missed. In addition, symptoms were self-reported every 2-3 hours, it is therefore possible that symptom events may have been missed or that symptoms occurring during these hours may have been reported even if not present at exactly the time of asking and it is not possible to determine if symptoms started earlier that exposure. Additionally, it was possible for participants to postpone or skip answering the questionnaire and the decision to do this may depend on symptoms and perceived exposure or on location. Finally, it is conceivable that some EMF sources (e.g. a phone call or internet use) may trigger symptoms independently of the EMF exposure. To avoid these limitations, experimental, double blind studies are the gold standard for acute symptom response.

In a longitudinal cohort, Park et al. (2019) analysed a population of South Korean adolescents interviewed in 2011, 2013 and 2015, when participants were 14, 16 and 18 years of age, respectively. Of 2280 participants at the first time point in the cohort, 1794 had a mobile phone at all follow-ups and were included in the present analysis. At each time point, mobile phone use, mobile phone addiction and depression was assessed. Multi group structural equation modelling was used to test effects across the time points. High mobile phone use did not predict addiction, but mobile phone addiction and depression predicted each other. Overall, girls scored higher on mobile phone use, addiction and depression scores compared to boys.

While this study did not directly address RF-EMF exposure from mobile phone use, it is interesting that excessive mobile phone use as such was not a predictor of addictive behaviour or depression symptoms. The longitudinal assessment, high response rates and information about potential confounders mean that this is an informative study.

The association between duration of mobile phone use and depressive symptoms was investigated in a cross-sectional survey of 11 831 adolescent Chinese students from Shandong (Liu et al., 2019). Data on mobile phone use, covariates and the outcomes (Center for Epidemiologic Studies Depression

Scale (CES-D) and Youth Self-Report (YSR) depression scales) were obtained by self-administered questionnaire. Statistical analyses were adjusted for gender, age, chronic disease/disability, ever smoking, ever drinking, family economic status, poor inter-parental relationship, fathers' educational level, farming, sleep duration on weekdays, and insomnia using dichotomized variables. The mean age of participants was 15.0 years and 51% were male. Both depression scales were correlated with mobile phone use in a dose-response manner. For instance, OR for increased CES-D depressive symptoms was 1.78 (95%CI: 1.48-2.15) for ≥ 2h/day mobile phone use during workdays and 1.67 (95%CI: 1.41-1.98) for ≥ 5h/day mobile phone use at weekends. In a mediation analysis, these associations were found to be partially mediated by short sleep duration or insomnia.

This is a large sample size with high participation rate (96%) and thus little selection bias. A limitation is the cross-sectional design and thus it remains unclear whether the observed associations are the consequences of mobile phone use, and if so, whether the symptoms were caused from RF-EMF exposure or from other aspects related to extensive mobile phone use. The mediation analysis suggested that excessive mobile phone use results in sleep deprivation, which in turn results in higher depression scores. The authors do not mention RF-EMF exposure in their paper, neither as a study hypothesis nor as a potential explanation for the observed associations.

The association between duration of mobile phone use and problematic mobile phone use (MPU), depressive symptoms (DASS-21), bodily pain (BPISF-C), and daytime sleepiness (CESS) was evaluated in a cross-sectional survey of 686 (participation rate: 94%) secondary school students from Hong Kong (Ng et al., 2020). Regression and mediation analyses were conducted, considering age, gender and grade. Female students spent more time on mobile phones and reported significantly more severe depression, pain and sleepiness, compared to male students. Problematic and prolonged mobile phone use correlated with negative health consequences. The author concluded that pain and daytime sleepiness mediated the relationship of mobile phone use with depression.

The researchers of this relatively small study with high participation rate were mainly interested in psychological and behavioural effects of prolonged and problematic mobile phone use. Because of the cross-sectional design, it remains unclear whether observed associations are due to causality, confounding or reverse causality. The authors do not discuss RF-EMF as a possible reason for the observed associations.

4.1.4. Other outcomes

In the above mentioned Airwave study (Gao et al., 2019) occupational exposure to TETRA personal radios was also evaluated with respect to sickness absence in workers (Elliott et al., 2019). From 53 000 enrolled participants 45 500 (86%) participated in a clinical health assessment. Information about sickness absence of any duration between March 2008 and January 2018 was extracted from employment records. Absence was analysed as sickness absence of more than 7 consecutive days, of more than 28 days, and as number of spells lasting for more than one day. After data cleaning, 35 102 persons were included in the analysis. Median personal radio use in the year before enrolment was about 30 min per month. While users compared to non-users had a similar risk of sickness absence lasting longer than 7 days (OR=0.99, 95%CI: 0.88-1.11), there was a positive association with amount of use with an OR of 1.04 (95%CI: 1.02-1.06) per doubling in use. Associations were also observed in users for sickness spells, but not for sickness absence lasting longer than 28 days.

This is a large study of persons occupationally exposed to TETRA, where high-quality exposure data and registry based data on sickness absence makes information bias unlikely. Analyses by underlying cause of sickness absence did not provide insights into a specific effect that could be associated with TETRA exposure, but nearly all analysed subcategories (14 of 15, e.g. flu and cold, musculoskeletal system, headache, injury etc.) resulted in OR >1 for increasing usage categories. Various confounders have been considered in the analysis (age, sex, rank, region, education, job satisfaction, salary, BMI, alcohol drinking and smoking). The authors discuss that observed associations may be attributable to different working patterns rather than RF-EMF exposure.

A longitudinal study in Australian primary schools was performed between 2011 and 2013 to investigate mobile phone use and cognitive function (Brzozek et al., 2019). For a representative sample of 412 students, data were collected at baseline and about one year later at follow-up. Guardians filled in questionnaires regarding mobile phone and device use; students completed a Stroop colour word test and computerised cognitive function. Cognitive function tests included simple reaction tests, choice reaction, working memory, visual recognition and memory, and response inhibition with a go/no-go task. Also, spatial and executive ability were assessed. The participation rate was 52% and the follow-up rate was 67%. Average age was 9.9 years at baseline and 11 at follow-up, 55% were girls. Mobile phone use during the whole study period was grouped into no use, low (0-2 calls/week) and high (>2 calls/week) and change in performance between baseline and follow-up was analysed. Of the 8 tests performed, children in the low exposure group, but not in the high exposure group, made more errors in the Groton maze learning task and were slower in filling one part of the Stroop colour word test.

This is an interesting study in a reasonably sized group of adolescents, with follow-up information regarding mobile phone use and cognitive tests. The results are consistent with what was previously reported from baseline results (Redmayne et al., 2016) and an analysis addressing change in exposure from baseline to follow-up (Bhatt et al., 2017). The additional information in this paper pertains to using Monte Carlo simulation to incorporate uncertainty in call exposure data into the calculation. The study indicates that mobile phone use was not associated with most cognitive outcomes tested in these children. A limitation is the low amount of exposure, with less than 20% of children making more than two calls per week (Bhatt et al., 2017).

Luna et al. (2019) evaluated if radiofrequency exposure from mobile phone base stations was associated with an increased risk of amyotrophic lateral sclerosis (ALS). All incident cases occurring in Limousin (France) between 2000 and 2012 were identified from a registry. Antenna data were collected from a French registry, from 1991 onwards until 3 years before diagnosis for each ALS case. A model was developed that estimated exposure per 50x50 m^2 raster and year, without explaining which parameters exactly went into the algorithm. The authors state that GSM exposure in the frequency range 900-2600 MHz were calculated, although it is unclear if the data set included also UMTS technology, and if frequencies ranged from 900-2100 MHz, given the time frame of the antenna data. EIRP of the antennas was approximated with 250 W for urban and 500 W for rural areas. Calculated exposure values ranged from 0-6.75 V/m, but apparently no model validation was performed. Maps were available that included all buildings in the area. While addresses were available for all cases, this was unfortunately not the case for the control population and therefore, a homogenous population distribution across all buildings was assumed. The authors calculated expected number of ALS cases for the unexposed population and categorised exposure along equally distributed number of cases in the exposed population. Clearly increasing risks (standardised incidence ratios, SIR and relative risks, RR) were reported across increasing exposure categories.

It is unclear whether authors may have introduced a flaw into their analysis by not knowing where the control population really lived, an equal population distribution across buildings was assumed. This is certainly not correct, as the average number of residents per building tends to be much higher in city areas – that display higher antenna density and higher exposure levels – than in more rural areas. To take account of this, available building heights were used to impute number of floors to derive a more realistic estimate of building surface areas. In addition, general differences between urban and rural areas were also taken into account. Nevertheless, possibly this was an underlying reason to observe more cases in areas with higher population counts (i.e. more densely populated urban areas), as more cases naturally occur where more people live. It is therefore unclear how to interpret a potential association of environmental RF-EMF exposure from mobile phone base stations and risk of ALS. In addition, validity of the exposure model is unclear.

