



Strål
säkerhets
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Swedish Radiation Safety Authority

Research

2013:19

Eighth report from SSM:s Scientific
Council on Electromagnetic Fields

SSM perspective

Background

The Swedish Radiation Safety Authority's (SSM) scientific council monitors the current research situation and gives the authority advice on the assessment of risks, authorization and optimization within the area. The council gives guidance when the authority shall give an opinion on policy matters when scientific testing is necessary. The council shall submit a written report on the current research and knowledge situation each year.

Objectives

The objectives of the report are to cover the last year's research in the area of electromagnetic fields (EMF). The report gives the authority an overview and provides an important base for risk assessment.

Results

In this report covering both 2011 and 2012 an update on key issues is included such as extremely low frequency (ELF) magnetic fields and childhood leukemia, effects from mobile phones, health risk from transmitters and self-reported electromagnetic hypersensitivity. It also covers different areas of EMF (static, low frequency intermediate and radio frequent fields) and different types of studies such as biological, human and epidemiological studies. The report also has a section covering other recent reports.

Project information

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Council on Electromagnetic Fields

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

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Preface

In Sweden, the responsible authority has had an international scientific council for electromagnetic fields (EMF) and health since 2002. Up to 2008 the responsible organization was SSI (the Swedish Radiation Protection Authority). In 2008 the Swedish government reorganized the radiation protection work and the task of the scientific council since 2008 lies under the Swedish Radiation Safety Authority (SSM). The task is to follow and evaluate the scientific development and to give advice to the SSM. With major scientific reviews as starting points the council in a series of annual reports consecutively discusses and assesses relevant new data and put these in the context of already available information. The result will be a gradually developing health risk assessment of exposure to EMF. The council presented its first report in December 2003. The present report is number eight in the series and covers the years 2011 and 2012.

The composition of the council during the preparation of this report has been:

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

Dr. Anke Huss, University of Utrecht, the Netherlands

Prof. Heikki Hämäläinen, University of Turku, Finland

Dr. Lars Klæboe, Norwegian Radiation Protection Authority, Oslo, Norway

Dr. Leif Moberg, Sweden (chair)

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

Prof. Martin Rössli, Swiss Tropical and Public Health Institute, Basel, Switzerland

Dr. Bernard Veyret, University of Bordeaux, Pessac, France (until 30 June 2012)

Mr. Lars Mjönes, M.Sc., Sweden (scientific secretary)

Declarations of conflicts of interest are available at SSM.

Stockholm in March 2013

Leif Moberg

Chair

Update on key issues

ELF magnetic fields - childhood leukaemia and other health endpoints

Extremely low frequency (ELF) magnetic fields, of the type that emanates from distribution and use of electricity, have been associated with an increased risk of acute lymphoblastic leukaemia (ALL) in epidemiologic research. It was classified in 2002 as a possible carcinogen to humans by WHO's International Agency for Research on Cancer (IARC). However, experimental and mechanistic research has been unable to confirm this association. Therefore, the question whether ELF magnetic fields have any influence on the development of childhood leukaemia is still unresolved.

A large number of other health endpoints have been studied in relation to ELF magnetic fields but mostly without consistent associations being found. One of those endpoints is Alzheimer's disease for which recent studies have generated a renewed interest because associations have been reported both in environmental and occupational epidemiological studies. However, a causal relationship has not been established. No new studies on residential exposure to ELF magnetic fields and Alzheimer's disease have appeared since the last Council report so the uncertainty remains unchanged.

Effects from use of mobile phones

Subsequent to the last Council report published in 2010, IARC in 2011 classified radiofrequency electromagnetic (RF) fields as possibly carcinogenic to humans (Group 2B) based on an increased risk for glioma and acoustic neuroma (vestibular schwannoma) associated with wireless phone use. Since then, numerous epidemiological studies on mobile phone use and risk of brain tumours and other tumours of the head (vestibular schwannomas, salivary gland) have been published. The collective of these studies, together with national cancer incidence statistics from different countries, is not convincing in linking mobile phone use to the occurrence of glioma or other tumours of the head region among adults. Although recent studies have covered longer exposure periods, scientific uncertainty remains for regular mobile phone use for longer than 13-15 years. It is also too early to draw firm conclusions regarding children and adolescents and risk for brain tumours, but the available literature to date does not indicate an increased risk.

The most consistently observed biological effect from mobile phone exposure is an increase of the power in the alpha band in the electroencephalogram in human volunteer studies. The observed effect is weak and does not translate into behavioural or other health effects. Recent studies suggest that considerable interindividual variation exists in the possible reactivity of the human brain to RF electromagnetic fields. The underlying mechanism is not yet understood.

Health risks from transmitters

Recent research on exposure from transmitters has mainly focused on cancer and symptoms, using improved study designs. These new data do not indicate health risks for the general public related to exposure to radiofrequency electromagnetic fields from base stations for mobile telephony, radio and TV transmitters, or wireless local data networks at home or in schools.

Self-reported electromagnetic hypersensitivity

While the symptoms experienced by patients with perceived electromagnetic hypersensitivity are real and some individuals suffer severely, studies so far have not provided evidence that exposure to electromagnetic fields is a causal factor. In a number of experimental provocation studies (mostly with radiofrequency fields), persons who consider themselves electromagnetically hypersensitive as well as healthy volunteers have been exposed to either sham or real fields, but symptoms have not been more prevalent during real exposure than during sham exposure in the experimental groups. Several studies have indicated a nocebo effect, i.e. an adverse effect caused by an expectation that something is harmful.

Executive Summary

Static fields

Exposure to static (0 Hz) magnetic fields much greater than the natural geomagnetic field can occur when someone is working close to some types of industrial and scientific equipment that uses direct current, such as some welding equipment and various particle accelerators. However, the main source of exposure to strong static magnetic fields (> 1 T) is the use of magnetic resonance imaging (MRI) for medical diagnostic purposes. Movement in such strong static fields can induce electrical fields in the body and sensations such as vertigo and nausea in some people. The thresholds for these sensations seem to vary considerably within the population. Volunteer studies have confirmed these effects.

The focus of the recent research on static fields has thus primarily been on the effects of movement in strong fields, an issue closely related to the delay in the implementation of the EU Physical Agents Directive (Directive 2004/40/EC) on minimum health and safety requirements for occupational exposure to EMF. In the meantime this Directive has been reformulated and is by the end of 2012 in the final stage of reaching agreement.

Cell studies

In vitro data obtained with static magnetic fields using a large set of exposure conditions and biological endpoints are difficult to interpret, and in particular do not address the issue of MRI high-strength fields.

Animal studies

The issue of oxidative stress has been studied in relation to exposure to static magnetic fields as well as to extremely low frequency (ELF) and radiofrequency (RF) fields. In theory, it may lead to increased damage to biomolecules, and thus may increase the risk of health effects. But more studies across the electromagnetic spectrum are needed to ascertain this.

Human studies

Strong static magnetic fields may affect the postural control and evoke subjective sensations in humans.

Extremely low frequency (ELF) fields

The exposure of the general public to ELF fields is primarily from 50 and 60 Hz electric power lines and from electric devices and installations in buildings. Regarding the exposure of ELF magnetic fields and the development of childhood leukaemia, the conclusion from previous Council reports still holds: a consistent association has been observed, but a causal relationship has not been established.

Cell studies

Most of the latest in vitro studies have not focussed on mechanisms to explain the observed association of ELF exposure with childhood leukaemia. The main conclusions on ELF in vitro studies are still those of the previous reports: There is a huge variety of exposure conditions and biological endpoints. Most data that are showing an effect of exposure were obtained at or above 1 mT. These levels are more than 1000 times higher than the levels found in the general environment and considerably above the current exposure limits.

Animal studies

A number of studies have indicated adverse effects of generally long-term exposure to ELF magnetic fields in the millitesla range on reproduction and development in various animal species. Other studies indicated increased oxidative stress, again mostly by exposures well over the current exposure limits. In general, however, the latest animal studies do not contribute to understanding a mechanism that could explain the association found in epidemiological studies between long-term exposure to ELF magnetic fields below 1 μ T and an increased risk of childhood leukaemia. Hence, there is still a need for dedicated studies in this area.

Unfortunately, there are still animal studies with a bad design, in particular in terms of exposure system and dosimetry. These studies cannot be used for drawing conclusions on a relation between exposure and response.

Human studies

The ELF magnetic fields do not seem to have effects on the general physiology (cardiovascular responses, postural control), but effects have been reported related to reactivity in the brain cortex, EEG, and short-term memory. The relation of these individual findings to each other remains to be further studied.

Epidemiology

Given some previous reports of an association between the exposure to magnetic fields and some neurological diseases, the observation of increased risks of neurological conditions in a study on survivors of electrical shocks (who were likely also exposed to elevated magnetic fields) is of interest because it may indicate that electric shocks, and not magnetic field exposure, are involved in the development of neurological diseases. However, due to the small number of cases, the study is not informative regarding those health outcomes that are of most interest, notably amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease and vascular dementia. Because no new studies on residential exposure to ELF magnetic fields and Alzheimer's disease have appeared since the last report, the corresponding uncertainty remains unchanged.

Only little new information regarding parental exposure and risk of childhood cancer has become available, which does not materially change the conclusion from the previous report: "There appears to be little support for the hypothesis relating parental exposure to cancer in the offspring." New evidence regarding adult brain tumours and leukaemia and exposure to high voltage power lines were compatible with an earlier meta-analysis that showed very small increased risks in those exposed.

Intermediate frequency (IF) fields

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

Radiofrequency (RF) fields

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

Cell studies

In line with the conclusion of the 2010 Council report the main conclusions on RF in vitro studies are the following: There is a large variety of exposure conditions and biological endpoints and many items of the WHO research agenda have been addressed. There are only a few positive studies in the RF range and there is still little evidence of non-thermal effects. Recent data from laboratory studies related to cancer do not seem to support the conclusion of IARC that RF EMF is a possible carcinogen.

Animal studies

Animal studies show that effects of RF EMF on brain function are possible and that in a number of tissues, including the brain, an increased oxidative stress may be induced by RF EMF exposure at levels around the current exposure limits. This may enhance the risk of health effects. The mixed effects in the carcinogenicity studies provide some, but unreplicated and not very reliable indications of increased DNA damage after RF EMF exposure. No increased cancer risks were observed, however.

The results of those fertility studies that have sufficient quality did not provide evidence for a detrimental effect of RF EMF exposure.

Human studies

Several human experimental studies have addressed effects from mobile phone exposure on EEG and cognitive functions using a randomized double blind experimental setting. The new studies support the lack of an association between acute mobile phone exposure and cognitive performance. However, an association with EEG has been repeatedly observed. The most consistent effect seems to be an enhanced alpha band activity during sleep if exposed to a mobile phone prior to sleep. The new studies also indicate that a substantial interindividual variation exists and this may explain some of the inconsistency observed between studies.

Epidemiology

The overall data on brain tumour and mobile telephony do not indicate an effect of mobile phone use on tumour risk, especially not when taken together with national cancer incidence statistics from different countries. There is still only limited data regarding risks of long term use of mobile phones, but compared to the previous report, the evaluated exposure duration has increased to approximately 13-15 years of use. Thus, current scientific uncertainty remains for regular mobile phone use for more than 13-15 years. It is also too early to draw firm conclusions about risk for brain tumours for children and adolescents, but the available literature to date does not indicate an increased risk.

The number of published studies regarding leukaemia and malignant melanomas is very limited, but the published studies so far do not suggest that mobile phone use increases the risk of these diseases.

Apart from cancer, new epidemiological studies have also addressed child development, reproductive health, multiple sclerosis, cognitive decline in elderly, auditory functions, bone mineralisation and hypertension. Some protective as well as some adverse effects have been observed, but methodological limitations prevent from firm conclusions in terms of causal associations. In addition, the number of studies per outcome is relatively small, and consistency of findings between various studies cannot be addressed.

Most intriguing are studies on child development and mobile phone use. However, to differentiate between effects from relevant exposure and effects from mobile phone use per se (e.g. social interaction, cognitive training) is a challenge and needs particularly well-designed studies. Studies might even suffer from reverse causality if behavioural problems result in an increased mobile phone use and not the other way round. Given the strong increase of mobile phone usage worldwide and therefore the potential of a large public health impact, effects of mobile phone use on child development should be followed up. Preferably, this should be addressed in prospective studies with the capability to disentangle effects from RF fields from other effects of mobile phone use.

Self-reported electromagnetic hypersensitivity and symptoms

Since the last Council report, research on electromagnetic hypersensitivity (EHS) and quality of life in the general population has progressed considerably. The EHS phenomenon has mainly been investigated in human laboratory studies applying extremely low frequency (ELF) electric or magnetic fields or mobile phone-like exposure. Two studies on ELF exposure reported effects, but methods were not adequately reported. Strikingly, in one study, a person had an almost perfect field perception. This deserves some attention and the exposure circumstances should be better described. Overall, however, new experimental EHS studies on mobile phone use did not indicate short-term effects.

Until the last Council report, only cross-sectional epidemiological research on symptoms and RF EMF was available. In the meanwhile, a few longitudinal studies have been published, which allow more reliable conclusions. A cohort study of mobile phone use in young adults with a follow-up time of one year reported a few associations between mobile phone use and health-related quality of life such as sleep disturbances and symptoms of depression. Since the study did not attempt to differentiate between exposure effects and non-exposure effects, the cause for this association cannot be resolved at this stage. Moreover, the possibility that quality of life status and use of mobile phone may be affected by some common latent variables cannot be excluded. Regarding exposure from fixed site transmitters, another cohort study did not consistently find effects after one year of exposure. Exposure gradients were relatively small in the study.

In conclusion, the new epidemiological studies on symptoms using an improved design rather indicate the absence of a risk from RF EMF exposure on health-related quality of life. Uncertainty concerns mainly high exposure levels from wireless phone use and longer follow-up times than one year.

Sammanfattning på svenska

Statiska fält

Exponering för nivåer av statiska fält (0 Hz) som är mycket högre än det naturliga geomagnetiska fältet kan inträffa när någon arbetar i närheten av industriell eller vetenskaplig utrustning som använder likström, som t.ex. elsvetsutrustning eller olika typer av partikelacceleratorer. Den viktigaste källan till exponering för starka statiska magnetfält (> 1 T) är dock användningen av magnetresonanstomografi (MR) för medicinsk diagnostik. Att röra sig i så starka statiska fält kan inducera elektriska fält i kroppen och orsaka yrsel och illamående hos en del människor. Tröskelvärdena för dessa effekter tycks dock variera avsevärt mellan olika individer. Studier på frivilliga försökspersoner har bekräftat dessa effekter.

Senare forskning om statiska fält har därför huvudsakligen inriktats på effekter av att röra sig i starka fält och varit starkt kopplat till det försenade införandet av EU:s direktiv 2004/40/EC som handlar om hälso- och osäkerhetskrav för EMF-exponering i arbetslivet. Under tiden har direktivet formulerats om och man närmar sig i slutet av 2012 en slutlig överenskommelse.

Cellstudier

I in-vitrostudier med statiska magnetfält har en stor mängd olika exponeringssituationer och biologiska utfall studerats. Denna stora spridning gör att data från studierna är svåra att utvärdera. Studierna har inte heller specifikt berört problemet med starka fält från magnetkameror.

Djurstudier

Oxidativ stress har studerats i relation till exponering för statiska fält, liksom för lågfrekventa (ELF) och radiofrekventa (RF) fält. Teoretiskt skulle oxidativ stress kunna leda till ökade skador på biomolekyler och således även kunna öka risken för skadliga hälsoeffekter. Fler studier fördelade över hela det elektromagnetiska spektret behövs för att klargöra detta.

Studier på människa

Starka statiska magnetfält kan påverka kroppskontroll (t.ex. balans) och orsaka obehagskänslor hos människor.