Palal & Stalin (2019) conducted a community-based case-control study on hypertension and mobile phone use in the urban field practice area of a medical college in Puducherry, India. Cases were defined based on a diagnosis of hypertension or an average blood pressure ≥140/90 mmHg on three readings. Controls (BP≤130/85 mmHg on three readings) were matched in terms of age and gender. Fifty cases and 50 controls were selected through a door-to-door survey and interviewed using a

structured questionnaire. Only one-third of the study population owned a smartphone. Based on logistic regression adjusted for age, gender, education, socio-economic status, family history, tobacco use, alcohol use, salt consumption and body mass index, odds ratio for high blood pressure was 6.2 (95%CI: 1.6–23.8) for people using a mobile phone for more than 8 years and 4.2 (95%CI: 1.1–16.7) for those who call for more than 60 min per day.

This study has several limitations including the small sample size and retrospective exposure assessment. The inclusion of a large number of variables in such a small dataset makes the study vulnerable to chance findings as indicated by the large difference between adjusted and unadjusted odds ratios.

Khaki-Khatibi et al. (2019) conducted a questionnaire study among 471 Multiple Sclerosis (MS) patients and 453 healthy controls. MS-patients reported significantly more frequent use of cell phones, sleeping more often with electronic devices near head and higher use of satellite TV. Their use of computers and TV-watching was also higher but not significantly so. The authors find the results support that "dirty electricity" increases risk of MS.

There are several limitations of the study. Reverse causality is of concern, because the observed exposure pattern may be the consequences of the disease and not the other way around. Cases were recruited from a neuroscience research centre. It is not described how controls were recruited. It is therefore not possible to determine if differences between the two groups relate to the evaluated exposures or other factors. In addition, the questionnaire items appear to relate to present usage of devices making it impossible to discern cause and effect and finally there is the inherent potential for recall/reporting biases between cases and controls.

Pedrami and Arbabi-Kalati (2019) compared salivary cytokines in 40 deaf people and 40 volunteers presenting at the Department for Oral Medicine, Zahendan, Iran between 2016 and 2017. Salivary IL-10 levels were significantly higher in mobile phone users than in deaf participants not using mobile phones. The authors attributed this entirely to RF-EMF exposure from mobile phones.

This study did not take into account underlying differences between deaf and non-deaf people that could be related to talking vs not talking which could be in turn associated to salivary IL-10 levels.

4.1.5. Conclusions on epidemiological studies

The thyroid gland is potentially highly exposed during mobile phone calls, but little research on thyroid cancer has been conducted so far. A case-control study of 701 cases from the USA study found no significant association between mobile phone use and thyroid cancer, although some suggestive elevated risk of thyroid micro-carcinoma associated with long-term and more frequent mobile phone use was observed. Recall bias of self-reported mobile phone use may be an alternative explanation for these results. A subsequent gene-environment analysis did not provide consistent evidence. New research on brain tumours and mobile phone use is in line with previous research suggesting mostly an absence of risk.

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. Noteworthy is the first paper from the COSMOS study. To date, this is the largest prospective study on headache, tinnitus and hearing loss using objective mobile phone usage data obtained from the network operators. No association with tinnitus and hearing loss were observed but headache was developed slightly more often in participants with the longest call time. The fact that this association was mainly found for the participants making calls in the UMTS network and not for those in the GSM network indicates that observed associations were unlikely to be caused by RF-EMF, because when making calls in the newer UMTS network, RF-EMF exposure is about 100 to 500 times lower than in the GSM network. Such innovative approaches allowing to differentiate between device usage and physical RF-EMF exposure are needed to better understand the causality of RF-EMF exposure for health.

4.2. Human studies

As usual, the number of studies addressing RF-EMF effects in human experimental studies is higher than for other exposure types. In 2019 six human studies investigating possible effects of radiofrequency electromagnetic field exposure were published. The outcome parameters were: biomarkers in electrohypersensitive subjects (Andrianome et al. 2019), brain activity (Loughran et al. 2019, Vecsei et al. 2018, and Wei et al. 2019), and cognitive functions (Vecsei et al. 2018) as well as sleep and symptoms (Lowden et al. 2019).

4.2.1. Saliva biomarker in electrohypersensitive subjects

Based on a previous observation from the same group that salivary alpha amylase (AA) was significantly increased in subjects with electrohypersensitivity (EHS) as compared to non-EHS subjects, Andrianome et al. (2019) investigated whether RF-EMF exposure was related to the concentration of this biomarker. In a double-blind sham-controlled cross-over study they furthermore looked at exposure related changes in the concentration of immunoglobulin A (IgA) and in the concentration of cortisol in EHS subjects. The sample was small, 10 subjects (8 females) and covered a broad age range (35 to 63 years, mean ± SD: 47.8 ± 9.7 years). The subjects attributed their symptoms to any of the following sources: GSM 900, GSM 1800, DECT, or Wi-Fi 2.45 GHz. The experiment consisted of two experimental sessions, one sham session and one with successive RF-EMF exposures to GSM 900, GSM 1800, Wi-Fi, and DECT (each delivered for 5 min with a 10 min stimulation free interval between exposures). Exposure was delivered by an antenna placed at about 2 m distance from the body. The electric field at the level of the head and the body as recorded by a dosimeter placed near the participant was about 1 V/m. Overall more detailed information on the exposure setting and source-specific SAR values (whole body and close to head) is missing. All sessions were scheduled to start at the same time in the morning in a shielded room with constant temperature and humidity with at least one week between sessions. Saliva samples were collected prior to exposure and after the end of each of the four exposures. At the end of the experiment subjects were asked which session they considered as the real exposure. The guess of three out of the 10 participants was correct. None of the biomarkers was significantly affected by exposure. Limitations of the study certainly are the small sample size (and the resulting low power) and the short duration of exposure. Both, however, are an inherent problem in provocation studies with EHS volunteers.

4.2.2. Brain activity

Based on the observation that RF-EMF exposure has repeatedly been shown to have an effect on the alpha frequency band of the resting state waking EEG, Loughran et al. (2019) investigated whether this effect might be thermally mediated. The double-blind, randomized, counterbalanced, cross-over study was performed in 36 healthy adults (18 females, 18 males; age range: 18 to 52 years; mean ± SD: 24.4 ± 6.3 years). Subjects had four laboratory sessions at individually constant times separated by at least seven days. Following an adaptation session to minimize practice effects on cognitive task performance and to determine individually appropriate difficulty levels, subjects had three session with different exposure conditions (sham; 0 W/kg, low RF: 1 W/kg, and high RF: 2 W/kg). Subjects were exposed to a 920 MHz GSM-like signal generated by an sXh920 planar exposure system (IT'IS Foundation, Zurich, Switzerland). The antenna was positioned at the left side of the participant's head at a distance of 115 mm in a predefined position. No participant was able to correctly identify all exposure conditions. EEG was recorded using a 19 channel cap in an eyes-open condition. Out of the 19 EEG channels 9 were used and grouped in to three brain regions: frontal, central and parietal. Skin temperature was measured by thermistors placed at the forehead, right chest, right scapula, right upper arm, right forearm, left dorsal hand, right anterior thigh, right calf, and at the dorsal surface of the distal phalanx of the left middle finger. The latter was used as a surrogate measure of local skin blood flow. Effects of ambient temperature were controlled by a water-perfusion suit, which covered the torso and the arms to the wrist level as well as the legs to the level of the ankles. Thus only three of the measuring sites for skin temperature were not covered by the suit. Exposure was delivered in two 30

min experimental blocks separated by a one minute rest period. The first block always was the exposure block, the second always a sham block. EEG and mean arterial blood pressure were recorded prior to exposure (baseline), at min 0-4 and 22-26 of each block. All tests were performed with one-tailed contrasts, which enhances the chance of finding significant results and which might not be warranted by the inconsistent findings in the literature. Mean arterial blood pressure was not significantly different in the high and the low RF exposure condition as compared to sham. The change in the resting EEG alpha power (8–12 Hz) from baseline (preceding exposure) to min 22-26 was significantly larger in the high RF condition as compared to sham and not significant for the low RF exposure condition. However, it is not clear on which locations the results are based. Finger temperature during the experiment was significantly higher during the low RF condition as compared to sham, while the temperature under the high RF exposure condition was not. No significant exposure effects were observed for mean arterial pressure.

Vecsei et al. (2018) also investigated the effect of RF-EMF exposure on EEG activity in the alpha frequency band (8–12 Hz). In two independent experiments they studied the effect of 20 min exposure to UMTS or LTE in altogether 60 healthy young university students (34 for UMTS, 20 females and 14 males, 20 ± 3 years; 26 for LTE, 13 females and 13 males, 21 ± 3 years). Subjects were exposed in separate sessions separated by at least one week with randomly and counterbalanced assigned exposure conditions. RF exposure was delivered by a patch antenna mounted to mimick the normal use of a mobile phone. UMTS operated at a 1947 MHz carrier frequency with a 5 MHz modulation of carrier frequency. The averaged SAR resulting from phantom measurements was below 2 W/kg in any position. LTE operated with a carrier frequency of 1750 MHz using 20 MHz bandwidth. The maximum peak SAR was set to 1.8 W/kg and the ear-antenna distance to 7 cm. Sessions were scheduled at 8 am and 6 pm. To avoid interference with circadian factors, times were balanced across participants. EEG was recorded with a cap mounted with 32 electrodes prior, during and post exposure with eyes open while the subjects watched a nature film (controlled visual stimulus). There is no information whether the authors checked possible interferences between exposure and the recording system. After a thorough artefact consideration alpha power was averaged across all EEG channels and analysed by a three way mixed ANOVA considering the within-subject factors: exposure (two levels: real and sham) and time (three levels: pre, mid and post) as well as the between subject factor RF type (UMTS or LTE). The results indicate that alpha power significantly decreased in the RF exposure condition and that this decrease persisted even after the cessation of exposure.
The results are contradictory to those reported by Loughran et al. (2019), indicating that the often stated increase in alpha power is not such a consistent finding as repeatedly quoted. The results thus contribute to the inconsistent findings with regard to RF-EMF exposure effects on the human resting state EEG, which have been described in two independent reviews published in 2019 (Danker-Hopfe et al. (2019), Wallace and Selmaoui (2019)).

Wei et al. (2019) investigated LTE effects on brain activity by looking at intra-regional connectivity using resting state functional magnetic resonance imaging (fMRI). A sample of 21 healthy young subjects (7 females, age range: 19–36 years, mean ± SD: 25.2 ± 4.1 years) was exposed to either sham or LTE-EMF (2.573 GHz) for 30 min in a double-blind cross-over, randomized and counterbalanced study design. In this study the subjects and the data analyst were blinded while the experimental operator, who controlled the order of exposure, was not. Experiments were performed on different days, separated by one day. It is not reported whether the time of the day was controlled. Each experiment consisted of two functional MRI scans (performed with a 3.0 T MR), one performed preceding a 30 min exposure (sham or LTE) and one performed immediately following the exposure. The specific absorption rate (SAR) was estimated for each subject using data from a structural MRI scan. Numerical simulation yielded mean spatial peak SAR_{10g} of 0.98 ± 0.27 W/kg, with a highest value of 1.52 W/kg. The outcome parameter investigated in this study was the regional homogeneity (ReHo) index. Results based on pre-post differences indicated a significant difference in connectivity in three regional clusters under LTE exposure while for sham no significant differences in the ReHo values were observed. These three clusters were defined as volumes of interest (VOI) to perform a seed-driven functional connectivity analysis, defined as temporal correlations between a selected seed

and all other voxels over the whole brain. For all three VOI the authors observed a significantly increased functional connectivity to other parts of the brain.

The authors found that acute LTE-EMF exposure modulated intra-regional and inter-regional connectivity in some brain regions.

Limitations of the study are that although none of the subjects reported falling asleep, this cannot completely be ruled out and that although SAR values do not indicate a temperature increase during exposure thermal changes could not be precluded.

4.2.3. Cognitive functions

The study on UMTS and LTE exposure effects by Vecsei et al. (2018) described above also considered performance in a Stroop task as outcome parameter. Although the EEG in the alpha frequency range was affected by RF exposure, executive function measures, processing speed and selective attention as assessed by the Stroop test were not.

4.2.4. Sleep-EEG, subjective sleep quality and symptoms

Lowden et al. (2019) studied the effect of a 3 h exposure to a 1930-1990 MHz signal, UMTS standard, prior to sleep (scheduled for 7.5 h starting from 23:30) on symptoms, performance in a cognitive test, the macrostructure of sleep, subjective perception of sleep and the power spectra of the sleep EEG in the frequency range from 0.5 to 32 Hz. Exposure to the UMTS signal was via a dipole antenna fixed to a helmet, specifically designed for the project. The $psSAR_{10g}$ was 1.6 W/kg. Data from 18 healthy subjects (7 females and 11 males, 18-19 years, mean ± SD: 18.6 ± 0.5 years) were analyzed in this double-blind crossover study. Nights were scheduled with a one week interval between two sessions of two consecutive nights for each exposure. Four out of originally 22 subjects had to be excluded due to technical problems with the EEG recorder. It is not reported whether this had consequences for an unbalanced order of exposures, which might affect the results. Before the start of exposure and after two hours of exposure altogether 19 symptoms including dermal complaints were self-rated on a seven-point Likert scale. Sleepiness was rated hourly from 19:00 to bedtime with the Karolinska Sleepiness Scale. At the end of exposure a computerized Stroop-like task was performed. Upon awakening subjects filled out the Karolinska Sleep Diary for subjective assessments of sleep parameters and sleep quality. Repeated measures ANOVA revealed that exposure had no significant effect on symptoms, sleepiness, reaction time in the Stroop test, subjective perception of sleep, and 13 measures of the macrostructure of sleep. An analysis of the power spectra calculated for 6 frequency bands separately for NREM and REM sleep revealed a significant reduction of the spectral power in the slow spindle frequency range under UMTS exposure during REM sleep. The authors discuss this result as conformation of previous findings. However, in some of the earlier studies the power in the spindle frequency range was increased. Furthermore, previous findings referred to NREM sleep, where spindles are a hallmark of stage S2 sleep, while in the present study effects were seen during REM sleep.

4.2.5. Conclusion on human studies

The studies published in 2019 support that RF exposure does not change the concentration of biomarkers in electro hypersensitive subjects. However, as in all studies in EHS subjects the power of test results is a problem. All three studies addressing brain effects during wake found physiological changes related to RF exposure, two of them with contradictory results. This underlines that effects which have been considered to be consistent in the past are less consistent than hypothesized. Effects at the physiological level, however, obviously do not translate into behavioural measures as reflected by cognitive performance. A sleep study revealed no effects of UMTS exposure on symptoms, sleepiness, reaction time, subjective perception of sleep and sleep macrostructure. The observed decrease of the spectral power in the slow spindle frequency range during REM sleep does not confirm previous findings.

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

Keleş et al. (2019) exposed 3-week-old male Sprague Dawley rats in groups of 7 to 900 MHz EMF for 1 h per day during 25 days at a whole-body SAR of 0.012 W/kg. Following the last exposure, behavioural tests were performed for seven days and after that the animals were sacrificed and the brains removed. (The results of the behavioural tests were published elsewhere (Keleş et al., 2018) and have been discussed in last year's report (SSM 2019).) They observed that the number of pyramidal and granule neurons in the hippocampus of the exposed group was statistically higher than in the sham controls. In addition, histopathological analysis showed that the cytoplasm of pyramidal and granular cells in the hippocampus of the exposed animals was disrupted.

Kim et al. (2019a) exposed C57BL/6 mice in groups of 5 to 835 MHz for 5 h per day during 12 weeks at a whole-body SAR of 4.0 W/kg. They observed that the number and size of the synaptic vesicles in the hypothalamic presynaptic terminals were significantly decreased after exposure. In addition, the density of docking and fusing vesicles in the active zones of the presynaptic terminal membrane was significantly decreased. The expression levels of synapsin I/II and synaptotagmin 1, two regulators of vesicle transport in neurons, were also significantly decreased. In parallel, the expression of calcium channels was significantly decreased. These changes may indicate a decrease in the release of neurotransmitters in hypothalamic presynaptic terminals.
The applied whole-body SAR of 4 W/kg is a thermal burden to the mice, so the effect of heat stress cannot be excluded and therefore it is difficult to conclude that the RF exposure *per se* caused the effects.