Lågfrekventa (ELF) fält

Allmänheten exponeras för lågfrekventa (ELF) fält i första hand från kraftledningar med frekvenserna 50 och 60 Hz och från elektriska installationer och apparater i byggnader. När det gäller sambandet mellan exponering för lågfrekventa magnetfält och utvecklingen av barnleukemi så är slutsatsen densamma som i tidigare rapporter från rådet: ett robust samband har observerats men något orsakssamband har inte kunnat fastställas.

Cellstudier

De flesta nya in vitro-studier har inte syftat till att försöka förklara det observerade sambandet mellan exponering för lågfrekventa (ELF) magnetfält och barnleukemi. De huvudsakliga slutsatserna från in vitro-studier med ELF är fortfarande de som angavs i de tidigare rapporterna från rådet: Det handlar om en mycket stor variation i exponeringssituationer och biologiska utfall. De flesta data som visar effekter av exponering har erhållits efter

exponeringar vid eller över 1 mT. Dessa nivåer är mer än 1 000 gånger högre än de nivåer som allmänheten normalt exponeras för och ligger långt över gällande rikt- och gränsvärden.

Djurstudier

Ett antal studier antyder skadliga effekter på reproduktion och utveckling för olika djurarter. Försöken gäller vanligen långtidsexponering för lågfrekventa magnetfält i milliteslaområdet. Andra studier har antytt ökad oxidativ stress, återigen oftast vid exponeringsnivåer långt över nu gällande rikt- och gränsvärden. Nyligen publicerade djurstudier har dock inte bidragit till att öka kunskapen om en mekanism som skulle kunna förklara det samband man funnit i epidemiologiska undersökningar mellan exponering för lågfrekventa (ELF) magnetfält under 1 μ T och en ökad risk för barnleukemi. Det finns alltså fortfarande behov av riktade studier inom detta område.

Tyvärr förekommer det fortfarande djurstudier med dåliga försöksupplägg, framför allt när det gäller exponeringssystem och dosimetri. Dessa studier kan inte användas för att dra slutsatser om samband mellan exponering och biologiska effekter

Studier på människa

Lågfrekventa (ELF) magnetfält verkar inte ha någon påverkan på den allmänna fysiologin (påverkan på hjärt-kärl-systemet och kroppens orientering och stabilitet), men effekter har rapporterats på hjärnbarken, EEG och korttidsminne. Sambanden mellan dessa olika observationer bör studeras ytterligare.

Epidemiologi

Utifrån några tidigare rapporter om samband mellan exponering för lågfrekventa (ELF) magnetfält och några neurologiska sjukdomar är observationen av en ökad risk för neurologiska komplikationer hos människor som överlevt kraftiga elektriska stötar av intresse (eftersom dessa personer förmodligen också varit exponerade för förhöjda elektromagnetiska fält). Detta skulle kunna tyda på att elektriska stötar och inte exponering för magnetfält har betydelse för utvecklingen av neurologiska sjukdomar. Eftersom antalet fall är litet ger studien dock inte tillräcklig information om de sjukdomar som är av störst intresse, framför allt amyotrofisk lateralskleros (ALS), multipel skleros (MS), Alzheimers sjukdom, Parkinsons sjukdom och blodkärlsdemens. Eftersom inga nya studier av exponering i bostaden för lågfrekventa magnetfält och Alzheimers sjukdom har publicerats sedan den senaste rapporten kvarstår den rådande osäkerheten om eventuella samband.

Endast begränsad ny information har blivit tillgänglig gällande föräldrars exponering och risk för cancer hos barn. Det gör att slutsatsen från rådets tidigare rapport kvarstår: ”Stödet tycks litet för hypotesen om ett samband mellan föräldrars exponering och cancer hos barn.” Nya resultat rörande samband mellan exponering från högspänningsledningarna och leukemi och hjärntumörer hos vuxna överensstämmer med en tidigare metaanalys som visade en mycket liten ökad risk hos de exponerade.

Intermediära (IF) fält

Det intermediära frekvensområdet av EMF-spektrat ligger definitionsmässigt mellan ELF- och RF-områdena och exponering kan uppkomma t.ex. vid användning av induktionsspisar, vid larmbågar i butiker och i vissa industrier. Endast ett fåtal experimentella studier rörande hälsoeffekter från exponering för IF-fält finns tillgängliga. Ytterligare studier skulle vara värdefulla eftersom människor exponeras för sådana fält i ökande grad, till exempel från

elektroniska övervakningssystem. Studier om möjliga effekter av kronisk exponering för låga exponeringsnivåer är särskilt betydelsefulla för att bekräfta storleken på gällande rikt- och gränsvärden.

Radiofrekventa (RF) fält

Allmänheten exponeras för radiofrekventa fält från en mängd olika källor: från radio- och TV-sändare, trådlösa telefoner och mobiltelefoner och deras respektive basstationer samt mängder av andra källor som t.ex. trådlösa datornätverk. Delar av allmänheten är orolig för möjliga hälsoeffekter från exponering för radiofrekventa fält. Framför allt har oron för användningen av trådlösa datornätverk i skolor ökat under senare år i en del länder.

Cellstudier

I överensstämmelse med slutsatsen i rådets senaste rapport är de huvudsakliga slutsatserna för in vitro-studier med radiofrekventa fält följande: Det är en stor variation i exponeringssituationer och biologiska utfall och många delar av WHO:s forskningsagenda har studerats. Det är bara några få studier i RF-området som visar på effekter och det finns fortfarande få tecken på icke-termiska effekter. Nya data från laboratoriestudier rörande cancer tycks inte stödja slutsatsen från IARC att radiofrekventa fält skulle vara ”möjlig cancerframkallande för människor”.

Djurstudier

Djurstudier visar att effekter av radiofrekventa fält på hjärnans funktion är möjliga och att en ökad oxidativ stress i ett antal vävnader, inklusive vävnader i hjärnan, skulle kunna orsakas av exponering för radiofrekventa fält vid nivåer runt gällande rikt- och gränsvärden. Detta skulle kunna öka risken för skadliga hälsoeffekter. De varierande resultaten i cancerstudierna ger vissa antydningar om ökade DNA-skador efter exponering för radiofrekventa fält. Antydningarna är dock inte särskilt pålitliga och har inte bekräftats i upprepade studier. Ingen ökad cancerrisk har emellertid observerats. Resultaten av de fertilitetsstudier som har tillräcklig kvalitet tyder inte på några skadliga effekter av exponering för radiofrekventa fält.

Studier på människa

Flera experimentella studier på människa har inriktats på effekter från exponering för mobiltelefoner på EEG och kognitiva funktioner med användning av ett dubbelblindt, slumpmässigt experimentupplägg. De nya studierna stödjer frånvaron av ett samband mellan akut mobiltelefonexponering och kognitiv prestationsförmåga. Ett samband med EEG har dock observerats vid upprepade tillfällen. Den mest robusta effekten tycks vara en ökad aktivitet i alfabandet under sömn om försökspersonen exponerats för en mobiltelefon före insomnandet. De nya studierna tyder också på en avsevärd skillnad i känslighet mellan olika individer och detta skulle kunna förklara varför resultaten från olika studier inte överensstämmer.

Epidemiologi

De sammantagna resultaten för hjärntumörer och mobiltelefoni tyder inte på någon påverkan på risken för hjärntumör från användning av mobiltelefon, speciellt inte när man beaktar resultaten av cancerincidensstudier från olika länder. Det finns fortfarande ett begränsat dataunderlag när det gäller risker från långtidsanvändning av mobiltelefon, men jämfört med rådets tidigare rapport så har den exponeringstid som utvärderats ökat till ungefär 13-15 års användning. Den rådande vetenskapliga osäkerheten kvarstår därför för regelbunden

användning av mobiltelefon i mer än 13-15 år. Det är också för tidigt att dra säkra slutsatser om risken för hjärntumör hos barn och ungdomar, men den tillgängliga litteraturen idag tyder inte på någon ökad risk.

Antalet studier som publicerats om leukemi och malignt melanom är mycket begränsat, men de studier som publicerats hittills tyder inte på att användning av mobiltelefon skulle öka risken för dessa sjukdomar.

Förutom cancer har nya epidemiologiska undersökningar också studerat barns utveckling, reproduktionsförmåga, multipel skleros (MS), försämrad kognitiv förmåga hos äldre, hörsselfunktioner, benmineralisering och förhöjt blodtryck. Några skyddande, liksom även en del skadliga effekter har rapporterats, men metodologiska begränsningar förhindrar säkra slutsatser vad gäller orsakssamband. Dessutom är antalet studier per undersökt utfall relativt litet och därför är det svårt att studera överensstämmelsen mellan olika studier.

Mest förbryllande är studierna av mobiltelefonanvändning och barns utveckling. Men att skilja mellan effekter från exponering från en mobiltelefon och användning av mobiltelefon som sådan (t.ex. social påverkan, kognitiv träning) är en utmaning och fordrar särskilt väl utformade studier. Studier kan till och med lida av omvänd kausalitet om beteendemässiga problem leder till en ökad användning av mobiltelefon och inte tvärtom. Den kraftiga ökningen av mobiltelefonanvändning över hela världen skulle kunna innebära stor påverkan på folkhälsan, därför bör effekter av mobiltelefonanvändning på barns utveckling studeras ytterligare. Detta bör helst göras i prospektiva studier med möjlighet att särskilja effekter från RF-fält och andra effekter från användning av mobiltelefon.

Egenrapporterad elkänslighet och symtom

Sedan rådets senaste rapport har forskningen om elkänslighet och livskvalitet hos allmänheten gjort stora framsteg. Fenomenet elkänslighet har framför allt studerats i experimentella laboratoriestudier på försökspersoner med exponering för lågfrekventa elektriska och magnetiska fält (ELF) eller med mobiltelefonlik exponering. Två studier med ELF-exponering har rapporterat effekter, men metoderna har inte beskrivits på ett adekvat sätt. Anmärkningsvärt är att i en studie hade en person en nästan perfekt bedömning av om fältet var på eller inte. Detta förtjänar viss uppmärksamhet och exponeringsförhållandena borde beskrivas bättre. Sammantaget tyder dock inte nya experimentella studier av elkänslighet på några korttidseffekter.

Fram till den senaste rapporten från rådet fanns det endast epidemiologiska tvärsnittsstudier som undersökte symptom till följd av RF-exponering. Sedan dess har ett fåtal longitudinella studier publicerats vilket möjliggör pålitligare slutsatser. En kohortstudie av mobiltelefonanvändning hos unga vuxna med en uppföljningstid av ett år rapporterade några få samband mellan användning av mobiltelefon och hälsorelaterad livskvalitet som sömnsvårigheter och symtom på depression. Eftersom studien inte försökt skilja mellan effekter av exponering och icke-exponering kan orsaken till detta samband inte fastställas för närvarande. Dessutom kan möjligheten att användning av mobiltelefon och livskvalitet kan påverkas av någon gemensam underliggande variabel inte uteslutas. När det gäller exponering från fasta radiosändare så har en annan kohortstudie inte kunnat hitta några robusta effekter efter ett års exponering. Skillnaderna i exponeringsnivåer var relativt små i denna studie.

Slutsatsen blir att de nya epidemiologiska studierna om symtom, med en förbättrad utformning, snarast tyder på att exponering för radiofrekventa fält inte innebär någon risk för försämrad hälsorelaterad livskvalitet. Kvarstående osäkerhet gäller i första hand höga exponeringsnivåer från trådlösa telefoner och längre uppföljningstider än ett år.

Preamble

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

As a general rule, only articles that are published in English language peer-reviewed scientific journals are considered by the Council. This does not imply that the Council considers all published articles to be equally valid and relevant for health risk assessment. On the contrary, a main task of the Council is to evaluate and assess these articles and the scientific weight that is to be given to each of them. The Council examines all studies that are of potential relevance for its evaluations published since the previous report. However, some studies may be sorted out either because the scope is not relevant, or because their scientific quality is insufficient. Such studies are normally not commented upon in the annual Council reports (and not included in the reference list of the report). Major review articles are briefly mentioned but not evaluated.

The Council considers it to be of importance to evaluate both positive and negative studies, i.e., studies indicating that EMF has an effect and studies not indicating the existence of such an effect. In the case of positive studies the evaluation focuses on alternative factors that may explain the positive result. For instance in epidemiological studies it is assessed with what degree of certainty it can be ruled out that an observed positive result is the result of bias, e.g. confounding or selection bias, or chance. In the case of negative studies it is assessed whether the lack of an observed effect might be the result of (masking) bias, e.g., because of too small exposure contrasts or too crude exposure measurements; it also has to be evaluated whether the lack of an observed effect is the result of chance, a possibility that is a particular problem in small studies with low statistical power. Obviously, the presence or absence of statistical significance is only a minor factor in this evaluation. Rather, 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 dosimetry, method for assessment of biological or health endpoint, the relevance of any experimental biological model used etc. For a further discussion of aspects of study quality, refer for example to the Preamble to the IARC (International Agency for Research on Cancer) Monograph Series (IARC, 2002).

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

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

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

Static fields

Exposure to static (0 Hz) magnetic fields much greater than the natural geomagnetic field of ~40-70 μT is associated with industrial and scientific equipment that uses direct current, such as some welding equipment and various particle accelerators. However, the main source of exposure to strong static magnetic fields ($> 1 \text{ T}$) is through the use of magnetic resonance imaging (MRI) for medical diagnostic purposes. Movement in such strong static fields can induce electrical fields in the body and sensations of vertigo in some people. The thresholds for these sensations vary considerably within the population. Volunteer studies have confirmed these effects.

The last time the Council reported on static magnetic fields was in the 2007 report (SSI, 2007:4). The focus then was on the effects of movement in a strong field, an issue closely related to the delay in the implementation of the EU Physical Agents Directive (Directive 2004/40/EC) on minimum health and safety requirements for occupational exposure to EMF.

The conclusion of the 2007 report was that movement in strong static magnetic fields can induce electrical fields in the body and sensations of vertigo and nausea in some people, but that thresholds vary considerably within the population. Since then, the discussion on MRI generated a number of experimental studies, both on animals and humans.

In the meantime the Directive has been reformulated and has reached by the end of 2012 the final stage of agreement.

Cell studies

Genotoxicity

In a Korean study, the genotoxic potential of 3 T MRI exposures was tested in human lymphocytes in vitro using several genotoxicity endpoints: chromosome aberrations, micronuclei and single-cell gel electrophoresis (Lee et al., 2011b). The electromagnetic fields were those of a typical clinical routine brain examination protocols for 22, 45, 67, and 89 min. Significant increases were observed in (i) the frequency of single-strand DNA breaks and (ii) chromosome aberrations and micronuclei in a time-dependent manner. The authors suggest that exposure to 3 T MRI induces genotoxic effects in human lymphocytes. However, the roles of each of the physical MRI exposure parameters were not studied. Moreover the relevance for human health is unknown.

In another Korean study (Sun et al., 2012) the effects of 8.8 mT static magnetic (SM) field exposure were assessed on the action of the chemotherapeutic agent, paclitaxel, which halts cell-cycle progression. K562 human leukaemia cells were exposed to paclitaxel in the presence or absence of the (SM) field and cell proliferation, cell cycle distribution, DNA damage and alteration of cell surface and cell organelle ultrastructure were assayed. The cell cycle of exposed K562 cells was arrested in the G2 phase by paclitaxel and this effect was correlated with DNA damage. In the presence of the static field, the threshold concentration of paclitaxel was decreased by a factor of 5, in terms of cell-cycle arrest. The authors concluded that there is a synergy between the actions of the paclitaxel and the static field in terms of killing cells, which may correlate with DNA damage induced, resulting in G2/M phase arrest.

Oxidative stress

Oxidative stress may be modified by exposure to electromagnetic fields. This hypothesis was tested in Canada (Belton et al., 2011) by assessing the combined effects of SM field exposure and glutathione (GSH) depletion on hsp70 production. The cells were exposed to heat, SM field, and diethylmaleate (DEM), which depletes GSH levels, alone and with various combinations of these parameters. Treatment with DEM significantly reduced the rate of hsp70 production, particularly in the presence of heat. There was no effect on hsp70 production of a 100 mT SM field exposure either alone or in combination with heat, DEM, or both. However there was a significant interaction between SM field exposure and DEM on hsp70 mRNA levels. This result suggests that more studies should be done under SM field exposure as a function of GSH depletion as it conditions the level of defence of cells against oxidative stress.

A Chinese study focused on the cellular effects of an 8.5 T homogeneous SM field exposure in human-hamster hybrid cells, mitochondria-deficient cells, and double-strand break repair-deficient cells (Zhao et al., 2011). Adenosine triphosphate (ATP) content was significantly decreased in the hybrid cells exposed at 8.5 T but not at 1 or 4 T for either 3 or 5 hours. ATP content significantly decreased in the two deficient cell lines at 8.5 T for 3 h. The levels of reactive oxygen species (ROS) in all cell lines increased after exposure to 8.5 T. The conclusion of the authors is that ROS were involved in the cellular perturbations caused by exposure to static magnetic fields.

Proliferation

The magnetic sensitivity of human umbilical vein endothelial cells (HUVECs) was studied in the USA (Martino, 2011) at low (0.2–1 μ T), and higher levels (30 and 120 μ T) in the range of the geomagnetic field. The low-level magnetic field exposure clearly inhibited proliferation compared to the 120 μ T SMF exposure. The action of superoxide dismutase (SOD), which scavenges some of the ROS, was interpreted as evidence of the involvement of a free radical mechanism.

Gene expression

The kinetics of ligand-gated ion channel was studied by an Italian team in mammalian transfected cells encoding adult mouse muscle acetylcholine (ACh) receptors (Tolosa et al., 2011). The macroscopic and single-channel currents using the outside-out and cell-attached patch-clamp configurations were measured. The cells were exposed to 180 mT inhomogeneous static magnetic fields at temperatures from 5 to 50 °C. There was negligible magnetic field influence on the channels' kinetics.

An Italian team (Potenza et al., 2010) had reported that exposure to a 300 mT SM field caused transient DNA damage and promoted mitochondrial biogenesis in human umbilical vein endothelial cells (HUVECs). In a new study (Polidori et al., 2012), the global gene expression profile showed that several genes (associated with cell metabolism, energy, cell growth/division, transcription, protein synthesis, destination and storage, membrane injury, DNA damage/repair, and oxidative stress response) were induced after exposure. Real Time quantitative Reverse Transcription (qRT-PCR) assays were performed at 4 and 24 h on four selected genes showing that HUVEC's response to exposure was transient. The authors conclude that exposure to 300 mT SM field may be harmless to human health, which obviously cannot be ascertained based on this single study.

Nervous system

A peripheral nerve model was used by a Japanese group (Okano et al., 2012) to investigate whether in vitro 6 hour exposure of frog sciatic nerve fibres to non-uniform static magnetic field up to 0.7 T modulates membrane excitation and refractory processes. Changes in the amplitudes of the electrically evoked compound action potentials were measured during exposure. The nerve conduction velocity of C fibres was reduced at 0.7 T but not at 0.21 T. The authors speculate that exposure to moderate-intensity gradient SM fields may attenuate pain perception as C fibres are involved in pain transmission. The mechanism of such effect is unknown.

Animal studies

Behaviour

Haupt et al. (Haupt et al., 2010, Haupt et al., 2011) exposed rats to a very strong, 14.1 T, static magnetic field. They observed that movement through the steep gradient of the magnetic field that occurs during inserting and removing the animals in the magnet suppressed rearing and induced a significant conditioned taste aversion. The induction of walking round in circles required a sustained exposure (in this case 30 min) to the homogenous centre of the magnetic field. They concluded that the vestibular system plays a crucial role in these effects.

Brain development and function

Zhu et al. (2011) exposed rats, either before or shortly after birth to a 7 T SM field, 35 min per day, for 4 days. No effects were observed on brain development and memory.

Physiology – oxidative stress

A research group from Tunisia has performed a series of studies on the effects of exposure to a 128 mT static magnetic field for 1 h per day on various rat tissues. They were particularly interested in various aspects of oxidative damage. Most studies employed either 5 or 30 days of exposure.

- In the first 5-day study, Elferchichi et al. (2011) found that the exposure had no effects on the motor skills of the rats. They did observe an increase in level of transferrin and a decrease in the iron level in plasma. Increased iron concentrations are considered to be able to mediate the induction of oxidative stress. The iron concentration in the brain was not altered, which the authors considered to be proof that the blood-brain barrier was not altered by the SM field.
- Ghodbane et al. (2011) investigated selenium levels in the brain and other organs. Selenium is considered to be an element that is essential in the scavenging of reactive oxygen species (ROS) and therefore to be working antagonistically to iron. The SM field exposure reduced selenium in the brain; selenium supplementation restored the level. In other organs the effect of SM field exposure was variable: in kidney and muscle selenium levels were reduced, while in the liver the levels of several antioxidant enzymes that depend on selenium such as glutathione peroxidase were increased.
- In spinal cord, Miryam et al. (2010) found increased calcium and iron levels after a 5-day treatment, but no change in those of magnesium and copper. The calcium concentration in plasma was unchanged, but the iron level decreased.
- In another study, Lahbib et al. (2010) observed a decrease in serum insulin and a concomitant increase in blood glucose after 5 days of treatment. No effect on body

weight and cholesterol level was observed. After 15 days of treatment, the insulin level was further decreased and the glucose level further increased, while the body weight was decreased and the cholesterol level increased. Thus, the effect of SM field exposure on glucose and lipid metabolism is time-dependent.

- In other studies the animals were exposed for 30 days. Amara et al. (2009a) found that this treatment induced oxidative stress in several parts of the brain, which was considered to be mediated by increased iron concentrations. This was not observed in the 5-day studies mentioned above (Elferchichi et al., 2011), thus duration of exposure is critical. Amara et al. (2011) observed that a 30-day SM field exposure augmented the oxidative damage induced by administration of cadmium chloride.
- In another paper the effect of 30 day exposures on heart and skeletal muscle were assessed (Amara et al., 2009b). Decreased antioxidant enzyme levels were observed in heart and skeletal muscle and an increased lipid peroxidation. Cadmium administration augmented these effects.

Sergeeva et al. (2011) exposed mice to a combination of a 25 μ T SM field and a 5 μ T 3.12 Hz field, for 5 days, 1 h per day. They observed an increase in antioxidant enzymes in Ehrlich ascites tumour cells, liver and bone marrow, which they concluded might indicate an increase of ROS induced by the combined exposure.

Human studies

Van Nierop et al. studied the effects of static magnetic stray fields emitted by a 7 T magnetic resonance imaging scanner on both postural body sway (van Nierop et al., 2012a) and cognitive performance (van Nierop et al., 2012b). In the first study subjects were exposed to sham, low intensity (0.24 T static and 0.49 T s⁻¹ time varying field) and high intensity (0.37 T static and 0.70 T s⁻¹ time varying) magnetic fields. Body sway was measured in eyes closed and feet in parallel (normal) and tandem (one in front of the other) position. The results showed a significant ($p < 0.05$) increase in body sway in feet parallel condition as a function of increasing the intensity of both static and time-varying magnetic fields, but only an almost significant increase in feet tandem condition in the group of 30 healthy volunteers (average age 28.8 years, 21 female). The authors concluded that a spatially heterogeneous static magnetic field affects postural body sway either by affecting cognitive functions (proprioceptive, visual, vestibular) or vestibular system, or both, which in turn affect the postural stability.

The cognitive performance under similar types of static fields (sham, low (0.5 T) and high (1.0 T); both static and time-varying field conditions) in 31 healthy volunteers (average age 23.8 years, 21 females) was determined (van Nierop et al., 2012b). Seventeen different measures of cognitive functions, covering those relevant for surgeons and medical professionals operating near MRI, were measured, as well as reported sensory symptoms of nausea and dizziness and spatial orientation and haptic (tactile, by touch) perception. The results showed a negative effect of the field increment on measures of attention and concentration, particular in situations where high working memory performance was required, and also visuospatial orientation was affected after exposure. The p-values were not corrected for multiple comparisons.

In contrast, in a similar type of a study, Heinrich et al. (2013) determined the effects of MR units of various field strengths (1.5, 3.0, and 7.0 T), including a mock imager with no magnetic field as a control, on memory, eye-hand coordination, attention, reaction time and

visual discrimination in a group of 41 healthy subjects (21 males, average age 26.4 years, 20 females, average age 24.8 years). In statistical analyses, a Bonferroni correction for multiple comparisons was applied. No effects of any of the field strengths on cognitive functions were found. Instead, dizziness, nystagmus, phosphenes (visual sensations) and head ringing were related to the strength of the static magnetic field.

Conclusions on static magnetic fields

In vitro data obtained with static magnetic fields using a large set of exposure conditions and biological endpoints are (i) difficult to interpret, and (ii) do not address the issue of MRI high-strength fields.

Prolonged repeated exposures of animals to SM fields in the millitesla range may lead to increased oxidative stress in various tissues. Whether this leads to health effects has not been assessed. The issue of oxidative stress has been studied in relation to exposure to extremely low frequency (ELF) and radiofrequency (RF) fields as well. In theory, it may lead to increased damage to biomolecules, and thus may increase the risk of health effects. But more studies across the electromagnetic spectrum are needed to ascertain this.

The recent in vitro and animal studies do not provide indications of adverse health effects of SM fields. Experimental studies of acute effects in humans show that strong static magnetic fields may affect the postural control and evoke subjective sensations in humans.

Extremely Low Frequency (ELF) fields

The exposure of the general public for ELF fields is primarily from 50 and 60 Hz electric power lines and from electric devices and installations in buildings.

Biological (experimental) studies

The last Council report (SSM, 2010:44) concluded on in vitro studies: “The trend is towards more studies performed with combined exposure to ELF magnetic fields and chemical or physical agents. This may help resolve the current uncertainty about the causality of the link between ELF exposure and childhood leukaemia.” The conclusion on animal studies was: “Animal studies have to use better designs in order to be useful for health risk analysis. However, new investigations are underway or planned that should provide more information in the next years.” The latest in vitro studies have not particularly focussed on mechanisms to explain the childhood leukaemia observed association, and there are still quite some animal studies with a bad design, in particular concerning exposure system and dosimetry. Nevertheless, new information on several issues has become available.

Cell studies

Genotoxicity

A Belgian team (Verschaeve et al., 2011) performed an investigation of the genotoxic effects of ELF magnetic field exposure (50 Hz, 100 and 500 μ T, 1 and 2 h exposures), alone and in combination with known chemical mutagens using the VITOTOX test that they had developed. It is a very sensitive reporter assay of *Salmonella typhimurium* bacteria based on a construct containing a luciferase gene which results in light production when DNA is damaged. There was no induction of mutagenicity in bacteria by the ELF MF or any synergetic effect when combined with chemical mutagens.

The same team (Maes and Verschaeve, 2012) recently published a review paper on the potential mechanism of an association between Alzheimer's disease (AD) and ELF MF exposure. AD is characterized by several events that have a genetic origin: e.g., trisomy of chromosomes 17 and 21 seems to be involved. There are some reports that indicate that ELF MF may enhance the effects of agents known to induce mutations or tumours and aneuploidy. This paper reviews the possibility of a cytogenetic association between ELF MF and AD.

A previous study of a Finnish team (Markkanen et al., 2008) had shown that pre-exposure to ELF MF altered cancer-relevant cellular responses to menadione-induced DNA damage, but actual genetic damage was not assessed. In the present study (Luukkonen et al., 2011), these same authors examined whether pre-exposure to ELF MF affected chemically induced DNA damage level, DNA repair rate, or micronucleus frequency (MN) in human SH-SY5Y neuroblastoma cells. ELF MF exposure (50 Hz, 100 μ T, for 24 hours) was followed by chemical exposure for 3 hours (menadione and methyl methanesulphonate (MMS)). Pre-treatment with ELF MF enhanced menadione-induced DNA damage, DNA repair rate, and MN in the cells. No effects were observed following ELF MF exposure alone.

The genotoxic effect of ELF MF on human primary fibroblast and cervical cancer cells was investigated by a Korean team (Kim et al., 2012c). Upon continuous exposure of cells (60 Hz, 7 mT, for 10–60 min), no significant change in cell viability was observed. However, DNA double-strand breaks (DSBs) were detected, and the DNA damage checkpoint pathway was activated in these cells without occurrence of apoptosis. There was no induction of

intracellular reactive oxygen species (ROS) production, suggesting that the observed DNA DSBs were not directly caused by ROS. After a 30-min exposure, the DNA DSBs mainly occurred in the central region of the Petri dishes, where the MF is strongest while at 90 min, the amount of DNA DSBs increased rapidly in the outer regions, where the eddy current are larger than at the centre. This point towards differential effects of electric and magnetic fields.

In a Korean study (Lee et al., 2012), aimed at assessing the effects of ELF MF exposure in combination with various external factors, via the micronucleus (MN) assay, mouse embryonic NIH3T3 fibroblasts and human WI-38 lung fibroblasts were exposed for 4 h at 60 Hz, to a 1 mT uniform magnetic field with or without 2 Gy ionizing radiation, 100 μ M H₂O₂, and cellular myelocytomatosis oncogene (c-Myc) activation. There was no effect of the field alone on any endpoint or synergistic effects with the external agents.

Nervous system

Two previous studies (Espinosa et al., 2006, Massot et al., 2000) had reported that exposure to 50-Hz MF decreased the binding affinity of the 1B receptor subtype of serotonin (5-HT) in rat brain membranes. The aim of this French study was to confirm these findings (Masuda et al., 2011a). Rat brain crude membrane fractions, including 5-HT1B receptor and C6-glia cells transfected with human 5-HT1B receptor gene, were exposed to 50-Hz MF at 1 mT under temperature-regulated conditions. In the rat crude membrane, there was no significant difference in the affinity constant of [3H]-5-HT between exposed and sham-exposed samples. Similar negative results in terms of affinity constant were obtained on the human 5-HT1B receptor in C6-glia cells. In addition, forskolin-stimulated cAMP production was inhibited by 5-HT administration in a dose-dependent manner in C6-glia cells, but exposure did not modify the inhibitory response. This study thus failed to confirm the previous results and the authors conclude that exposure to MF below the current occupational limit does not affect the physiological function involved in 5-HT1B receptor subtypes.

Calcium ion

The effects of ELF MF on the calcium ion have been less investigated in the last few years. In Korea (Hwang et al., 2011) intracellular calcium ion (Ca²⁺) mobilization and cellular function were assessed in RBL 2H3 cells (60 Hz, 0.1 or 1 mT for 4 or 16 h). No cytotoxic effects were observed. The effect of exposure on exocytosis was also investigated. Neither basal nor chemically-induced releases were affected by ELF exposure.

Gene expression in bacteria

A Swiss group (Huwiler et al., 2012) investigated the transcription of *Escherichia coli* K-12 MG1655 in response to ELF MF (sinusoidal CW, sinusoidal intermittent and power line intermittent; 50 Hz, 1 mT). Gene expression was monitored at the transcript level using an Affymetrix whole-genome microarray. For all three types of MF investigated, neither bacterial growth nor counts were affected. Likewise, no change greater than twofold in the expression of 4,358 genes and 714 intergenic regions were detected after MF exposure for 1.4 or 8.7 cell generations. These data thus showed no effect on gene expression in bacteria.

Oxidative stress

The aim of a Korean study was to study the effects of ELF MF exposure on intracellular ROS levels and antioxidant enzyme activity (Hong et al., 2012a). MCF10A human breast epithelial cells were exposed to 1 mT 60 Hz ELF MF for 4 h. There were no changes in level of intracellular ROS, activity of superoxide dismutase (SOD), or reduced/oxidized glutathione

ratio (GSH/GSSG). Positive controls were obtained by ionizing radiation exposure which, as expected, altered all three parameters.