In a study by Bodera et al. (2019), male Wistar rats (n= 8 per group) were either treated or not treated with complete Freund's adjuvant in a hind paw to induce a local inflammation, and then exposed or sham exposed to 1800 MHz either once or 5 times for 15 min per day at a whole-body SAR of 0.024-0.028 W/kg. In healthy animals neither the single nor the repeated exposures influenced pain perception. Treatment of the animals with morphine 15 min before the real or sham exposure resulted in a temporary increase in pain tolerance, between 30 and 60 min after single or repeated exposure, which was partly counteracted by the exposure. In the animals with an inflammation, exposure had no influence on pain perception, but it increased the pain tolerance at 30 and 60 min when exposure was preceded by morphine administration.

Kumar et al. (2019) exposed male Wistar rats in groups of 6 to 900, 1800 and 2450 MHz for 2 h per day, 6 days per week, during 30 days, at whole body SAR levels of 0.00058, 0.00059 and 0.00067 W/kg, respectively. After the exposure, the brain was dissected and the hippocampus isolated. They assessed the expression of three transcription factors that are involved in so called endoplasmatic reticulum stress, which is associated with accumulation of unfolded and therefore inactive proteins. The expression of all three factors after exposure to all three frequencies changed in such a way as to indicate increased endoplasmatic reticulum stress.

4.3.2 Effects on behaviour

Sharma et al. (2019) exposed male Wistar rats in groups of 6 to 2100 MHz for 4 h per day, 5 days per week, for 3 months. The brain SAR was 0.453 W/kg. They observed a decrease in cholinesterase activity in the brain, in muscular strength and in learning ability and an increase in anxiety in the

exposed animals compared to the control group. Exposure was also associated with an increased oxidative stress in brain tissue and with degeneration of the hippocampus.

Broom et al. (2019) exposed C57BL/6J mice (n=6 per group) to 1846 MHz 4G (LTE) signals for 30 min per day, 5 days per week from late pregnancy (gestation day 13.5) to weaning (postnatal day 21). The whole-body SAR was 0.5 or 1 W/kg. A behavioural tracking system measured movements, drinking, and feeding behaviour in the home cage from 12 to 28 weeks of age. Compared with sham-exposed controls, exposure at 0.5 W/kg significantly decreased drinking frequency and distance moved. In contrast, exposure at 1 W/kg significantly increased drinking frequency and moving duration.

Gupta et al. (2019) exposed groups of 6 male Charles-Foster rats to either 900, 1800 or 2450 MHz EMF for 1 h per day during 28 days. The SAR in the head was 0.131 W/kg. Behaviour was assessed after day 1 of exposure and every 7 days thereafter, the last time after the last exposure. After that, the animals were sacrificed and the blood and brains used for further analysis. The whole experiment was repeated once. No behavioural effects were observed in the 900 and 1800 MHz groups, but in the 2450 MHz group anxiety was increased and normal behaviour decreased at 21 and 28 days of exposure. Plasma corticosterone levels were increased after 2450 MHz exposure, but not with the other frequencies. Also a number of parameters in the brain were changed only with 2450 MHz: the mitochondrial membrane potential was decreased and oxidative stress and apoptosis were increased.

Bouji et al. (2020) used an Alzheimer model in Long-Evans male rats plus non-Alzheimer controls (n=4-6 per group) to study the effect of exposure to 900 MHz fields for 5 days per week during 1 month. Daily exposures were with a brain SAR of 1.5 W/kg for 15 min and 6 W/kg for 15 min or 45 min. No effect on memory of any of these exposures was observed in both the Alzheimer and normal rats. However, Alzheimer rats showed higher oxidative stress in the hippocampus and reduced corticosterone with the higher SAR.
But this SAR level most likely resulted in heat stress in the brain.

4.3.3. Genotoxicity

Smith-Roe et al. (2020) report on the analysis of genotoxicity in the NTP long-term carcinogenesis study (reported in the 2018 SSM report). Briefly, male and female Sprague Dawley rats and B6C3F1/N mice were exposed from gestation day 5 (rats) or postnatal day 35 (mice) to EMF over 18 hours per day, at 10-min intervals, at whole-body SARs of 1.5, 3, or 6 W/kg (rats, 900 MHz, GSM or CDMA modulation) or 2.5, 5, or 10 W/kg (mice, 1900 MHz, GSM or CDMA modulation). After 19 (rats) or 14 (mice) weeks of exposure, animals were examined for genotoxicity. Using the alkaline comet assay, DNA damage was assessed in brain cells, liver cells, and peripheral blood leukocytes; using the micronucleus assay, chromosomal damage was assessed in immature and mature peripheral blood erythrocytes. Results of the comet assay showed significant increases in DNA damage in the frontal cortex of male mice (both modulations), leukocytes of female mice (CDMA only), and hippocampus of male rats (CDMA only). Increases in DNA damage judged to be equivocal were observed in several other tissues of rats and mice. No significant increases in micro nucleated red blood cells were observed in rats or mice.
The study has been criticized by Vijayalaxmi et al. (2020) who conclude that the statement in the paper that the results suggest that exposure is associated with an increase in DNA damage is unjustified, and needs to be taken with great caution.

4.3.4. Oxidative stress

Alkis et al. (2019) exposed male Sprague Dawley rats in groups of 7 to either sham or real exposure for 2 h per day during 6 months at 3 frequencies. The SAR in the brain was 0.085 W/kg for 900 MHz, 0.046 W/kg for 1800 MHz and 0.040 W/kg for 2100 MHz. After exposure serum was collected and

the brains were removed and processed for further investigation. Significant changes in parameters indicating increased oxidative stress in the brain frontal lobe were observed with all 3 frequencies, as well as in serum with 1800 and 2100 MHz. An indication for DNA damage was observed in the 2100 MHz group, but this was only with one parameter (tail density)of the Comet assay, which is in itself not very reliable and easily prone to artefacts.

Ismaiil et al. (2019) exposed both normal Sprague Dawley rats and rats made diabetic (12 per group) to 900 MHz at an E-field level of 25 V/m for 24 h per day over 28 days. In normal rats this treatment had no effect on blood glucose, but changes in some parameters indicating increased oxidative stress in the liver were observed. In diabetic rats they observed no significant effects on hyperglycemia and hyperinsulinemia, and inconsistent effects on parameters indicating oxidative stress, that differed from those in normal rats.

Okatan et al. (2019) exposed female rats (n= 7 per group) to 900 MHz fields for 1 h per day during 24 days at a whole-body SAR of 0.0096 W/kg. After the exposures, the liver was removed for analysis. Histological examination showed occasional irregularities in the radial arrangement of hepatocytes, cytoplasmic vacuolization, hemorrhage, sinusoid expansion, hepatocyte morphology and edema in the exposed, but not in the sham-exposed animals. In the livers of the exposed animals, oxidative stress parameters were reduced compared to the sham-exposed group.

4.3.5. Male fertility

Houston et al. (2019) exposed male C57BL/6 mice to 905 MHz fields for 12 h per day during 1, 3, or 5 weeks, in groups of 6-8. The whole-body SAR was 2.2 W/kg. No histological changes were observed in the testes at any time. However, after 5 weeks exposure the motility and vitality of spermatozoa was reduced, and after 1 week exposure increased oxidative stress in spermatozoa was observed. Nevertheless, the fertilization ability of the spermatozoa was not affected.

Yu et al. (2020) used a 4G smartphone to expose the testes of Sprague Dawley rats to 2575-2635 MHz fields at a local SAR of 1.05 W/kg (n=10-15). Exposure was for 1 min every 10 min, during 6 h per day and 50, 100 or 150 days. They observed a decreased sperm quality and pup weight after 150 days exposure, but not after the shorter exposures. Also expression of genes in the testes that are involved in the blood-testis barrier was changed, indicating changes in the blood-testis barrier. The derivation of the SAR level is not described.

Azimzadeh and Jelodar (2019) exposed Sprague Dawley rats (10 per group) to 900 MHz fields at a SAR in the testis of 0.33 W/kg. Exposure lasted for either 2 or 4 h per day during 30 days. Reduced testosterone was observed in both groups. Several changes in inflammatory factors were observed as well, which were greater in the longer exposed animals. They conclude that exposure changes factors important in steriodogenesis, and inflammatory factors which regulate Leydig cell functions.

4.3.6. Development

Calis et al. (2019) exposed pregnant Wistar rats for 1 h per day during the entire pregnancy to 900 MHz fields. The E field was 17.25 V/m (the authors provide a SAR level, but this was incorrectly calculated using the external E field). Female offspring (n=4 per group) was sacrificed at the age of 42 days and the number of follicles in the ovaries assessed. The number of follicles in RF-exposed animals was reduced compared to sham-exposed animals (p=0.006 for primordial follicles; numbers for other type of follicles were very low). An oxidative stress parameter (FOXO-1A) was increased in the exposed animals (p=0.002). TUNEL analysis (indicative of DNA fragmentation and apoptotic cell death) showed an increase in the exposed group (not quantified).