Proliferation

A Spanish team (Trillo et al., 2012) investigated the response of two proliferating human cell lines (neuroblastoma, NB69 and hepatocarcinoma, HepG2) under exposure to an ELF MF (42 h, intermittent, 100 μ T, 50 Hz) alone or in combination with 0.5 μ M all-trans-retinol (ROL), used in oncostatic therapies. The proliferative response was determined by cell counting, BrdU incorporation, and by spectrophotometric analysis of total protein and DNA content. The two treatments, MF and ROL, each significantly enhanced cell proliferation in both cell lines. In NB69 cells simultaneous exposure to MF and ROL induced an additive effect on cell proliferation, while in HepG2, ROL-induced cell proliferation was partially blocked by simultaneous exposure to MF. The authors therefore concluded that the mechanisms underlying the cellular response to each of the two agents could be cell type-specific.

Another study by the same group (Martinez et al., 2012) aimed at determining whether a 50 Hz 100 μ T MF exposure lasting 63 h induces cell proliferation in the human neuroblastoma line NB69, and whether the signalling pathway MAPK-ERK1/2 is involved in that proliferative response. The continuous treatment did not induce significant changes in cell proliferation, while intermittent exposure caused an increase in the percentage of cells in phase S of the cell cycle. An early transient and repetitive activation of ERK1/2 was also induced. Both effects were blocked by PD98059, a specific inhibitor of MAPK/ERK Kinase-1/2.

Mobile DNA is dispersed in the genome of all organisms and can be a major cause of genomic instability. In this context, Del Re et al. (2012) in Italy exposed human neuroblastoma BE(2) cells to ELF pulsed magnetic fields PEMF (48 h, 1 mT, 50 Hz) to assess the mobility of retrotransposons, which are genetic elements that can amplify themselves in a genome. In vitro retro-transposition was assessed in terms of DNA double-strand breaks (DSB). PEMF-exposed cells had a lower number of DNA DSB compared with sham-exposed samples.

The effects of 1 mT 50 Hz ELF MF exposure was studied by a Korean group on human bone marrow-derived mesenchymal stem cells (hBM-MSCs) which have the potential to differentiate into nerve type cells (Cho et al., 2012). ELF exposure inhibited the growth of hBM-MSCs in 12 day exposures. Expression of the nestin neural stem cell marker was decreased but expression of MAP2, GFAP, and O4, which are markers of differentiation, were increased. The conclusion of the authors was that EMFs can induce neural differentiation in BM- mesenchymal stem cells in the absence of chemicals or differentiation factors.

In the context of recent data published on the effects of exposure of human spermatozoa to EMF, An Italian group studied sperm motility under exposure to a square waveform 5 mT 50 Hz ELF MF (Iorio et al., 2011). Sperm exposure resulted in a progressive and significant increase in mitochondrial membrane potential and levels of ATP, ADP and NAD(+) and a progressive and significant increase in sperm kinematic parameters. Glycolysis was not involved in mediating the MF stimulatory effect on motility. However, when pyruvate and lactate were provided instead of glucose, the energy status and motility increased in exposed sperm. The authors concluded that the key role was played in eliciting the effect by mitochondrial oxidative phosphorylation rather than glycolysis.

The same Italian group investigated the effects of ELF exposure (2 mT, 50 Hz, up to 8 h) on the growth rate and antibiotic sensitivity of *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 (Segatore et al., 2012). The growth rate of both bacterial strains was decreased in the presence of subinhibitory concentrations of kanamycin (1 µg/ml) and amikacin (0.5 µg/ml), respectively. At 24 h of incubation, the percentage of cells increased (*P. aeruginosa* ca. 42%; *E. coli* ca. 5%) in treated groups with respect to control groups suggesting a progressive adaptive response. However the amplitude of the effects was small and the extrapolation of data obtained on bacteria remains difficult.

The aim of a Chinese study was to assess the effects of 60 Hz magnetic fields using the micronucleus (MN), alone or in combination with various external factors, on a normal cell line (Jin et al., 2012). NIH3T3 mouse embryonic and WI-38 human lung fibroblasts were exposed for 4 h to a 60 Hz, 1 mT, uniform magnetic field with or without ionizing radiation (2 Gy), 100 µM hydrogen peroxide and cellular myelocytomatosis oncogene (c-Myc) activation. There were no significant differences in MN between cells exposed to ELF MF and sham cells, nor synergistic effects with ionizing radiation, H₂O₂, or c-Myc activation.

Several Dutch research groups have teamed (Bouwens et al., 2012) to test a complex multiple ELF waveform field (from the Immument BV company), and a 50 Hz sine wave (both signals at 5 µT). They determined the kinetics of cytokine and other inflammation-related genes in a human monocytic leukaemia cell line, THP-1, and primary monocytes and macrophages, as well as cytokine protein levels in THP-1 monocytes. Exposure to either of the two signals had no significant effect on gene and protein expression in the immune cells. Additional experiments using non-immune cells showed no effects on cytokine gene expression. The authors conclude that that these two ELF exposure conditions did not modulate innate immune signalling.

Conclusion on ELF cell studies

The main conclusions on ELF in vitro studies are still those of the last reports: (i) there is still a huge variety of exposure conditions and biological endpoints, (ii) most positive data have been obtained with field levels at or above 1 mT and (iii) very little has been done to address the main question about leukaemia and power frequency exposure.

Animal studies

Brain and behaviour

Cui et al. (2012) exposed mice to 0.1 or 1 mT 50 Hz ELF magnetic fields for 12 weeks and measured learning and oxidative stress in the brain. Exposure to 1 mT impaired learning, the lower level did not. Oxidative stress was found to be induced in the brain structures responsible for the learning activities.

Frilot et al. (2011) exposed rats for 45 min to a 0.25 mT, 60 Hz field, either on-off or continuous, and measured energy consumption in the brain by positron emission tomography (PET). Increased energy consumption was found in the hindbrain with the on-off, but not with the continuous exposure, and only when the direction of the field did not change. The authors hypothesize that the potentials that are induced by the on and off switching of the field may result in opening of transmembrane ion channels, that mediate signal transduction. In daily life, where exposure to ELF is more continuous, this effect is not important.

Cuccurazzu et al. (2010) exposed mice to 50 Hz magnetic fields at 1 mT for 1 to 7 h per day for 7 days. They observed increased formation of new neurons in the hippocampus of the brain with both treatment times and significant up-regulation of several enzymes involved in neuron differentiation. About half of the newly formed neurons were found to be fully functional. This suggests new therapeutic applications of low frequency magnetic fields.

Reproduction and development

Borhani et al. (2011) exposed female mice to a 50 Hz magnetic field at 0.5 mT 4 h per day, 6 days a week for 2 weeks. About halfway the treatment mice were mated. At the end of the exposure period embryos were harvested. The mean number of embryos was decreased and DNA damage in the embryonic cells increased in the exposed animals, but there was no difference between exposed and controls in the number of pregnant mice and the mean number of embryonic cells.

Bayat et al. (2011) exposed pregnant mice to a 6 mT 50 Hz field for 10 h per day at days 1-5, 6-10, 11-15, or 16-20 of pregnancy. They observed that in all four periods, exposure reduced the total body weight of the offspring, the volume of spleen, and the number of megakaryocytes, a specific type of immune cells. There was a trend that the effects were largest in the first period of pregnancy and decreased thereafter.

Tenorio et al. (2011) studied rat testicular development after exposure to 60 Hz at 1 mT, 3x30 min per day, between the 13th day of gestation and the 21st postnatal day. Histological analysis showed a decreased development of several components of the testis, while an increase was observed in the number of connective tissue cells and the volume of blood vessels volume in the testis. These observations indicate a delay in testicular development.

Several studies were performed on fertilized chicken eggs. Roda et al. (2011) exposed them to pulsed magnetic fields (bursts of 50 or 100 Hz fields at 10 μ T for 1 second at 1.5 seconds intervals). The exposures hindered normal embryonic development and altered several markers indicative of neural function.

Lahijani et al. (2011b) exposed freshly fertilized chicken eggs to 50 Hz fields at 1.33, 2.66, and 7.32 mT for 24 h. After 14 days of incubation the number of apoptotic cells and degeneration in brains were increased. It is not clear whether the level of effect was intensity-dependent.

In a second study, Lahijani et al. (2011a) exposed the eggs to a 7.32 mT field for 24 h. At 13, 14, 15, and 19 days of incubation embryos were removed. Histological analysis showed extensive haemorrhages in various tissues, an increase in the number of apoptotic cells, and a decrease in the levels of expressions of c-Fos, indicative of cell proliferation, and of β -Catenin. Inhibition of β -Catenin is considered to decrease cell proliferation and to increase apoptosis.

Kolodziejczyk et al. (2010) exposed eggs of a snail liver parasite for 10 days to a 2 mT 50 Hz field. This accelerated hatching of the eggs and increased mortality of the snail hosts.

Cancer

Tatarov et al. (2011) used a 100 mT, 1 Hz half-sine wave unipolar magnetic field to expose mice injected with mammary cancer cells. The animals were exposed to the field for 4 weeks,

for 1, 3 or 6 h daily. Exposure at the longest treatment time suppressed tumour growth by about a factor of 10. However, only small numbers of animals were used in the study.

Sergeeva et al. (2011) exposed mice to a combination of a 25 μ T static magnetic field and a 5 μ T 3.12 Hz field, for 5 days, 1 h per day. They observed an increase in antioxidant enzymes in Ehrlich ascites tumour cells, liver and bone marrow, which they conclude might indicate an increase of ROS induced by the exposure.

Physiology

Prato et al. (2011) had shown previously that when mice were repeatedly introduced for 1 h daily in a shielded environment that reduces the ambient static and ELF magnetic fields by approximately 100 times, analgesia is induced. Adding 10-240 Hz magnetic fields to the shielded environment at 25-500 nT attenuated the analgesic effect. They suggest that there is a detection mechanism that is dependent on the (MF intensity) x (frequency) product, with a threshold at or below 1000 nT-Hz.

Sert et al. (2011) exposed rats to 0.25 mT 50 Hz magnetic field for 14 days, 3 h per day. This resulted in increased calcium accumulations in cells of the cardiac ventricles.

Coskun and Comlekci (2011) investigated the effect of exposure to a 50 Hz electric field at 10 kV/m for 10 or 30 days. Plasma cholesterol and triglyceride levels were found to be decreased.

Kargul et al. (2011) exposed rats to 50 Hz magnetic fields at 100 and 500 μ T for 2 h/day and 10 months and measured the microhardness of teeth. The 500 μ T exposure resulted in some negative effects on the enamel mineralisation.

Fedrowitz et al. (2012) studied α -amylase, a stress marker in humans, in the mammary gland of two rat strains with different stress sensitivity. The animals were exposed to a 50 Hz, 100 μ T magnetic field for 24 h per day. In F344 rats an increase in α -amylase was observed after 2 and 4 weeks of exposure, while no effects were found in Lewis rats.

Finally, in several studies the influence of ELF magnetic field exposure on oxidative stress was investigated. Ciejka et al. (2011) exposed rats to a 40 Hz field at 7 mT, for 30 or 60 min per day and 10 days. The 30 min exposure increased free radical generation in the brain, but the longer exposures caused adaptation. Chu et al. (2011a) exposed mice to a 60 Hz magnetic field at 2.3 mT for 3 hours. They observed changes in various parameters in the cerebellum indicating increased oxidative stress. Emre et al. (2011) investigated oxidative stress in rat liver and cell death in kidney. They exposed the animals to pulsed square-wave magnetic fields at 1.5 mT with frequencies of 1, 10, 20 and 40 Hz in subsequent pulse trains. They found an increased level of oxidative stress, and a suggestion of increased cell death.

Conclusion on ELF animal studies

A number of studies indicated adverse effects of generally long term exposure to ELF magnetic fields in the millitesla range on reproduction and development in various animal species. Other studies indicated increased oxidative stress, again mostly by exposures at levels well above the current exposure limits. One study showed indications for tumour growth inhibition by a 100 mT field, but with only small numbers of animals. Replication is necessary to obtain more insight. In general, the latest animal studies do not contribute to understanding a mechanism that could explain the association found in epidemiological

studies between long term exposure to ELF magnetic fields below 1 μT and an increased risk of childhood leukaemia. Hence, there is still a need for dedicated studies in this area using new animal models.

Human studies

Recent studies in humans have mainly focused on cardiovascular responses and the reactivity of the human brain to ELF MF.

McNamee et al. targeted the cardiovascular system with a 1 hour 1800- μT , 60 Hz (McNamee et al., 2010) and 200- μT 60 Hz (McNamee et al., 2011) magnetic fields. The group of 58 healthy volunteers (mean age 27 years, 19 females) did not show effects of the 1 h exposure by 1800 μT 60 Hz MF on any of the measured parameters (skin blood perfusion, heart rate, heart rate variability; (McNamee et al., 2010)). In the second study, a group of 10 healthy volunteers (mean age 24.0 years, 4 females) did not show any effects of a 1 h 200- μT 60 Hz MF exposure on any of the measured parameters (skin blood perfusion, heart rate, heart rate variability, mean arterial pressure). As an overall conclusion McNamee et al. (2011) stated on the basis of these two studies that the only detectable but not significant effects were due to decreasing body temperature and reduced physiological arousal during the experiment.

As with static fields, possible effects of the ELF fields on human standing balance as well as voluntary motor function, physiological tremor and brain electrical activity (EEG) have been recently determined (Legros et al., 2012). A large group (73 participants, mean age 28 years, 27 females) was exposed for 1 hour to 60 Hz, 1800 μT MF. The standing balance oscillations produced by the subjects during MF exposure were slower and smaller in amplitude as compared to those produced during the sham exposure. No other physiological measures (motor or EEG) showed any effects by the EMF exposure. The authors concluded that the 1 h ELF MF exposure may affect human involuntary motor control without being detected in the cortical electrical activity.

Capone et al. (2009) applied a new and promising method, transcranial magnetic stimulation (TMS), to study the possible excitability changes of the neural networks in the human brain due to ELF EMF in a pulsed mode (PEMF) in a group of 22 healthy volunteers (mean age 27.6 years, 13 females). After 45 min of PEMF exposure (peak intensity of the MF 1.8 ± 0.2 mT, pulsing frequency 75 ± 2 Hz, pulse duration 1.3 ms) intracortical facilitation produced by paired pulse brain stimulation by TMS was significantly enhanced by 20 %, while other parameters of cortical excitability remained unchanged. The increase in paired-pulse facilitation is related to glutamatergic activity, suggesting that PEMF exposure may produce an enhancement in cortical excitatory neurotransmission. This is an interesting finding, and should be replicated in order to verify the result, which then may lead to neurobiological experiments in animal models.

Cvetkovic and Cosic (2009) demonstrated the effects of MF exposures of ELF in a large frequency range (4-50 Hz) on human EEG in a double-blind, counter-balanced design with Bonferroni correction. They particularly showed the effects of ELF MF on narrow alpha and beta bands in the human EEG in a group of 33 subjects (mean age 30 years, 9 females). The authors conclude that it is possible to alter the human EEG activity of alpha and beta bands with exposure to MF at corresponding frequencies, depending on the order and period of MF conditions. They also speculated about the possibilities of application of these MF stimulations as therapeutic treatments of particular neurophysiological abnormalities.

Finally, Corbacio et al. (2011) evaluated the effects of 60 Hz, 3 mT MF on cognitive performance in 99 participants (mean age 23.5 years; 60 female) in a double-blind experimental setup. Performance improvement as a function of test repetition (practice effect) was seen in 11 out of 15 psychometric parameters. However, in a short-term memory test no practice effect was observed in the exposed groups (exposure/sham, sham/exposure) compared to the control group (sham/sham). Therefore, the authors conclude that their study did not establish any clear MF effect on human cognition, but they further speculated that the ELF MF may interfere with the neuropsychological processes responsible for short-term learning. This finding indeed corresponds to some earlier results on effects of ELF MF on short-term learning and memory in animals (e.g. (Sienkiewicz et al., 1998)) and man (e.g. (Preece et al., 1998)).

Conclusions on ELF human studies

In conclusion, ELF MF do not seem to have any effects on general physiology (cardiovascular responses, postural control), but effects have been reported related to cortical reactivity, EEG, and short-term memory. The relation of these individual findings to each other remains to be further studied.

Epidemiological studies

In the previous Council report, the epidemiological association between ELF magnetic fields and the risk of childhood leukaemia was judged to be consistent. Evidence regarding breast cancer spoke rather against an increased risk, and only little new information had become available concerning parental exposure and risk of childhood cancer. Regarding some indications for an association of Alzheimer's disease with ELF magnetic field exposure, it was concluded that further research was warranted.

Childhood leukaemia

The relationship between residential magnetic field exposure and contact currents (Kavet et al., 2011) and childhood leukaemia (Does et al., 2011) was assessed in a case-control study in California. 30-minute measurements of contact currents as well as of magnetic fields were taken in homes of 245 leukaemia cases and 269 controls. No association was found for either contact currents or magnetic field exposures and childhood leukaemia. ORs for magnetic field exposures above 0.2 or 0.3 μT compared to $\leq 0.1 \mu\text{T}$ were around unity or below one. In the analysis by Does et al., the correlation between the two exposures measures was low (Spearman < 0.3), meaning that effects could be assessed independently. However, Kavet highlights that the correlation was high enough to be a problem in other analyses if not accounted for. Contact currents depend on the electricity system configuration and might therefore be particular to the system applied in the US. Contact currents have not been evaluated elsewhere.

In an Australian case-control study, the association between maternal and paternal exposure to ELF MF and childhood acute lymphoblastic leukaemia (ALL) was evaluated (Reid et al., 2011). Occupational exposure information was obtained for 379 case and 854 control mothers and 328 case and 748 control fathers. Participation rate was somewhat higher in case parents than in control parents with 73% case mothers and 63% case fathers, compared to 63% control mothers and 55% control fathers who provided occupational information. Occupational exposure was assigned based on job title and on questions to the parents regarding working with or nearby different types of electrical equipment. The exposure assessment was not validated with measurements. The exposure prevalence was very high, with 61-69% of parents classified as "exposed" who were subsequently compared to the

“unexposed” parents. (In comparison, in the study by Hug et al. (2010); see previous report from 2010 for more details) that analysed the same association, only 24% of fathers and 6% of mothers were exposed to levels above 0.2 μT .) No increased risks of childhood ALL emerged from the analyses although an OR of 1.33 (95% CI 0.88-1.99) was obtained for paternal exposure in the year prior to the child’s birth. This is similar to a meta-analysis presented by Hug et al. (2010) on paternal exposure with a summary OR of 1.35 (95% CI 0.95-1.91).

Health effects of exposure during pregnancy

Two short reports by Auger et al. (Auger et al., 2011, Auger et al., 2012) assessed the risk of adverse birth outcomes for persons living close to overhead power lines in registry-based studies. All singleton live births were identified for 1990-2004 of Montreal and Quebec City (about 700,000 children) in the first study, and all live births and stillbirths for 1998-2007 of six metropolitan areas of Quebec (about 500,000 children) were included in the second study. Odds ratios for children of parents living within 50 m of a power line were around unity regarding preterm birth, small-for-gestational age or low birth weight. However, there was a slight but statistically not significant increased risk for stillbirths in people residing within 25 m of a power line with an OR of 1.44 (95% CI 0.87-2.38) and an OR of 1.13 (95% CI 0.73-1.73) for those living within 25-50 m of a power line. Strengths of the studies include the use of registry data. However, the actual magnetic field exposure levels of the parents could not be assessed. Along the same lines, Malagoli et al. assessed birth defects (still births and aborted fetuses with congenital anomalies) in Reggio Emilia, a region in Northern Italy (Malagoli et al., 2012). Exposure from all high-voltage power lines with levels above 132 kV were modelled and exposure at the home address was categorised into levels of < 0.1 , ≥ 0.1 - < 0.2 , ≥ 0.2 - < 0.4 and ≥ 0.4 μT , using a case-control study design. 228 cases were identified and matched (on year of birth, maternal age and hospital) to the same number of controls, but exposure to high levels of magnetic fields from power lines was rare. The study was underpowered and detected only 1 case and 3 controls exposed to levels higher than 0.2 μT ; the relative risks were below one and had wide confidence intervals.

Two recent publications by Li et al. followed up an earlier study by himself, in which a sample of 969 pregnant women performed 24 h magnetic field measurements during their first or second trimester of pregnancy. All three studies analyse data from the same group of participants. In the study from 2002, an increased risk of miscarriage was reported for women with maximum magnetic field exposures above 1.6 μT compared to lower maximum exposures (Li et al., 2002). In the second analysis, 626 mother-child pairs were followed-up for up to 13 years and the diagnosis of asthma was evaluated (Li et al., 2011). The exposure was categorized into low, medium and high according to cut-offs at the 10th and 90th percentile of mothers’ median magnetic field readings. This corresponded to levels of ≤ 0.03 , > 0.03 - 0.2 and > 0.2 μT . A strong increase in risk over these exposure categories was reported with adjusted Hazard Ratios of 1.74 (95% CI 0.93-3.25) in the medium exposed group, and 3.52 (95% CI 1.68-7.35) in the high exposed group. As reported by the author, asthma prevalence in this group was much higher than in the general public (21% vs. 13%). Socio-demographic factors, as well as some risk factors for asthma were accounted for in the analysis. In an accompanying commentary, Yost and Burch (2011) discussed that other exposures such as air pollution that could be correlated with high magnetic field levels as well as with asthma were not assessed. They also suggested for future studies to investigate potential effects of magnetic field exposure on the immune system, as the immune system plays a role in both asthma and childhood leukaemia.

In the third report by Li et al., obesity was analysed in 733 children (Li et al., 2012b). Exposure was categorized into low, medium and high exposures at cut-offs at the 33rd and 66th percentile, this time of mothers' 90th percentile of the magnetic field readings. This corresponded to exposure levels of < 0.15, 0.15-0.25 and > 0.25 μ T, respectively. Elevated risks of obesity were observed with a dose-response relationship in the medium exposed group with adjusted ORs of 1.5 (95% CI 0.81-2.77) and the high exposed group with 1.84 (95% CI 1.05-3.22) compared to low exposed. There was no clear hypothesis as to how magnetic field levels would impact body weight levels. A strength of all three reports by Li is that a prospective study design was applied. It remains unclear, however, why different exposure metrics and cut-offs were used in all three studies, since this introduces some concern that the data analysis was data driven in order to obtain significant associations.

Adult cancer

In a Brazilian case-control study (Marcilio et al., 2011), death certificate information was analysed. Cases were adults above 40 years of age who had died from leukaemia (n=1857), brain cancer (n=2357) or amyotrophic lateral sclerosis (ALS) (n=367). Controls were persons who had died from another cause. Exposure was assessed in two ways: by assessing distance to overhead power lines of 88-440 kV, as well as by modelling residential exposure. For leukaemia, slightly increased risks were observed for those exposed to levels above 0.3 μ T at home compared to \leq 0.1 μ T with an OR of 1.61 (95% CI 0.91-2.86), and for those living within 50 m of a high-voltage power line with an OR of 1.43 (95% CI 1.03-2.01). For brain tumours, the OR was 1.16 (95% CI 0.6-2.07), and the study was underpowered to analyse ALS, only one exposed case was identified. A strong side of the study is the use of registry data, which excludes the possibility of participation bias, as well as the exposure assessment evaluating magnetic field exposures. The OR for brain tumours is in line with a relatively recent meta-analysis by Kheifets et al. on occupational magnetic field exposures resulting in a RR of 1.14 (95% CI 1.07–1.22) for those exposed compared to not exposed. The risk estimate for leukaemia of the Brazilian study is somewhat higher than that reported in the meta-analysis (1.16, 95% CI 1.11–1.22) (Kheifets et al., 2008).

In a multi-centre case-control study from Denmark, Latvia, France, Germany, Italy, Sweden, Spain, Portugal and the UK, Behrens et al. assessed uveal melanoma, a relatively rare tumour of the eye (Behrens et al., 2010). For 17 types of magnetic field sources, study participants reported their exposure. In particular, they were asked if they had worked close to e.g. power lines, lifting trucks or a range of other magnetic field sources. All results were stratified by sex and eye colour, resulting in a considerable amount of analyses. The authors report inconsistent patterns of increased ORs across sex and eye colour. For example, increased risks of uveal melanoma were reported for light-eyed women who had ever worked close to any electrical transmission installation (an overhead high-voltage power line, a transformer or a substation). For dark-eyed men, however, risks were increased for those persons who had ever worked in any room with "complex electronic devices". Self-reported exposure assessment was a drawback of this analysis, but the authors also analysed occupational exposure levels. Occupational exposure was assessed by assigning exposure levels to job titles with a job exposure matrix, and this was analysed in microtesla-years. Increased risks for uveal melanoma were observed for men and women with dark eyes only: for men the upper 5% exposed compared to the lower 95% exposed had higher risks with an OR of 3.57 (95% CI 1.20-10.68), as had the upper 40% exposed women compared to the lower 60% exposed women with an OR of 2.87 (95% CI 1.09-7.55). While the cumulative exposure ranged from 0.008 microtesla-years to about 12 in women and 13 in men, it is not explained to which exposure levels the above mentioned percentiles pertain.

In a French population-based case-control study, the association between occupational and residential exposure to electromagnetic fields from RF and ELF and risk of brain or other central nervous system tumours was performed by Baldi et al. (2011). A total of 221 (response rate 70%) cases and 442 (response rate 69%) controls participated in the study. The data collection was performed during the period May 1999 to April 2001, using face-to-face questionnaires including the use of mobile phones. Cases with gliomas, meningiomas or vestibular schwannomas (acoustic neuromas) were included in the study. Occupational ELF and RF exposure was assessed through expert judgement based on self-reported information about job titles, type of industry and duration of the respective occupation. Residential exposure was not measured or calculated, but categorised using residential distance of more or less of 100 m to any power line (or underground cable) above 90 kV. Elevated risk estimates were observed especially for ELF exposure and meningioma, with ORs of 3.02 (95% CI 1.10–8.25) for occupational ELF exposure and 2.99 (95% CI 0.86–10.40) for living within 100 m of a power line. Risk estimates for mobile phone exposure were all below one. Odds ratios for persons occupationally exposed to RF were 1.50 (95% CI 0.48–4.70). Exposure proxies of occupational RF exposure were not validated, which renders the results difficult to interpret.

Other health endpoints in children

The effect of incubators on melatonin levels was assessed in a study in Siena, Italy (Bellieni et al., 2012). The incubators generated magnetic field levels between 0.45 μT (periphery of mattress, low power setting) and 8.8 μT (centre of mattress, full power). The authors analysed urine melatonin levels (6OHMS, 6-hydroxy-melatonin-sulfate) in 27 children that were placed in incubators, and after they had been transferred for 48 h to a crib with background magnetic field exposures ($<0.01 \mu\text{T}$). Data were compared to two 6OHMS measurements done in 27 babies that had only been in a crib. Incubated children started with slightly lower melatonin levels during the exposure period and had slightly higher levels afterwards, compared to the control children, but the difference between the groups was not statistically significant. However, the authors attributed the increase in melatonin levels in the incubated children to the magnetic field exposure. It remains unclear if this increase could also, at least partly, be due to the fact that children who had been in the incubator were on average a bit younger than control children, and that they had a health issue that predisposed them to the incubator in the first place.

Electrical injury

A Danish study from Grell et al. (2012) analysed whether persons surviving an electrical accident in the past had higher risks of neurological diseases later on. 3,133 persons registered to have experienced an electrical accident that had occurred between 1968 and 2008 were included in the analysis. Their records were matched to the Danish patient register (hospital data). The authors assessed whether persons with an electrical accident in their past were diagnosed with either peripheral nerve disease, migraine, vertigo, epilepsy, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease or vascular dementia. The observed number of cases was compared to standardised hospitalisation ratios (the expected numbers). Increased risks were observed for peripheral nerve disease, migraine, vertigo and epilepsy with standardised hospitalisation rates of 1.66 (95% CI 1.22–2.22), 1.80 (95% CI 1.23–2.54), 1.60 (95% CI 1.22–2.05) and 1.45 (95% CI 1.11–1.85), respectively. Inconclusive results were reported for amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease and vascular dementia, but numbers were very small (1 to 7 cases). It is likely that many of the persons experiencing electrical accidents had worked in occupations

with elevated magnetic field exposure. Since magnetic field exposure was not assessed in this study, the effects of these exposures cannot really be disentangled.

Overall conclusion on epidemiology

Given some previous reports of an association between the exposure to magnetic fields and some neurological diseases, the observation of increased risks of neurological conditions in survivors of electrical shocks (who were likely also exposed to elevated magnetic fields) is of interest because it may indicate that electric shocks, and not magnetic field exposure, are involved in the development of neurological diseases. However, due to the small number of cases, the study is not informative regarding those health outcomes that are of most interest, notably amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease and vascular dementia. Because no new studies on residential exposure to ELF-magnetic fields and Alzheimer's disease have appeared since the last report, the corresponding uncertainty remains unchanged.

Only little new information regarding parental exposure and risk of childhood cancer has become available, which does not materially change the conclusions from the previous report: "There appears to be little support for the hypothesis relating parental exposure to cancer in the offspring." New evidence regarding adult brain tumours and leukaemia and exposure to high voltage power lines were compatible with an earlier meta-analysis that showed very small increased risks (around 10%) in those exposed.

Intermediate Frequency (IF) Fields

The intermediate frequency (IF) region of the EMF spectrum is defined as being between the ELF and RF ranges. Only few experimental studies are available on health effects of IF electromagnetic fields. Additional studies would be important because human exposure to such fields is increasing due to new and emerging technologies, for example surveillance systems. Studies on possible effects associated with chronic exposure at low exposure levels are particularly relevant for confirming adequacy of current ELF and RF exposure limits.

There are few papers published relevant to this frequency range.

In a Japanese study (Sakurai et al., 2012), the authors evaluated the effects of intermediate frequency (IF) magnetic fields generated by induction heating cookers on gene expression profiles. Human fetus-derived astroglia cells were exposed to magnetic fields at 23 kHz and 100 μ T for 2, 4, and 6 h and gene expression profiles assessed using cDNA microarrays. There were no effects of exposure on the gene expression profile, whereas the positive controls (heat treatment at 43 °C for 2 h), affected gene expression including inducing heat shock proteins (HSP).

Radiofrequency (RF) fields

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

There are reports suggesting that relatively weak amplitude-modulated RF EMF have specific biological effects different from the well-known thermal effects of RF energy. A Finnish review (Juutilainen et al., 2011) describes recent studies on biological effects of modulated RF fields with a focus on studies comparing the effects of modulated and un-modulated (CW) RF, or as a function of type of modulation. Most of the recent studies have reported no modulation-specific effects, but there are a few exceptions related to the human central nervous system.

Biological (experimental) studies

The great majority of studies in the field of EMF is still focussed on effects of RF fields associated with wireless communication (both speech and data). New applications for this emerge continuously, and exposures continue to increase. In combination with the classification of RF EMF by IARC as ‘possibly carcinogenic for humans’ (Baan et al., 2011), this results in a continuing attention in society for possible adverse health effects associated with RF exposure. And this has thus resulted in many in vitro and animal studies.

Cell studies

Genotoxicity and apoptosis

The extent of genetic damage in human cells, assessed from various end-points, viz., single-/double-strand breaks in DNA, incidence of chromosomal aberrations, micronuclei and sister chromatid exchanges, reported in a total of 88 peer-reviewed scientific publications during 1990–2011 was considered in a meta-analysis (Vijayalaxmi and Prihoda, 2012). Among the several variables in the experimental protocols used, the influence of 5 specific variables related to RF exposure characteristics was investigated: (i) frequency, (ii) specific absorption rate, (iii) exposure as continuous wave, pulsed wave and occupationally exposed/mobile phone users, (iv) duration of exposure, and (v) different cell types. The data indicated the following:

- The magnitude of difference between RF-exposed and sham-/unexposed controls was small with some exceptions.
- In certain RF exposure conditions there was a statistically significant increase in genotoxicity assessed from some endpoints, but the effect was only observed in studies with small sample size and was largely influenced by publication bias. Studies conducted within the generally recommended RF exposure guidelines showed a smaller effect.
- The multiple regression analyses and heterogeneity goodness of fit data indicated that factors other than the above five variables as well as the quality of publications have contributed to the overall results of the metaanalysis.
- More importantly, the mean indices for chromosomal aberrations, micronuclei and sister chromatid exchange end-points in RF-exposed and sham-/unexposed controls were within the spontaneous levels reported in a large data-base.