Kim et al. (2019b) exposed new-born ICR mice (n=4-29) for 5 h per day from postnatal day 1 up to day 5 to 1850 MHz EMF at a whole-body SAR of 4 W/kg. At day 8 part of the animals were sacrificed and various components of the auditory system assessed. An increase was observed in the release of synaptic vesicle from presynaptic nerves, but no morphological changes in the inner hair cell ribbon synapses. In animals tested at postnatal day 15, no significant changes were found in the hearing threshold of the auditory brainstem response.

4.3.7. Physiology

Kim et al. (2020) exposed free moving male Sprague Dawley rats of either an average weight of 225 or 339 g to 915 MHz RF EMF at a whole-body SAR of 4 W/kg for 8 h. They compared the body temperature, measured every hour during exposure with a rectal probe, with and without anaesthesia by injection of chloral hydrate. Both the sham and exposed non-anaesthetized groups were 20 animals, while the anaesthetized groups were n=6 for the 225 g animals and n=5 for the 339 g animals. The body temperature was not affected in the non-anaesthetized animals. In the anaesthetized animals, the temperature increased in the 225-g animals by 1.9 °C after 5 h of exposure and in the 339-g ones by 3.3 °C at 6 h of exposure. Three of the five 339 g anesthetized and exposed rats died after 6 h of RF exposure.

Perov et al. (2019) exposed male Wistar rats (n=12 per group) to 171 MHz RF EMF at whole-body SARs of 0.006, 0.023 and 0.038 W/kg. Exposure was for 6 h per day during 15 days. The animals were kept in metabolic cages and the urine was collected every day, pooled by group, and analysed. The corticosterone concentration in urine did not increase during the lowest exposure level. During 0.023 W/kg exposure it started to increase after 7 d, peaked at approximately 2.5x the control level at day 10 and returned to control level thereafter. During 0.038 W/kg exposure the urinary corticosterone level already started to increase at day 3, peaked at day 8-10 at approximately 4.5x the control level and also declined thereafter to control level. The electrolyte excretion paralleled the changes in corticosterone levels.

4.3.8. Conclusions

As in previous years, there is again a variety of endpoints with mixed and sometimes contradicting results. Some studies show effects of exposure, other do not. The exposure parameters, such as frequency, duration and exposure level, also 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, as are effect on behaviour and spermatozoa (without an effect on male fertility, however). But there is not much consistency. Indeed, the conclusion from last year's SSM report that there is a need for systematic reviews of these studies before any conclusions concerning the possible implications for human health can be drawn, is still valid. It is good that such reviews are now underway as part of the major review on effects of RF EMF exposure that is performed by WHO.

Table 4.3.1. Animal studies on exposure to radiofrequency fields

Endpoint	Reference	Species	Exposure and duration	Effect
Effects on brain	Keles et al. (2019)	Sprague Dawley rats	900 MHz, 1 h/d, 25 d, WBA SAR 0.012 W/kg	Increased number of neurons in hippocampus, with cytoplasmic damage
	Kim et al. (2019a)	C57BL/6 mice	835 MHz, 5 h/d, 12 wk, WBA SAR 4.0 W/kg	Decreased number and size of synaptic vesicles in

				hypothalamus; decreased regulators of vesicle transport in neurons
	Bodera et al. (2019)	Wistar rats	1800 MHz, 1x or 5x 15 min/d, WBA SAR 0.024-0.028 W/kg	No effect on pain perception, counteraction analgesic effect morphine in healthy animals, reinforcement in animals with inflammation
	Kumar et al. (2019)	Wistar rats	900, 1800 and 2450 MHz, 2 h/d, 6 d/wk, 30 d, WBA SAR 0.00058, 0.00059, 0.00067 W/kg, respectively	Increased endoplasmatic reticulum stress in hippocampus
Effects on behaviour	Sharma et al. (2019)	Wistar rats	2100 MHz, 4 h/d, 5 d/wk, 3 mo, brain SAR 0.453 W/kg	Decreased learning ability and increased anxiety, increased oxidative stress in brain tissue, degeneration of hippocampus
	Broom et al. (2019)	C57BL/6J mice	1846 MHz, 30 min/d, 5 d/wk, gestation day 13.5 to postnatal day 21, WBA SAR 0.5 or 1 W/kg	Drinking frequency and distance moved decreased with 0.5 W/kg and increased with 1 W/kg
	Gupta et al. (2019)	Charles-Foster rats	900, 1800 or 2450 MHz, 1 h/d, 28 d, head SAR 0.131 W/kg	No effect with 900 and 1800 MHz; with 2450 MHz increased anxiety, plasma corticosterone, brain oxidative stress and apoptosis
	Bouji et al. (2020)	Long-Evans rats (wild-type and Alzheimer model)	900 MHz, 5 d/wk, 1 mo; brain SAR 1.5 W/kg: 15 min/d; 6 W/kg: 15 or 45 min/d	No effect on memory in both rat types; increased oxidative stress in hippocampus and decreased corticosterone with high SAR in Alzheimer rats
Genotoxicity	Smith-Roe et al. (2020)	Sprague Dawley rats, B6C3F1/N mice from NTP study	Rats: 900 MHz (GSM, CDMA), 18 h/d, 19 wk, WBA SAR 1.5, 3, 6 W/kg Mice: 1900 MHz (GSM, CDMA), 18 h/d, 14 wk, WBA SAR 2.5, 5, or 10 W/kg	Increased DNA damage in frontal cortex of male mice (both modulations), leukocytes of female mice (CDMA only), and hippocampus of male rats (CDMA only) Criticized by

				Vijayalaxmi et al. (2020)
Oxidative stress	Alkis et al. (2019)	Sprague Dawley rats	2 h/d, 6 mo, brain SAR 0.085 W/kg (900 MHz), 0.046 W/kg (1800 MHz), 0.040 W/kg (2100 MHz)	Increased oxidative stress in brain frontal lobe
	Ismaiil et al. (2019)	Sprague Dawley rats (wild-type and diabetic)	900 MHz, 24 h/d, 28 d, E-field 25 V/m	Normal: no effect blood glucose, increased oxidative stress liver Diabetic: no effects hyperglycemia, hyperinsulinemia, inconsistent effects oxidative stress, different from normal rats
	Okatan et al. (2019)	Rats	900 MHz, 1 h/d, 24 d,WBA SAR 0.0096 W/kg	Increased oxidative stress, histological damage liver
Male fertility	Houston et al. (2019)	C57BL/6 mice	905 MHz, 12 h/d, 1, 3, 5 wk, WBA SAR 2.2 W/kg	1 wk: increased oxidative stress spermatozoa; 5 wk: reduced motility, vitality spermatozoa; no effect fertility
	Yu et al. (2020)	Sprague Dawley rats	2575-2635 MHz, 1 min every 10 min, 6 h/d, 50, 100, 150 d, testes SAR 1.05 W/kg	150 d: decreased sperm quality, pup weight, changes blood-testis barrier
	Azimzadeh and Jelodar (2019)	Sprague Dawley rats	900 MHz, 2, 4 h/d, 30 d, testes SAR 0.33 W/kg	Reduction testosterone, changes inflammatory factors testes
Development	Calis et al. (2019)	Wistar rats	900 MHz, 1 h/d during pregnancy, E field 17.25 V/m	Reduced number of follicles, increased oxidative stress
	Kim et al. (2019b)	ICR mice	1850 MHz, 5 h/d, postnatal d 1-5, WBA SAR 4 W/kg	D 8: increase in release synaptic vesicle from presynaptic nerves, no morphological changes in inner hair cell ribbon synapses D 15: no effect auditory brainstem response
Physiology	Kim et al. (2020)	Sprague Dawley rats	915 MHz, 8 h, WBA SAR 4 W/kg, with / without anaesthesia	No anaesthesia: no effect body temperature Anaesthesia: weight-dependent increase
	Perov et al. (2019)	Wistar rats	171 MHz, 6 h/d, 15 d, WBA SAR 0.006, 0.023, 0.038 W/kg	Dose-dependent temporary increase urinary corticosterone, electrolytes

4.4. Cell studies

In the new in vitro studies several endpoints have been investigated and in most cases no effect of the exposure was detected, although in few cases slight variations were recorded. Some investigations also deal with frequencies between 6 and 60 GHz. As for the past years, several studies have been recognized but not considered, due to the scanty quality of the experimental set-up.
In addition, three review papers have been published on genotoxicity (Vijayalaxmi and Prihoda, 2019b, Vijayalaxmi and Prihoda, 2019a) and on millimeter waves (Simkó and Mattsson, 2019).