- The authors concluded that the classification of RF as possibly carcinogenic to humans in group 2B was not supported by genotoxicity-based mechanistic evidence.

The objective of a French study was to investigate whether exposure to GSM RF induces aneuploidy in cultured human cells (Bourthoumieu et al., 2011). Exposures of human amniotic cells were performed in wire-patch cells for 24 h at 0.25, 1, 2 and 4 W/kg in the 36.3–39.7°C temperature range. The rate of aneuploidy of chromosomes 11 and 17 was determined by interphase FISH (Fluorescence In Situ Hybridisation). In agreement with results of previous research, no significant change in the rate of aneuploidy was found following exposure to a 900 MHz GSM for 24 h at an average SAR up to 4 W/kg.

In Italy, the Scarfi group exposed rat pheochromocytoma (PC12) cells, as a model of neuron-like cells, to UMTS 1950 MHz RF (24 h, 10 W/kg) to assess possible adverse effects (Zeni et al., 2012b). DNA integrity, cell viability, and apoptosis were the cellular endpoints relevant for carcinogenesis and other diseases of the central nervous system. There was no effect in the selected cellular endpoints in undifferentiated PC12 cells, in spite of the high SAR level.

Oxidative stress

In France, the effects of the Enhanced Data rate for GSM-1800 Evolution (EDGE) signal were investigated on three human brain cell lines, SH-SY5Y, U87 and CHME5, used as models of neurons, astrocytes and microglia, respectively, as well as on primary cortical neuron cultures (Poullietier de Gannes et al., 2011). Four exposure conditions in waveguides were tested: 2 and 10 W/kg for 1 and 24 h. The production of reactive oxygen species (ROS) was measured by flow cytometry using the dichlorofluorescein diacetate (DCFH-DA) probe at the end of a 24-h exposure or 24 h after a 1-h exposure. Rotenone treatment was used as a positive control. All cells tested responded to rotenone treatment by increasing ROS production. Exposure to the EDGE signal did not induce ROS under these test conditions. These negative results are in agreement with earlier findings by the same group that RF exposure alone does not increase ROS production.

In Korea, a similar study was performed to determine whether the exposure to either single or multiple RF signals could induce oxidative stress in cell cultures (Hong et al., 2012b). Exposures of human MCF10A mammary epithelial cells was done at a single frequency (837 MHz alone or 1950 MHz alone) or multiple frequencies (837 and 1950 MHz) at 4 W/kg for 2 h. Intracellular levels of ROS, the antioxidant enzyme activity of superoxide dismutase (SOD), and the ratio of reduced/ oxidized glutathione (GSH/GSSG) were not altered whatever exposure regimen while treatment with ionizing radiation, used as a positive control, induced changes in all endpoints.

Gene expression

In a Chinese study (Chen et al., 2012), *Saccharomyces cerevisiae* yeast cells were used to identify genes responding to ELF MF and RF EMF exposures. The yeast cells were exposed for 6 h to either 0.4 mT 50 Hz MF or 1800 MHz RF at 4.7 W/kg. Gene expression was analysed by microarray screening and confirmed using reverse transcription polymerase chain reaction (RT-PCR). Out of the 40 potential RF responsive genes, only the expression of structural maintenance of chromosomes 3 (SMC3) and aquaporin 2 (AQY2 (m)) were confirmed. The conclusion of the authors is that the response to RF exposure is limited to a very small number of genes. The possible biological consequences of these changes induced by RF await further investigation.

In view of the increasing use of millimeter waves (MMW) in wireless communications around 60 GHz, there is still a need to assess the health effects of related exposures. Under these conditions the main target of the MMW is the skin. A French team (Le Quement et al., 2011) has investigated the potential responses of skin cells to MMW by exposing primary human skin cells for 1, 6, or 24 h at 60.4 GHz and 1.8 mW/cm² corresponding to a local SAR of 42.4 W/kg. Gene expression micro-arrays containing over 41,000 unique human transcript probe sets were used and there was no significant difference in gene expression when data were subjected to a stringent statistical analysis. However, when a t-test was employed to analyse the data, 130 transcripts were found to be potentially modulated after exposure. To further quantitatively analyse these preselected transcripts, real-time PCR was performed on 24 genes with the best combination of high fold change and low p-value. Five of them were confirmed as differentially expressed after 6 h of exposure.

In Italy a group (Calabro et al., 2012) exposed neuron-like cells, obtained by retinoic-acid-induced differentiation of human neuroblastoma SH-SY5Y cells, for 2 and 4 h at 1800 MHz using a mobile phone placed 3 cm from the cultures (estimated SAR of 0.09 W/kg). Cell stress response was evaluated using the MTT assay and heat shock protein expression (Hsp20, Hsp27 and Hsp70) and caspase-3 activity levels, as biomarkers of apoptosis. Cell viability, Hsp27 expression and caspase-3 activity were not altered but a significant decrease in Hsp20 expression was observed with both durations of exposure, whereas Hsp70 levels were significantly increased only after the 4 h exposure. The authors conclude that modulation of the expression of Hsps in neuronal cells can be an early response to RF exposure. However, in view of the lack of dosimetry and inappropriate exposure system, this conclusion cannot be trusted at this time.

Proliferation

The effects on cellular neoplastic transformation were investigated by a Chinese group under exposure to 916 MHz CW signals (Yang et al., 2012). NIH/3T3 cells were exposed for 2 h per day at power densities of 10, 50, and 90 W/m². The morphology and proliferation of the cells were examined and furthermore soft agar culture and animal carcinogenesis assay were carried out to determine the extent of neoplastic promotion. The morphology and proliferation of the cells changed after 5–8 weeks of exposure. In the animal carcinogenesis study, lumps developed on the back of SCID mice after inoculation with NIH/3T3 cells exposed for more than 4 weeks. However, in view of a lack of dosimetry in this work (no determination of the SAR, no absorbing material on the walls of the incubator, etc.), the results have to be taken with caution.

Immune system

In Italy, The Scarfi group (2012a) studied the induction of an adaptive response (AR) in human peripheral blood lymphocytes exposed to RF (UMTS-1950 MHz; 1.25, 0.6, 0.3, and 0.15 W/kg). Cells from 9 healthy human volunteers were stimulated for 24 h with phytohaemagglutinin and then exposed for 20 h to RF. Following treatment at 48 h with a challenge dose (CD) of 100 ng/ml mitomycin C (MMC), lymphocytes were collected. The cytokinesis-block method was used to assess the frequency of micronuclei (MN). When lymphocytes from six donors were pre-exposed to RF at a SAR of 0.3 W/kg and then treated with MMC, there was a significant reduction in MN. This result is indicative of induction of AR. Based on these data and previous ones obtained by the same group with GSM-900 MHz, the conclusion is that the induction of AR depends on RF frequency, type of signal and SAR level.

A French team investigated potential alteration of the chaperone-mediated autophagy (CMA) which is a pathway for protein degradation in the lysosomes and increases under stress conditions as a cell defence response (Terro et al., 2012). The rationale was that GSM might constitute a stress signal, and could thus alter the CMA process. Cultured cerebral cortical cells were sham-exposed or exposed to GSM-900 MHz at 0.25 W/kg for 24 h using a wire-patch cell. Apoptosis was analysed by DAPI stain of the nuclei and Western blot of cleaved caspase-3. The expression of proteins involved in CMA (HSC70, HSP40, HSP90 and LAMP-2A) and α -synuclein were analysed by Western blot. During the 24 h exposure to GSM-900 the temperature elevation was ca. 0.5°C. Exposure did not induce apoptosis but increased HSC70 by 26% and slightly decreased HSP90. It also decreased α -synuclein by 24% independently of CMA, since the localization of active lysosomes was not altered. Comparable effects were observed in cells incubated at 37.5°C. These changes are most likely linked to the temperature elevation. There was no effect on cell viability.

Genome instability of somatic cells may be linked to cancer development and is increasingly studied in relation to RF exposure. The same French group (Bourthoumieu et al., 2013) investigated whether the exposure to GSM RF may induce expression of the p53 protein and its activation by post-translational modifications in human amniotic cells. Exposure was done in a wire-patch cell using a GSM-900 MHz signal at SARs of 0.25, 1, 2, and 4 W/kg for 24 h at 36.3–39.7 °C. Bleomycin-exposed cells were used as positive control. There were no significant changes in expression and activation of p53.

A Korean group (Lee et al., 2011c) studied the effects of single or combined RF exposure on the cell cycle and its regulatory proteins in MCF7 cells (DMA 837 MHz or combined 837 and WCDMA 1950 MHz at 4 W/kg for 1 h). After exposure, the rate of DNA synthesis and the cell cycle were assessed. The levels of cell cycle regulatory proteins, p53, p21, cyclins, and cyclin-dependent kinases were assessed. The positive control group was exposed to ionizing radiation and changes in DNA synthesis and cell cycle distribution were observed as expected, as well as the levels of p53, p21, cyclin A, cyclin B1, and cyclin D1. In contrast, neither the single RF nor combined RF exposures elicited alterations in DNA synthesis, cell cycle distribution, and levels of cell cycle regulatory proteins.

The same Korean group used a cellular stress response to investigate whether single or combined RF fields could induce stress response in MCF10A human breast epithelial cells (Kim et al., 2012b). Exposure was performed with CDMA or CDMA plus WCDMA or 2 h RF radiation on 3 consecutive days. The SAR was 4.0 W/kg for CDMA alone exposure and 2.0 W/kg each, i.e., 4.0 W/kg in total for the combined signals. Expression levels and phosphorylation of specific HSPs and mitogen-activated protein kinases (MAPKs) were analysed by Western blot. Neither single (CDMA) nor repeated single (CDMA alone) or combined (CDMA plus WCDMA) RF exposure altered HSP27 and ERK1/2 phosphorylations in MCF10A cells. This is one of the few studies using combined exposure to two RF signals.

Apoptosis

In the context of the potential epidemiological association between glioma and RF exposure, it is most important to assess the effects of RF on astrocytes and glioma cells. In a Chinese study (Liu et al., 2012), rat astrocytes and C6 glioma cells were exposed to 1950 MHz CDMA signals for 12, 24, and 48 h. RF exposure had differential effects on rat astrocytes and C6 glioma cells. After 48 h of exposure the mitochondria in astrocytes were damaged and a significant apoptosis was induced. Moreover, caspase-3 was increased in astrocytes

accompanied by a significantly increased expression of bax and reduced level of bcl-2, all of these being markers of apoptosis. The tumorigenicity assays demonstrated that astrocytes did not form tumours. In contrast, C6 glioma cells showed no significant differences in both biological features and tumour formation ability after exposure.

Cardiovascular system

Kumar et al. (2011) exposed rat long bones in vitro to a 900 MHz field at a SAR of 2 W/kg for 30 min. No effects were found on the proliferation rate of bone marrow cells and lymphocytes, erythrocyte maturation rate and DNA damage in lymphocytes.

Conclusion on cell studies

In line with of the previous Council report (SSM, 2010:44), the main conclusions on RF in vitro studies are that (i) there is still a large variety of exposure conditions and biological endpoints with little coordination among research groups, (ii) many recommendations of the WHO research agenda are being addressed, (iii) there are fewer reported positive effects than with exposure in the ELF range, (iv) there is still little founded evidence of non-thermal effects and (v) recent data from laboratory studies related to cancer do not seem to support the conclusion of IARC that RF fields are possibly carcinogenic to humans.

Animal studies

As in previous years, the focus of animal studies has mainly been on effects on the brain (because of the close vicinity of mobile telephones during calls). In addition, there is growing interest in oxidative stress, as an increase in this might attribute to an increased health risk through a rise in the level of damage to biomolecules.

Brain function and behaviour

Prochnow et al. (2011) exposed the brain of rat to a UMTS signal at 2 and 10 W/kg for 120 min and measured stress hormones (corticosteron and adrenocorticotrophic hormone) and hippocampal derived synaptic long-term plasticity (LTP) and depression (LTD) indicative for memory storage and consolidation. Corticosteron was higher after 2 W/kg and lower after 10 W/kg exposures compared to sham exposure, adrenocorticotrophic hormone did not change. LTP and LTD were not altered after 2 W/kg, but reduced after 10 W/kg. The 10 W/kg was considered to be 'most likely non-thermal' on the basis of measurements at 8.2 W/kg in dead and anaesthetized animals. So memory may be influenced by high-level UMTS signals, but a thermal effect cannot be excluded.

Sirav and Seyhan (2011) studied the effect of continuous-wave 900 and 1800 MHz exposure on the permeability of the blood-brain barrier (BBB) in rats. The animals were exposed for 20 min at SARs of 4.26 mW/kg and 1.46 mW/kg, respectively, under anaesthesia. No effect was observed in female rats, but in male rats BBB permeability was detected. Similar observations were made in a previous study by the same group using higher SARs of approximately 35 mW/kg (900 MHz) and 10 mW/kg (1800 MHz) (Sirav and Seyhan, 2009). These findings are in contradiction with the current consensus of an absence of effect of RF exposure on the permeability of the BBB.

Bodera et al. (Bodera et al., 2012) studied the effect of a 15-min exposure to a continuous 1500 MHz field at 90 V/m, or a 1800 MHz GSM field at 20 V/m on the efficacy of the painkiller tramadol in rats (injected at the beginning of EMF exposure), using paw withdrawal to a thermal stimulus. Both types of EMF exposure reduced the effect of tramadol at 30 min after treatment, but the effect subsided at 60 min.

French researchers previously observed increased levels of glial fibrillary acidic protein (GFAP) in the brain of adult rats after exposure to a 900 MHz GSM signal, suggesting increased activity of astrocytes and possibly loss of neural tissue (Brillaud et al., 2007);(Mausset-Bonnefont et al., 2004). They repeated this experiment with older rats (Bouji et al., 2012). Six weeks old and 12 months old animals were exposed for 15 min at a SAR of 6 W/kg. GFAP expression, brain interleukins, plasma corticosterone, and emotional memory were also assessed. The result from the previous study was not reproduced: no effect was found on GFAP. They did find increased interleukin and enhanced contextual emotional memory in the older rats, and increased corticosterone in the young adults. This indicates an age dependence of the response to GSM exposure in neuro-immunity, stress and behavioural parameters.

Hao et al. (2013) exposed rats to a continuous 916 MHz field for 6 h per day, 5 days per week and 10 weeks. In the 4th and 5th week the average completion time and error rate of a spatial memory task in the exposed animals was increased compared to that of the controls. In the first and last three weeks there was no difference. Implanted electrodes revealed altered neuron activity throughout the experimental period. The dosimetry of this study was incomplete: while the authors state that the power density near the centre of the cage was 10 W/m^2 , the animals were free roaming, and the antenna was at some distance from one side of the cage. So the exposure was very inhomogeneous.

Ntzouni et al. (2011) assessed the effect of exposure to a 1800 MHz field at a SAR of 0.22 W/kg on an object recognition task in mice. In the "acute exposure" protocol, the animals were exposed during the habituation, training and test sessions, but not during the 10 min inter-trial interval where consolidation of stored object information takes place. Starting 10 days later, the same mice were exposed in the "chronic exposure-I" protocol for 17 days at 90 min per day. On the last day the memory task was performed with exposure now present only during the inter-trial interval. Daily exposure then continued for another 14 days (the "chronic exposure-II" protocol). One day later the memory test was performed without exposure present in any of the sessions. An effect was found only in "chronic exposure-I" suggesting an interaction of EMF with the consolidation phase of recognition memory processes.

The studies are summarized in the following table.