4.4.1. Adaptive response

The phenomenon of RF-induced adaptive response (AR) has been further investigated. Sannino and co-workers pre-exposed human peripheral blood lymphocytes of three male donors and a Chinese hamster lung fibroblast cell line for 20 h to 1950 MHz, UMTS signal. On the bases of previously published results, a SAR level of 0,3 and 1,25 W/kg was used to expose human lymphocytes and lung fibroblasts, respectively. Cell cultures were then treated with Mitomycin-C (Sannino et al., 2019). In three independent experiments for each cell type, by comparing exposed and sham-exposed samples, they confirmed the induction of an AR in terms of reduction of micronuclei formation, and observed that such a response was negated by treatments with 3-aminobenzamide, an inhibitor of poly (ADP-ribose) polymerase enzyme, involved in DNA repair. These results support the involvement of DNA repair mechanisms in radiofrequency-induced adaptive response.

In a further study, the same research group evaluated the influence of modulation and bandwidth in eliciting the RF-induced AR in human lymphocytes (Romeo et al., 2019). Blood cultures from four healthy donors were exposed to 1950 MHz, and Continuous Wave (CW), Wideband Direct-Sequence Code Division Multiple Access (WCDMA, 4.5 MHz bandwidth), and Additive White Gaussian Noise (AWGN, 9 MHz bandwidth) signals were considered. For each signal, SAR values of 0.15, 0.3, 0.6, 1.25 W/kg were tested. RF exposure alone never induced DNA damage in the micronucleus assay. When RF exposure was followed by mitomycin-C (MMC) treatment, the effect depended on modulation and bandwidth. CW exposure never altered the MMC-induced DNA damage, while such damage was reduced when either signals WCDMA at 0.3 W/kg SAR or AWGN at 0.15 and 0.3 W/kg were applied. These results indicate the influence of modulation for the occurrence of the protective effect, with a relation between the bandwidth and the power absorbed by samples. In addition, since the effect was detected at the lower SARs investigated, a window effect cannot be excluded.

4.4.2. DNA damage

Durdik et al. (2019) exposed umbilical cord blood (UCB) cells to 900 MHz, GSM (4 and 40 W/kg SAR) and 1950 MHz, UMTS, (40 W/kg) RF-EMFs and evaluated several biochemical markers of cellular damage including reactive oxygen species (ROS), DNA single and double strand breaks, preleukemic fusion genes (PFG, a specific chromosomal translocation often detected in childhood leukemia) and apoptosis in UCB cells and sub-populations distinguished by cluster of differentiation (CD) markers. The analysis was conducted by applying several techniques, such as flow cytometry, automated fluorescent microscopy, comet assay, and RT-qPCR. For each parameter investigated at least three independent experiments were carried out, except for comet assay, where two experiments in triplicate were performed. No difference between exposed and sham-exposed samples was detected in DNA damage, evaluated as foci formation, following short (1-4 h) and long (17 h) exposure duration to GSM at 4 and 40 mW/kg, or following 3 h exposure to UMTS at 40 mW/kg. Similar results were found in terms of DNA migration (alkaline and neutral comet assay) and PFG induction. Apoptosis and cell viability also resulted unaffected by 2 h exposure to UMTS (37 mW/kg) and GSM (40 mW/kg) signals. However, increased ROS levels were detected after 1 h of UMTS exposure that was not evident 3 h post-exposure. Such an increase resulted dependent from the degree of cellular differentiation. The alteration of repetitive DNA (RE-DNA) transcription can be induced by environmental stress conditions, causing human pathological effects.

Del Re et al. (2019) investigated whether exposure to RF-EMF is able to affect the transcription of RE-DNA. To this purpose, three different human cell lines (HeLa, BE(2)C and SH-SY5Y) were exposed to 900 MHz, GSM-modulated, at SAR of 1 W/kg or sham-exposed. After 48 h of exposure, mRNA levels of RE-DNA were evaluated through quantitative real-time PCR. Three RE-DNA types were investigated: Long Interspersed nucleotide Element 1 (LINE-1), DNA alpha satellite (SATA) and Human Endogenous Retroviruses-like (HERV-H) sequences. The results of five independent experiments, obtained by applying a blind procedure, indicate different responses on the base of the cell type investigated. In particular, the transcription of the three RE-DNA types was decreased in Hela cells ($p<0.05$), increased in SH-SY5Y cells ($p<0.05$) and unaffected in BE(2)C cells, indicating that RF exposure can affect RE-DNA transcription and that the effects strongly depend on the cellular context and the tissue type. Since the increase of the mRNA levels of the RE-DNA examined could cause both genomic instability and alteration of the expression of other genes, while the increase can result in an effect against the onset of genomic instability, further studies have to be carried out to evaluate whether epigenetic effects are involved.

Two studies were carried out at higher frequencies. Koyama et al. (2019) evaluated the induction of genotoxic effects and effects on heat shock protein expression in human corneal epithelial (HCE-T) and human lens epithelial (SRA01/04) cells. Cell cultures were exposed to 40 GHz, 1 mW/cm^2, for 24 h. Genotoxicity was investigated by applying the micronucleus test (MN) and the alkaline comet assay. The results of six independent experiments for each cell type did not show statistically significant increase in the MN frequency and in the level of DNA strand breaks. At variance, treatments with bleomycin as positive control induced a significant increase of DNA damage, as expected.

To evaluate the effect of 40 GHz exposure on the expression of heat shock proteins (Hsp), three widely studied Hsp were investigated: Hsp27, Hsp70 and Hsp90α. Also in this case, no differences were detected between exposed and sham-exposed cultures (three independent experiments). Heat treatment at 43 °C was used as positive control and gave the expected increase in protein expression. Same results were obtained when the research group exposed HCE-T cells for 24 h to 5.8 GHz, 1 mW/cm^2. No differences were detected in terms on MN frequency (3 independent experiment), DNA strand breaks (5 experiments) and Hsp expression (3 experiments). Also in this case bleomycin and heat treatment were used as positive control for DNA damage and Hsp expression, respectively (Miyakoshi et al., 2019).

4.4.3. Other cellular endpoints

Le Pogam et al. (2019) exposed HaCaT human keratinocytes at 60.4 GHz, 20 mW/cm², for 24h and endo- and extracellular extracts were recovered and submitted to a metabolomic and lipidomic workflow. A limited number of altered features in lipidomic sequences and in intracellular metabolomic analyses was detected, while dysregulations were detected in extracellular metabolomic profiles. The authors concluded that it is reasonable to assume that the dysregulations reported in their experiments "do not stem from alterations of gene expression but rather from alterations in membrane permeability"; but at the same time they phrase "that our model, purely *in vitro*, haven't to be lead to a direct extrapolation of our results at the organism level."

von Niederhäusern et al (2019) investigated the effects of RF-EMF on neuronal differentiation, neurodegeneration and mitochondrial function in human neuroblastoma cell line SH-SY5Y undifferentiated and differentiated using retinoic acid or staurosporine to obtain cholinergic and dopaminergic neurons. In particular, intermittent (120 s on/120 s off cycles) exposures were carried out for 24 h at 935 MHz, 4 W/kg SAR, and several markers of signal pathways involved in neuronal differentiation and neurodegeneration, mitochondrial integrity and function during neuronal differentiation were measured. SH-SY5Y cells were exposed or sham-exposed before differentiation (DIV1) or on the last differentiation day (DIV7). The results of at least three independent experiments

carried out in double blind indicated that RF-EMF exposure did not alter the neuronal phenotype after neuronal differentiation. Mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinases (Erk) 1 and 2 (p-Erk1/2) and protein kinase B (Akt), glycogen synthase kinase 3 β (GSK3β) and Wnt/β-catenin were not affected by RF-EMF compared to sham-exposed samples. RF-EMF-impaired mitochondrial respiration only in cells under glucose deprivation (p<0.05) but glutathione levels and mitochondrial fission and fusion markers were not altered. These findings indicate that RF-EMF might lead to an impairment of mitochondrial function that is only manifest at maximal respiration and additional stressors such as glucose deprivation.

The effect of RF exposure on the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor that controls several cellular processes including proliferation and survival, was investigated by Zong et al. (2019). To this purpose, mouse bone marrow stromal cells (BMSC) from male Kunming mice were exposed to 900 MHz, 120 μW/cm^2, 4 h/day for 5 days and the expression levels of NF-κB in the cytoplasm and nucleus of RF-exposed cells were compared to sham controls following 30 min, 2 h and 24 h from the exposure. In three independent experiments, at 30 min and 2 h post exposure, a significant decrease in protein expression of NF-κB in the cytoplasm and a concomitant increase in nuclear NF-κB protein expression was detected (p<0.05), with a return to control concentrations at 24 h post exposure, indicating that the effects of RF was transient. Treatments with BAY 11-7082, a chemical inhibitor of NF-κB, prevented such effects.

4.4.4. Summary and conclusions for cell studies

The new in vitro studies confirm the previous Council conclusions: several endpoints have been investigated and in most cases no effect of the exposure was detected. As for the past years, several studies have been recognized but not considered due to the scanty quality of the experimental set-up.

Table 4.4.1. Cell studies on exposure to radiofrequency fields

Cell type	Endpoint	Exposure conditions	Effect	References
Human peripheral blood lymphocytes n=3 Chinese Hamster fibroblasts n=3	MN frequency	1950 MHz, UMTS, 0,3 or 1,25 W/kg 20 h Co-exposure: MMC	No effect of RF alone. Reduced MMC damage in both cell types pre-exposed to RF (AR). AR negated by treatments with 3AB.	Sannino et al (2019)
Human peripheral blood lymphocytes n=4	MN frequency	1950 MHz, CW, WCDMA, AWGN, 0,15, 0,3 0,6 or 1,25 W/kg 20 h Co-exposure: MMC	No effect of RF alone. Reduced MMC damage as a function of signals and SAR values.	Romeo et al (2019)
Umbilical cord blood (UCB) cells	DNA damage (neutral and alkaline comet assay, foci formation, PFG), ROS formation, apoptosis, viability	900 MHz, GSM, 4 and 40 W/kg 1950 MHz, UMTS, 40 W/kg 1-4 h, 17 h	No effects except for an increase in ROS formation after 1 h of UMTS exposure that disappeared 3 h post-exposure	Durdik et al (2019)
Human neuroblastoma (SH-SY5Y) cells Human neuroblastoma BE(2)C cells Human cervical cancer (HeLa) cells n=5	RE-DNA transcription	900 MHz, GSM, 1 W/kg 48 h	Decrease (HeLa), increase (SH-SY5Y) or no effect (BE(2)C) transcription	Del Re et al (2019)

Human corneal epithelial (HCE-T) cells Human lens epithelial (SRA01/04) cells	DNA damage (comet assay, MN), Hsp27, Hsp70 and Hsp90α expression	40-GHz, 1 mW/cm^2 24 h	No effects	Kojama et al. (2019)
Human corneal epithelial (HCE-T) cells	DNA damage (comet assay, MN), Hsp27, Hsp70 and Hsp90α expression	5.8 -GHz, 1 mW/cm^2 24 h	No effects	Miyakoshi et al. (2019)
Human keratinocytes (HaCaT) cells	metabolomic and lipidomic profiles	60 GHz, 20 mW/cm^2 24 h	Slight variation in lipidomic and intracellular metabolomics profiles. Disregulation in extracellular metabolomic profiles.	Le Pogam et al. (2019)
Human neuroblastoma (SH-SY5Y) cells n=3	Neuronal differentiation, neurodegeneration and mitochondrial function	935 MHz, 4 W/kg 24 h (120s on/120s off cycles)	No effect on neuronal phenotype. Impairment of mitochondrial function only in presence of a stressor (glucose deprivation).	von Niederhäusern et al (2019
Mouse bone marrow stromal cells (BMSC) n=3	Protein expression	900 MHz, 120 µW/cm^2 4 hr/day for 5 days	Transient cytoplasmic decrease and nuclear increase in NF-κB expression.	Zong et al. (2019)

Abbreviations: 3AB: 3-aminobenzamide; AR: adaptive response; AWGN: Additive White Gaussian Noise; CW: Continuous Wave; GSM: Global System for Mobile Communication; Hsp: heath shock protein; MMC: mitomycin-C; MN: micronuclei; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PFG: preleukemic fusion genes; RE-DAN: repetitive DNA; ROS: reactive oxygen species; UMTS: universal mobile telecommunications system; WCDMA: Wideband Direct-Sequence Code Division Multiple Access;

5. Recent expert reports

This chapter briefly summarizes an expert report published since the previous Council report. The summary is direcly edited from this report. The Council does not evaluate or comment the report.

5.1. Mobile Radio and Radiation

Published by the working group on Mobile Radio and Radiation of the Federal Department of the Environment, Transport, Energy and Communications (DETEC), Switzerland (18 November 2019). English summary of the Swiss report:

This report describes technical facts about 5G, addresses the operation of the Swiss mobile radio networks and their regulation, estimates the exposure of the population to non-ionising radiation (NIR) and summarises the scientific findings on possible health consequences.
In Switzerland, typical exposure to NIR from environmental sources like mobile phone base stations or WiFi hotspots is around 0.2 V/m, which remained fairly constant between 2008 and 2015. The absorbed radiation dose due to one's own mobile phone may be several orders of magnitude higher than that from base stations, in particular in the case of poor connections to the base station. This means that by far the greatest part of NIR to which the average user is exposed originates from terminals which are close to the body (approximately 90%).

The working group determined that to date, for the mobile radio frequencies currently in use, no health effects below the ICNIRP guidelines have been consistently scientifically proven. Further, the evidence for various health effects was rated on four-tiered scale based on the European Health Risk Assessment Network on EMF (sufficient, limited and inadequate evidence as well as evidence suggesting a lack of effects). The evidence for a carcinogenic effect from mobile phone use was assessed as limited. In terms of RF-EMF exposure from fixed site transmitters, the evidence for carcinogenic effects was judged to be inadequate. The evidence for co-carcinogenesis was considered to be limited. There was sufficient evidence for effects on human brain physiology for local exposure of the brain. Based on a series of new studies from the Netherlands and Switzerland insufficient evidence was found for a link between symptoms and residential long term RF-EMF exposure up to 1 V/m. No robust data was available for higher long term exposure levels. In medical practice, there are cases in which patients plausibly attribute their complaints to high NIR exposures in their everyday life. However, proof of a causal effect cannot be provided in individual cases. Human experimental research on acute symptoms is suggesting a lack of effects. In-vitro and in-vivo vivo research often finds biological effects, but the results are not consistent and these studies were not assessed in depth by the working group. About 100 in-vitro and in-vivo studies on millimetre waves (30 to 65 GHz) were not considered sufficiently robust for an evaluation of the evidence.

Finally, the report outlined for various regulation scenarios the costs involved and the number of additional mobile phone base stations. In addition, several recommendations were made for accompanying measures during the introduction of 5G in Switzerland.

Reference:
English summary of the Swiss report:
https://www.newsd.admin.ch/newsd/message/attachments/59387.pdf

And here the German website about it (with reference to the full German report).
https://www.bafu.admin.ch/bafu/de/home/themen/elektrosmog/mitteilungen.msg-id-77294.html

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Appendix: Studies excluded from analysis

Articles were identified in relevant scientific literature data bases such as PubMed as well as in the specialized database EMF Portal. 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[17] 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.

Reference	Reason for exclusion
Al-Quzwini et al. (2016)	H
Asl et al. (2019)	K
Bamdad et al. (2019)	I
Cabré-Riera et al. (2019)	H
Calderon et al. (2019)	B
Choi et al. (2019)	B
Christopoulou and Karabetsos (2019)	B
Dieudonné (2019)	C
Esmailzadeh et al. (2019)	G
Gallastegi et al. (2019)	B

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[17] 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.