Studies on brain function and behaviour				
Reference	Exposure type, schedule	Exposure level	Effect	Response
Prochnow et al (2011)	UMTS 120 min	SAR = 2, 10 W/kg	Stress hormones, memory	+, possibly thermal effect
Sirav and Seyhan (2011)	900, 1800 MHz 20 min	SAR = 1.46, 4.26 mW/kg	Blood-brain barrier	- females + males
Bodera et al (2012)	1500 MHz CW 15-min	20 V/m	Effect painkiller	+ @30 min - @60 min
Bouji et al, 2012	900 MHz GSM 15 min	SAR = 6 W/kg	GFAP expression, brain interleukins, plasma corticosterone, memory	- GFAP + interleukin, memory (adults) + corticosterone (young)
Hao et al (2012)	916 MHz 6 h/d, 5 d/wk, 10 wk	10 W/m ²	Memory	+ inhomogeneous exposure
Ntzouni et al (2011)	1800 MHz Acute:during testing Chronic: 90 min/d, 17 d	SAR = 0.22 W/kg	Memory	+

Conclusion on brain function and behaviour

In the previous Council report it was concluded that studies indicated that exposure to a mobile telephone signal at a SAR of 1.5 W/kg and higher may result in a response in hippocampal neurons that indicates activation in response to injury. This might have an effect on memory and cognitive functions. Several recent studies discussed in the present report also indicate effects on memory, also at low SAR levels. Because of the variety of types and schedules of exposure and endpoints used, it is very difficult to draw any general conclusions, but it cannot be excluded that there are effects also at non-thermal exposure levels. If this can be extrapolated to humans is still an open question, primarily because the exposure in the animals is always to the entire brain, while it is only local in humans.

Brain chemistry and physiology

Masuda et al. (2011b) locally exposed rat brain cortex tissue to 2-GHz RF at 10.5, 40.3, 130, and 263 W/kg for 18 min. Local cerebral blood flow (CBF) and temperatures in the target area and the rectum increased. The CBF elevation seemed to be related to the rise in target temperature, but not to the rectal temperature.

Noor et al. (2011) exposed young and adult rats to a 900 MHz GSM signal for 1 h per day at a SAR of 1.165 W/kg and assessed the levels of amino acid neurotransmitters in the midbrain, cerebellum and medulla after 1 hour, 1 month, 2 months and 4 months of exposure and 1 month after discontinuing exposure at 4 months. They found changes in various neurotransmitters at various points in time, but without any clear pattern. Moreover, most of the statistically significant changes were very small and the larger ones could not be logically explained. These seemingly random observations might be explained by the small number of 5-8 animals per group. The authors also provide an “equilibrium ratio%” between the inhibitory and excitatory amino acids which was supposed to indicate a state of neurochemical inhibition. It is not clear how this was calculated and at what percentage the states of excitement and inhibition were thought to be present. So it is not possible to draw any conclusions from this paper.

Jorge-Mora et al. (2011) investigated the effects of single and repeated exposure to 2.45 GHz RF fields on the rat hypothalamus, which regulates homeostasis, in particular those structures that respond to a variety of stimuli, such as heating or immobilization stress. They assessed the expression of the protein c-Fos that is considered to be indicative of activation of these structures. The animals were exposed once or ten times in 2 weeks at a midbrain SAR level of 0.08 W/kg or 0.3 W/kg. These SAR levels were assessed in great detail. The high SAR triggered an increase in c-Fos marker at 90 min and at 24 h after exposure, while the low SAR did so only after 24 h. Repeated exposure at the low SAR resulted in a more than 2 times stronger response than a single exposure. These results show that the hypothalamus is responsive to RF exposure at non-thermal levels, and that there is an exposure response and an accumulation of effect, or, as the authors suggested, a reduction of the threshold for stimulation after repeated exposures.

Paulraj and Behari (2012) exposed rats to 9.9 GHz (square wave modulated, 1 kHz) at an estimated whole body SAR of 1.0 W/kg for 2 h per day for 35 days and studied biochemical changes in brain tissue. In vitro calcium ion efflux from brain tissue was increased already after 20 min exposure and did not increase any further in the brains of animals repeatedly exposed. Calcium-dependent protein kinase (PKC) was decreased in the exposed animals, while ornithine decarboxylase (ODC) was increased. Similar effects were also observed in an earlier study employing 2.45 GHz exposure and an SAR of 0.11 W/kg (Paulraj and Behari, 2002). The authors speculated that these alterations may affect the development and functioning of the brain.

The same group, Kesari et al. (2012), exposed rats to 2.45 GHz for 2 h a day for 45 days, at an estimated whole-body SAR of 0.14 W/kg. Pineal melatonin was reduced and brain creatine kinase, caspase 3, and calcium ion concentration increased after exposure, thus confirming results from previous studies.

Maskey et al. (2012) exposed three groups of 9 mice each to 835 MHz RF EMF at 0, 1.6 and 4.0 W/kg, for 8 h per day and 1 month. They subsequently studied the immunoreactivity of several proteins involved in calcium homeostasis in the brain under the assumption that disturbance of calcium levels may lead to cell death and brain injury. Such effects were indeed observed in both groups exposed to the RF fields, with a stronger effect in the higher SAR group.

Nittby et al. (2012) used RF EMF exposure to induce analgesia in snails. They exposed snails for 1 h to a 1900 MHz mobile phone signal at a SAR of 48 mW/kg. Before and after exposure, the snails were subjected to thermal pain by being placed on a hot plate and the reaction time for retraction from the hot plate was measured. The exposed snails were less sensitive to thermal pain as compared to the sham controls.

Carballo-Quintás et al. (2011) used an experimental epilepsy rat model to study the effects of a 900 MHz GSM signal on seizures and brain physiology. They exposed the animals for 2 h, starting 5 min after administration of a sub-convulsive dose of picrotoxin or sham treatment, at levels resulting in a brain SAR of 1.32-1.44 W/kg. At 90 min and even more at 24 h after GSM exposure alterations in c-fos expression were observed, both in picrotoxin treated and untreated animals. The effect subsided, but was still observable in some brain areas at three days after treatment. So both RF EMF as well as picrotoxin resulted in effects in brain tissue, and the effects of both agents added up.

Fragopoulou et al. (2012) performed a proteomics analysis in the brain of mice exposed to either a mobile phone or a DECT signal. The animals were exposed to a GSM 900 MHz signal for 3 h per day daily for 8 months, at a SAR of 0.17-0.37 W/kg, or to a 1900 MHz DECT base station signal at a SAR of 0.012-0.028 W/kg for 8 h/day daily for 8 months. The expression of 143 proteins was altered, including several proteins related to neural function. The relevance of these changes cannot be determined, however, and the inference of the authors that they might explain human health problems such as headaches, sleep disturbance, fatigue, memory deficits, and brain tumour induction is yet unfounded.

The studies are summarized in the following table.

Studies on brain chemistry and physiology

Reference	Exposure type, schedule	Exposure level	Effect	Response
Masuda et al (2011)	2 GHz 18 min	SAR = 10.5, 40.3, 130, 263 W/kg	Cerebral blood flow	+
Noor et al (2011)	900 MHz GSM 1 h/d	SAR = 1.165 W/kg	Neurotransmitters	+, no pattern
Jorge-Mora et al (2011)	2.45 GHz 1x, 10x in 2 wk	SAR = 0.08, 0.3 W/kg	c-fos in hypothalamus	+
Paulraj and Behari (2012)	9.9 GHz, 1 kHz square wave modulated 2 h/d, 35 d	SAR = 1.0 W/kg	Calcium ion efflux Ca-dependent protein kinase Ornithine decarboxylase	+
Kesari et al (2012)	2.45 GHz 2 h/d, 45 d	SAR = 0.14 W/kg	Pineal melatonin Creatine kinase, caspase 3, and calcium ion concentration	+
Maskey et al (2012)	835 MHz 8 h/d, 1 mo	SAR = 0, 1.6, 4.0 W/kg	Immunoreactivity of several proteins involved in calcium homeostasis	+
Nittby et al (2012)	1900 MHz mobile phone 1 h	SAR = 48 mW/kg	Analgesia	+
Carballo-Quintás et al (2011)	900 MHz GSM 2 h	SAR = 1.32-1.44 W/kg	c-fos expression	+
Fragopoulou et al (2012)	900 MHz GSM 3 h/d, 8 mo 1900 MHz DECT 8 h/d, 8 mo	SAR = 0.17-0.37 W/kg SAR = 0.012- 0.028 W/kg	Proteomics	+

Conclusion on brain chemistry and physiology

These studies indicate that repeated exposure to mobile phone signals may result in changes in expression of proteins and changes in calcium homeostasis and cerebral blood flow. However, whether these alterations lead to, or are indicative of, adverse health effects is not clear.

Brain oxidative stress

Several studies have investigated oxidative stress in brain tissue. An increase in oxidative stress may result in damage to biomolecules and alterations in functioning and survival of brain cells.

Maaroufi et al. (2011) investigated a possible relationship between iron status, exposure to EMF, and brain oxidative stress in young adult rats. Animals were exposed to 150 kHz EMF at 6.25 μ T, 1 h per day for 21 days, combined with iron overload. Iron did not induce oxidative stress, but stimulated antioxidant defences in the brain. EMF exposure, on the contrary, stimulated lipid peroxidation, and did not affect antioxidant defences. EMF combined with iron overload further increased oxidative stress and abolished the increase in antioxidant defences triggered by iron overload.

Dasdag et al. (2012) studied the effect of 900 MHz GSM signals on oxidative stress in rat brain (by measuring malondialdehyde) and on proteins associated with Alzheimers disease (beta amyloid protein and protein carbonyl). The latter was triggered by studies of Arendash et al (2010) and Söderqvist et al (2010) that indicated beneficial effects of RF EMF exposure on molecular markers of Alzheimer's in mice and men, respectively. In the present experiments, the rats heads were exposed for 2 h per day, 7 days per week, for 10 months. The SAR was calculated at 0.17-0.58 W/kg. The levels of both proteins and oxidative stress markers were increased in the brains of exposed animals, but only protein carbonyl statistically significant so.

Jing et al. (2012) exposed pregnant rats for 20 days during 0, 10, 30 or 60 min 3 times per day to RF EMF from a mobile phone. They aimed to study oxidative stress and the level of neurotransmitters in the brains of foetal rats. The day after the last exposure, foetal rats were removed and the levels of several antioxidants and neurotransmitters were determined in brain tissue. Markers showed an increased oxidative stress in the 30 min and 60 min groups. Neurotransmitter levels were increased in the 10 min group and decreased in the 60 min group. No information was provided on exposure level and frequency, so this study cannot be interpreted.

The following studies are reported, but have not been taken into account in the overall analysis because of incomplete or missing dosimetry.

Dogan et al. (2012) exposed rats to the multiband signal from a 3G mobile phone, operating with a complex signal type and sequence for 40 min per day during 21 days. They determined the levels of several marker substances for brain metabolism and oxidative status. No differences were observed between exposed and sham exposed animals, but the exposure was not well defined. The mobile phones were attached to the bottom of the cages, where the animals could roam freely. No SAR levels were provided.

Kesari et al. (2011a) exposed rats to a GSM signal from a mobile phone for 2 h per day for 45 days. The phone was said to be in standby mode responding to a missed call, which resulted in 1-min transmissions separated by 15 sec. The maximum SAR of the phones was 0.9 W/kg, but the actual SARs are not provided. Several parameters indicative for oxidative stress were determined and showed an increase in those endpoints.

Imge et al. (2010) investigated the effect of exposure of rats to a 900 MHz GSM signal on oxidative stress in brain tissue. The phones were located above the cages at circa 10 cm from

the animals and in standby mode, and were called 4 x 10 min per day for 4 weeks. Also in this study, only the maximum SAR of the phones was given (in this case 0.95 W/kg), and the actual SARs not provided. Several parameters indicative for oxidative stress were determined and showed an increase in oxidative stress that was partly counteracted by administration of vitamin C.

Avci et al. (2012) exposed rats to 1.8 GHz, 1 h per day for three weeks, resulting in a whole body SAR of 0.4 W/kg. The SAR in the brain was probably higher, since the animals were kept in restrainers facing the antenna and consequently were exposed head-on. The effect of this exposure on oxidative stress parameters in brain and serum was determined, and the effect on this of administration of garlic extract. In the brain, protein oxidation was increased after RF exposure and garlic administration reduced this. The serum nitric oxide levels also increased after RF exposure, but in this case there was no effect of garlic administration. The levels of an indicator of lipid oxidation, malondialdehyde, in both brain and serum were not altered by RF exposure

The results of the oxidative stress studies are summarized in the following table. RF EMF do seem to be able to induce oxidative stress in brain tissue, but most studies cannot be properly interpreted due to lack of adequate exposure information.

A summary of these results is presented in the following table.

<u>Studies on oxidative stress in brain</u>			
Reference	Exposure type, schedule	Exposure level	Effect
Maaroufi et al (2011)	150 kHz 1 h/d, 21 d	6.25 μ T	+
Dasdag et al (2012)	900 MHz 2 h/d, 7 d/wk, 10 mo	SAR=0.17-0.58 W/kg	+
Jing et al (2012)	0, 10, 30 or 60 min 3x/d, 20 d	No exposure info	- but not interpretable
Dogan et al (2012)	3G mobile phone 40 min/d, 21 d	No exposure info	- but not interpretable
Kesari et al (2011)	GSM phone 2 h/d, 45 d	No exposure info	+ but not interpretable
Imge et al (2010)	900 MHz GSM 4 x 10 min/d, 4 wk	No exposure info	+ but not interpretable
Avci et al (2012)	1.8 GHz 1 h/d, 3 wk	SAR=0.4 W/kg	+ but incomplete dosimetry

Conclusion on oxidative stress in brain

There are indications of oxidative stress in brain tissue, but a number of studies lack adequate dosimetry and are hence not interpretable.

Oxidative stress – other tissues

A number of studies looked at oxidative stress in several other tissues.

Ozgur et al. (2010) exposed guinea pigs to an 1800 MHz GSM signal at a whole body SAR of 0.38 W/kg, for 10 or 20 min per day for 7 days. They observed changes in various parameters in the liver that are indicative of oxidative stress, with the extent dependent on exposure time. Treatment with antioxidants reduced the effects.

In another study from the same group, Esmekaya et al. (2011) observed oxidative stress in heart, lung, testis and liver of rats. In this study, exposure was to a 900 MHz pulse-modulated field for 20 min per day for 3 weeks, at a SAR of 1.20 W/kg.

Jelodar et al. (2012) exposed rats to a 900 MHz base station signal for 4 h per day for 45 days. The SAR level was not provided, but the exposure was at a power density of 0.68 mW/cm² which was considered typical for environmental exposures. Several parameters indicated increased oxidative stress in the eye. Vitamin C administration counteracted these effects.

Aydin and Akar (2011), using the same exposure design as Avci et al.(2012), exposed young and adult rats to a 900 MHz GSM signal for 2 h/day for 45 days. The SAR was calculated to be 0.38-0.78 W/kg for the immature animals and 0.28-0.48 W/kg for the adults. Several parameters indicative for oxidative stress were measured in lymphoid organs (spleen, thymus, bone marrow), leukocytes and plasma. Exposure did increase oxidative stress in all these, and stronger in the young than in the adult animals. A 15-day recovery period after exposure showed only limited improvement, especially in the young rats.

Again, some data are not interpretable due to lack of proper dosimetric information.

Using the same exposure design as Dogan et al. (2012) described above, Demirel et al. (2012) studied oxidative stress parameters in the eye and blood of rats. No effects were observed, but the exposure was not well defined. The mobile phones were attached to the bottom of the cages, where the animals could roam freely. No SAR levels were provided.