Hansson Mild et al. (2019)	K
Hirsh-Yechezkel et al. (2019)	B
Hosseini et al. (2019)	F
Iyare et al. (2019)	B
Jadia et al. (2019)	I
Jalilian et al. (2019)	B
Jamir et al. (2019)	A
Koppel et al. (2019)	B
Lahham and Ayyad (2019)	B
Lin et al. (2019)	K
Liu et al. (2019)	A
Madrigal and Escoffery (2019)	A
Magiera and Solecka (2019)	K
Martínez (2019)	K
Massardier-Pilonchery et al. (2019)	B
Mazloum et al. (2019a)	B
Mazloum et al. (2019b)	B
Miller et al. (2019)	K
Mireku et al. (2019a)	A
Mireku et al. (2019b)	A
Mortazavi et al. (2019b)	B
Mortazavi et al	B
Ohayon et al. (2019)	K
Pishchalnikov et al. (2019)	F
Pritchard et al. (2019)	K
Ramirez-Vazquez et al. (2019)	B
Röösli et al. (2019)	K
Shoukat (2019)	C
Singh et al. (2018)	K
Su et al. (2019)	G
Wada et al. (2019)	C
Wdowiak et al. (2019)	H
Weldu et al. (2019)	A
Yang et al. (2019)	A
Zarei et al. (2019)	I

Human studies

Radiofrequency (RF) fields

Reference	Reason for exclusion
Parmar et al. (2019)	Insufficient information on study design (e.g. on blinding)
Hosseini et al. (2019)	Incorrect assumptions concerning exposure and wrong/contradicting numbers for power flux density

Animal studies

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

Reference	Reason for exclusion
ANSES opinion (2019)	National (French) scientific expert assessment on ELF (50 Hz, ≤1 mT) - based on a literature search from 2000-2015.
Bainbridge et al. (2020)	GMF, magnetic orientation in C. elegans.
Barbic (2019)	Theoretical paper on possible magneto-mechanical & -thermal mechanisms of ion channel activation in magnetogenetics. Not experimental.
Bouché and McConway (2019)	Analysis revisiting the impact of ELF-MF on melatonin levels in humans and rats – using a Bayesian logistic regression. Not experimental.
Chan et al. (2019)	Treatment related. PEMF reduce acute inflammation in injured rats.
Cresci et al. (2109)	Methodological video article how to study magnetic sensitivity and rheotactic behavior of aquatic species, exemplified on zebrafish.
Demirkazik et al. (2019)	Imprecise and confusing description of experimental setup. Rehandled ELF-MF-induced analgesia in rats [see SSM 2019 & Ozdemir et al., 2017 & 2019]. Related to treatment of analgesia.
Ding et al. (2019)	Treatment-related (psychological intervention & healthcare of astronauts). Topic: Hypomagnetic fields and anxiety in mice.
Dufor et al. (2019)	Treatment-related. Neural circuit repair after specific low-intensity magnetic stimulation (patterns).
Gholami et al. (2019)	No sham control, daytime for hormone sampling and behavioral testing is missing.
Kerpal et al. (2019)	Theoretical paper: Radical pair mechanism & avian magnetoreception. Not experimental.
Khan et al. (2020)	Registry of Finnish buildings with transformer station as basis for epi studies.
Kosta et al. (2019)	Treatment-related. Magnetic neural stimulation of rat sciatic nerve.
Kubo et al. (2019)	Treatment-related. Twitch contraction induced by magnetic stimulation and effects on skeletal muscle fibrosis in rats.
Kwan et al. (2019)	Review. Treatment-related: Healing of diabetic skin wounds in cell and animal studies.
Li et al. (2020)	Treatment-related: PEMF & spinal cord injury in rats.
Mahaki et al. (2019)	Review. ELF-MF effects on cytokines and immunity.
Mattsson and Simkó (2019)	Review. Treatment-related. 0 Hz – 10 THz.
Naarala et al. (2019)	Review discusses system biology of EMF (ELF to RF).
Nishimura et al. (2019)	Imprecise exposure description. More than 10 year-old experiments: Impact of lunar phase, magnetoreception, 6-8 Hz 2.6 µT ELF-MF and other environmental factors on tail-lifting behaviour of lizards.
Ozdemir et al. (2017)	Imprecise and confusing description of experimental setup. Rehandled ELF-MF-induced analgesia in rats [see SSM 2019 & Ozdemir et al., 2017]. Related to treatment of analgesia.
Paasonen et al. (2020)	Diagnosis-/Treatment-related. MB-SWIFT images at 9.4 T & preclinical brain mapping in rats.
Pereira et al. (2020)	Report on (number and causes of) electrocutions in free-living marmosets in Brazil, 2015-2018.
Player and Hore (2019)	Theoretical paper: Radical pair mechanism & avian (compass) magnetoreception. Spin dynamics simulations. Not experimental.
Recordati et al. (2019)	No well-defined experimental exposure. Effects of wireless technology-use in housing systems on mice.
Saeedi Goraghani et al. (2019)	No sham control. Treatment-related: NMDA receptor antagonist MK-801 (Dizocilpine).

Shang et al. (2019)	Treatment-related. Poor description/justification of exposure and group sizes for the different parameters tested.
Soffritti and Giuliani (2019)	Minireview on carcinogenic potential of 50Hz MF and 1.8 GHz exposures.
Tian et al. (2019)	Magnetoreception. Magnetic compass & direction of foraging in a bat.
Torres et al. (2019)	Treatment related. *Myrciaria dubia* ("camu camu" with high vitamin C content (2–3% of fresh fruits)) protects oxidative damaging effects of (60 Hz, 610 µT) ELF-MF in mouse spermatogenesis.
Ye and Kaszuba (2019)	Review of neuropathological clinical cases. Epilepsy. Time-varying MF.
Yu et al. (2019)	Diagnostics-related. Passive eye movements induced by EM force (via implanted small magnetic discs on the eyeball) in rats.
Zheng, Cheng et al. (2019)	Treatment related. *Ex vivo* / *in vitro* ELF-MF exposure of (rat) hippocampal slices and subsequent recording of field excitatory postsynaptic potentials (fEPSP).
Zheng, Tian et al. (2019)	Treatment related. *Ex vivo* / *in vitro* ELF-MF exposure of (rat) hippocampal slices and subsequent recording of fEPSPs.
Zhou et al. (2019)	Treatment-related. ELF-MF increases peak bone mass in rats.

Intermediate frequency fields (IF)

Reference	Reason for exclusion
Bodewein et al. (2019)	Review in biological effects of fields in the IF range (300 Hz to1 MHz)
Driessen et al. (2019)	Review: EM-interference between IF and cardiac electronic devices
Kobylkov et al. (2019)	Orientation of Eurasian blackcaps. No effect of 0.1 – 100 kHz.
Tirpak et al. (2019)	Imprecise description of 93 kHz (hand-held metal detector) exposure of bovine cryoconserved semen. Field strength missing.

Radiofrequency (RF) fields

Reference	Reason for exclusion
Tumkaya et al. (2019)	No sham, unclear exposure and exposure assessment
Odemer and Odemer (2019)	Insects
Amandokht Saghezchi et al. (2019)	No dosimetry
Kinney et al. (2020)	No dosimetry
El-Maleky and Ebrahim (2019)	No dosimetry
Gautam et al. (2019)	No sham, incomplete description exposure
Yahyazadeh and Altunkaynak (2019)	No sham
Yahyazadeh et al. (2020)	Incomplete dosimetry
Seymen et al. (2019)	No sham, incorrect dosimetry
Sistani et al. (2019)	No dosimetry, no sham

Cell studies

Static fields (SF)

Reference	Reason for exclusion
Baek et al. (2019)	No sham-control
Ho et al. (2019)	No sham-control
Jalali et al. (2019)	No sham-control

Extremely low frequency (ELF) fields

Reference	Reason for exclusion
Ahmadi-Zeidabadi et al. (2019)	No sham-control
Arnold et al. (2019)	No sham-control
Bergandi et al. (2019)	No sham-control
Huang et al. (2019)	No sham-control
Jang et al. (2019)	No sham-control
Jing et al. (2019)	No sham-control
Lai (2019)	Review paper on SMF/ELF & oxidative stress
Liang et al. (2019)	No sham-control
Oladnabi et al. (2019)	No sham-control
Pi et al. (2019)	No sham-control
Tang et al. (2019a)	No sham-control
Tang et al. (2019b)	No sham-control, insufficient description of the exposure system.
Yan et al. (2019)	No sham-control

Radiofrequency fields (RF)

Reference	Reason for exclusion
Stefi et al. (2019)	No dosimetry. Cell phone used to expose cell cultures
Mortazavi et al. (2019a)	No dosimetry. Cell phone used to expose cell cultures
Tomruk et al. (2019)	Incomplete dosimetry; not clear if sham-control has been carried out
Alessio et al. (2019)	No dosimetry. Exposure performed with a commercial device
Asano et al. (2020)	No sham-control
Průcha et al. (2019)	No dosimetry. Exposure performed with a commercial device
Koohestani et al. (2019)	No dosimetry. Cell phone used to expose cell cultures
Mumtaz et al. (2020)	No sham-control
Tsoy et al. (2019)	No sham-control

Jooyan et al. (2019)	No sham-control
Panagopoulos (2019)	No dosimetry
Qin et al. (2019)	Numerical dosimetry performed, but no technical details provided to judge about accuracy and goodness of the assessment
Vijayalaxmi and Prihoda (2019b)	Review paper
Vijayalaxmi and Prihoda (2019a)	Review paper
Simkó and Mattsson (2019)	Review paper
Sisakht et al. (2020)	Review paper

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

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

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