Studies on oxidative stress in other tissues

Reference	Exposure type, schedule	Exposure level	Tissue / organ	Response
Ozgur et al (2010)	1800 MHz GSM 10, 20 min/d, 7 d	SAR = 0.38 W/kg	Liver	+
Esmekaya et al (2011)	900 MHz GSM 20 min/d, 3 wk	SAR = 1.20 W/kg	Heart, lung, testis, liver	+
Jelodar et al (2012)	900 MHz base station signal 4 h/d, 45 d	Power density = 0.68 mW/cm ²	Eye	+
Demirel et al (2012)	3G mobile phone 40 min/d, 21 d	No exposure info	Eye and blood	+ but not interpretable
Aydin and Akar (2011),	900 MHz GSM 2 h/d, 45 d	SAR = 0.38-0.78 W/kg (young); SAR = 0.28-0.48 W/kg (adults)	Lymphoid organs, leukocytes, plasma	+

Conclusion on oxidative stress in other tissues

Indications of oxidative stress after repeated exposures to mobile phone signals have been observed in tissues other than brain tissues. The exposure scenarios were not always reflecting real-life situations, but these studies showed in a variety of tissues that RF exposure may increase oxidative stress. This might increase the risk for adverse health effects, but as of yet these have not been demonstrated.

Genotoxicity

Kumar et al. (2010) exposed rats for 2 h a day for 45 days continuously at 10 GHz (SAR=0.014 W/kg) or 50 GHz (SAR=8.0 x10⁻⁴ W/kg). At the end of both treatments, micronuclei formation in blood cells was observed, as well as an increased ROS production and antioxidant enzyme activity in serum.

Trosic et al. (2011) exposed rats to a 915 MHz GSM signal at a whole-body SAR of 0.6 W/kg for 1 h per day, 7 days per /week and two weeks. They used the Comet assay to study DNA damage in kidney, liver and brain cells. Small effects were observed, but these were not significant.

Jiang et al. (2012) used the alkaline comet assay to assess DNA damage in blood leukocytes of mice after exposure to a dose of ionizing radiation preceded by exposure to 900 MHz RF EMF at a SAR of 0.55 W/kg for 4 hours per day. A 1 day pre-exposure did not modify DNA damage induced by ionizing radiation. Pre-exposure for 3, 5, 7 and 14 days progressively reduced the damage induced by ionizing radiation. This indicates that RF pre-exposure is capable of inducing an adaptive response.

Khalil et al. (2012) examined the effect of exposure to an 1800 MHz GSM signal on DNA damage in rats. The animals were exposed for 2 h at a SAR of 0.4-0.7 W/kg. A marker for free radical-induced DNA damage was measured in urine collected during the exposure and up to 2 h afterwards. DNA marker levels were increased in both exposed and sham exposed animals at 1 h of exposure and thereafter, but significantly stronger in the exposed animals. This indicates an effect of exposure on overall DNA damage in the animals.

The following study has not been included in the overall analysis due to incomplete dosimetry.

Güler et al. (2010) investigated DNA damage and lipid peroxidation in rabbit livers after exposure to an 1800 MHz GSM signal. Pregnant females were exposed or sham exposed for 15 min per day during 7 days. One month after birth, equal numbers of male and female rabbits from each of the two prenatal exposure groups were divided over exposure and sham groups. This resulted in four experimental groups: prenatal unexposed/postnatal unexposed; prenatal unexposed/postnatal exposed; prenatal exposed/postnatal unexposed; prenatal exposed/postnatal exposed. Whereas the prenatal exposure was the same for both sexes, the postnatal exposure differed: females were exposed for 15 min per day for 7 days and males for 14 days. The SAR was calculated at 1.8 W/kg, but it is not clear whether this applies to the pregnant dams or the young animals. In any case a homogeneous rabbit model was used and this does not take into account the inhomogeneous tissue distribution. In female animals one of two markers of lipid peroxidation and the marker for free radical-induced DNA damage were found to be increased in relation to postnatal exposure, while in male animals both markers for lipid peroxidation were increased in relation to prenatal exposure and no effect was found on DNA damage. These inconsistent results are difficult to explain, also in the light of the longer postnatal exposure of the males.

Cancer

Paulraj and Behari (2011) used two mouse tumour models to investigate the effect of exposure to RF fields. Skin tumours were induced by 7,12-dimethylbenz(a)anthracene (DMBA) and the animals were exposed to 16 Hz modulated 112 MHz at a SAR of 0.75 W/kg, or to 2.45 GHz at an SAR of 0.1 W/kg, for 2 h per day, 3 days per week during 16

weeks. In the other model, mice were transplanted intraperitoneally with Ehrlich ascites carcinoma cells and exposed to both types of fields for 14 days. Exposure to the RF alone did not result in tumour development and in neither of the two tumour models did RF exposure result in a significant effect of tumour incidence or growth.

Lee et al. (2011c) exposed lymphoma-prone mice to a combination of two types of mobile telecommunication signals: single code division multiple access (CDMA) and wideband code division multiple access (WCDMA) for 45 min per day, 5 days per week and 42 weeks. The total SAR was 4.0 W/kg. No effects were observed on survival and lymphoma incidence. Only for the occurrence of metastasis infiltration to the brain in lymphoma-bearing mice a difference was observed between exposed and control mice, but there was no consistent correlation (increase or decrease) observed between male and female mice. Infiltration in other organs was not different.

Bartsch et al. (2010) reported on four rat experiments involving long-term (24 and 17 months) and lifelong (36 and 37 months) exposure to a 900 MHz GSM signal at a SAR of 38-80 mW/kg that had been published earlier. No health effects were observed in the 24 and 17-months experiments, but in the life-long studies median survival was significantly shortened in the exposed animals. There appeared also to be an overall difference in mean survival time between the two experiments, which the authors suggest might be due to the different month of birth. From a comparison with other long term studies they also suggest that there may be an additional modulatory influence on a year-to-year basis related to changing solar activity during the 11-year sunspot cycle.

The following table provides a short summary and overview of the studies discussed above.

Studies on genotoxicity and cancer

Reference	Exposure type, schedule	Exposure level	Effect	Response
Kumar et al (2010)	10, 50 GHz 2 h/d, 45 d	SAR = 0.014 W/kg (10 GHz) SAR = 8.0 x10 ⁻⁴ W/kg (50 GHz)	micronuclei formation, ROS production	+
Trosić et al (2011)	915 MHz GSM 1 hd, 7 d/wk, 2 wk	SAR of 0.6 W/kg	DNA damage	-
Jiang et al (2012)	900 MHz 4 h/d, 1-14 d	SAR of 0.55 W/kg	DNA damage	+
Güler et al (2012)	1800 MHz GSM prenatal: 15 min/d, 7 d; postnatal:15 min/d, 7 d (female) 14 d (male)	SAR = 1.8 W/kg	DNA damage	+ (females) - (males)
Khalil et al (2012)	1800 MHz GSM2 h	SAR = 0.4-0.7 W/kg	DNA damage	+
Paulraj and Behari (2011)	16 Hz modulated 112 MHz, 2.45 GHz 2 h/d, 3 d/wk, 16 wk	SAR = 0.75 W/kg SAR = 0.1 W/kg	Skin tumours ascites carcinoma	-
Lee et al (2011)	CDMA, WDCMA 45 min/d, 5 d/wk, 42 wk	SAR = 4.0 W/kg	Lymphoma	-
Bartsch et al (2010)	900 MHz GSM24- 37 mo	SAR = 0.038-0.08 W/kg	Survival	+

Conclusion on genotoxicity and cancer

In previous SSM reports it was concluded that there are no indications that RF EMF by itself may have a carcinogenic effect. The newer studies discussed here show mixed results. Some studies indicate an increase in DNA damage, others do not, while no effect was observed on various types of tumours.

Fertility

Possible effects on, especially male, fertility have received increasing attention lately. This concern is related to the fact that many people keep their mobile phone in a trouser pocket.

Imai et al. (2011) exposed young male rats to a 1.95 GHz signal used in Japanese mobile telecommunication, for 5 h per day, 7 days per week and 5 weeks (during the period of reproductive maturation in the rat). The whole-body SAR was 0.4 or 0.08 W/kg. They did not observe any changes in testicular morphology or function, with the exception of an increased sperm count with the SAR of 0.4 W/kg.

Lee et al. (2011a) exposed rats to a combination of two types of mobile telecommunication signals: single code division multiple access (CDMA) and wideband code division multiple access (WCDMA) for 45 min per day, 5 days per week and 12 weeks. The total SAR was 4.0 W/kg. On the basis of morphological and various biochemical parameters they conclude that the exposure did not have any observable adverse effects on rat spermatogenesis.

The following studies are reported but not used in the overall analysis because of incomplete and unclear dosimetry.

Kesari et al. (2010) exposed male rats to the signal from an unspecified mobile phone that resulted in a maximum SAR of 0.9 W/kg according to the manufacturer. This gives no information about the actual exposure of the animals. The authors observed a decrease in sperm count and an increase in apoptosis, but due to the lack of adequate dosimetric information these results cannot be properly interpreted.

In another publication (Kesari et al., 2011b) the same authors did specify that the mobile phone emitted a GSM 900 MHz signal and that was used in standby mode. The animals were thus exposed for 2 h per day and 35 days. The results were contrasting. The levels of several antioxidant enzymes decreased, while that of another was increased. Reactive oxygen was also increased and regulator enzymes decreased. The number of micronuclei, indicative for DNA damage, decreased. A change in sperm cell cycle was also observed. The authors suggest that these findings indicate that exposure might affect the fertilizing potential of spermatozoa, but this is not supported by the contrasting observations. Furthermore, it is highly unlikely that in standby mode a SAR of 0.9 W/kg is obtained, since mobile phones in standby only emit a very short signal at certain intervals. Exposure from phones in standby mode is effectively nil (Hansson Mild et al., 2012).

A third paper of this Indian research group describes effects of a combination of a RF field and a pulsed low frequency field on the reproductive system of male rats (Kumar et al., 2011). The animals were exposed to either a 50-Hz modulated 2.45 GHz field, or a pulsed 100 Hz field or a combination of the two for 2 h per day and 60 days. They calculated a SAR for the 2.54 GHz exposure of 0.014 W/kg. The exposure level of the pulsed 100 Hz fields is not provided. Significant increases in markers of apoptosis and sperm abnormalities and significant decreases in testosterone and the antioxidant melatonin were observed after RF

exposure. The low frequency field reduced these effects, but this field by itself also induced a small increase in the apoptosis marker and a decrease in melatonin and testosterone. The authors suggest that their observations indicate that reactive oxygen species are the primary cause of DNA damage, but this cannot be directly derived from the data. The finding that pulsed low frequency field exposure reduces the effect of the RF exposure is puzzling, since the low frequency field also induces the same effects, but to a lesser extent, by itself.

In yet another study on fertility of male rats exposed to mobile phone RF fields, Kesari and Behari (2012) exposed the animals 2 h per day for 45 days, presumably again with the phone in standby mode. They observed a decrease in the level of testosterone and an increase in a marker enzyme of apoptosis, as well as changes in sperm morphology. In a separate experiment, male and female animals were exposed using the same protocol and mated after the last exposure. Compared to sham-exposed animals, the number and weight of progeny from the exposed rats was decreased. Since also females were exposed, it is difficult to attribute this to changes in male fertility. Again, the authors suggest that their observations indicate that reactive oxygen species are the primary cause of the observed effects, but again this cannot be directly derived from the data.

Al-Damegh (2012) exposed male rats to the signal from a mobile phone placed at 50 cm from the cage, but it is not clear at what frequency the phone operated and what the exposure level was. The exposure was for 15, 30 or 60 min per day for 14 days. Morphological alterations in the testes were observed in the exposed animals, markers for oxidative stress were increased, and levels of two antioxidants were decreased and that of a third one increased. The biochemical effects were mostly counteracted by daily administration of vitamins C or E during the exposure period.

Atasoy et al. (2012) exposed rats to the signal from an indoor Wi-Fi Internet access device operating at 2.437 GHz. Exposure was continuous for 24 h per day for 20 weeks. The exposure level is unknown, however, and most likely also not identical for all animals. Increased levels of markers for oxidative DNA damage were observed as well as decreased levels of antioxidants. Other markers for oxidative stress did not change.

Reproduction and development

Sambucci et al. (2010) prenatally exposed mice to a Wi-Fi signal of 2.45 GHz at a SAR of 4 W/kg for 2 h per day and 14 days. They did not observe any effects on mating success, average number of progeny per litter and body weight at birth. In a follow-up study, Sambucci et al. (2011) exposed new-born mice to a Wi-Fi signal of 2.45 GHz at a SAR of 0.08 or 4 W/kg for 2 h per day, 5 days per week, and 5 consecutive weeks. This did not result in any effects on body weight and development.

Orendáčová et al. (2011) investigated the effect of RF exposure on the development of the nervous system in rats. The animals were exposed at an age of 7 or 28 days to pulsed 2.45 GHz fields for 2 h at a mean power density of 2 – 6.7 mW/cm². A marker of cell death was increased in the subventricular zone in the brains of rats of both ages. This was not the case in the rostral migratory stream (RMS), a zone of formation of new cells. Exposed 7-d old animals also showed early maturation of cells within the RMS, while no such effects was seen in the 28-d old animals. This indicates that the exposure resulted in age-related changes in the production and maturation of new neurological cells.

The studies are summarized in the following table.

Studies on fertility, reproduction and development

Reference	Exposure type, schedule	Exposure level	Effect	Response
Kesari et al (2010)	Mobile phone 2 h/d, 35 d	Not provided	Sperm count, apoptosis	+ but not interpretable
Kesari et al (2011)	GSM 900 MHz 2 h/d, 35 d	Not provided	Oxidative stress testes, sperm cell cycle	+ but not interpretable
Kumar et al (2011)	2.45 GHz, 50 Hz modulated; 100 Hz, pulsed 2 h/d, 60 d	SAR = 0.014 W/kg (2.54 GHz)	Sperm development, testosterone, oxidative stress testes	+ but not interpretable
Kesari and Behari (2012)	GSM 900 MHz 2 h/d, 45 d	Not provided	Sperm development, testosterone, oxidative stress testes, fertility	+ but not interpretable
Imai et al (2011)	1.95 GHz 5 h/d, 7 d/wk, 5 wk	SAR = 0.08, 0.4 W/kg	Testicular morphology, function	+ (increased sperm count @ 0.4 W/kg)
Al-Damegh (2012)	Mobile phone 15, 30, 60 min/d, 14 d		testicular morphology oxidative stress	+ but not interpretable
Lee et al (2011)	CDMA + WCDMA 45 min/d, 5 d/wk, 12 wk	SAR = 4.0 W/kg	testicular morphology, biochemistry	-
Sambucci et al (2010)	2.45 GHz WiFi 2 h/d, 14 d	SAR = 4 W/kg	Reproductive success	-
Sambucci et al (2011)	2.45 GHz WiFi 2 h/d, 5 d/wk, 5 wk	SAR = 0.08, 4 W/kg	Development	-
Orendáčová et al (2011)	2.45 GHz, pulsed 2 h	2 – 6.7 mW/cm ²	Production and maturation of new neurological cells	+ (age related)

Conclusion on fertility, reproduction and development

In general, an influence on male fertility has been observed in a series of studies by one research group from India, but not by several other groups. The Indian results, however, are not possible to interpret due to a bad experimental design and missing information on exposure.

Auditory system

Effects on hearing are also studied because of the close vicinity of a mobile phone to the ear during speech calls.

Kayabasoglu et al. (2011) investigated the effect of exposure to RF fields from a 900 MHz and a 1800 MHz mobile phone on inner ear function in new-born and adult rats. Exposure was for 6 h per day on 30 consecutive days, but information on the level of exposure and which groups were exposed to what frequency is not provided. Before and after the exposure

period, distortion product otoacoustic emissions as a measure of inner ear function were determined. No effects were found in either the new-born or adult rats. However, since actual exposure levels are not provided, this study cannot be properly interpreted.

Kaprana et al. (2011) used rabbits to study the effects of a 900 MHz GSM signal on auditory brainstem responses during a 1 h exposure with an average output power of 0.22 W. A small delay in signal transduction in the exposed ear was observed after 15, 45 and 60 min of exposure. No effects were observed in the other ear. At 24 h after the exposure the effect had disappeared. According to the authors the observed effect fits the pattern of general responses to a stressor.

Immune system

In the 1970's and 1980's studies performed in the Soviet Union showed immunological and reproductive effects of long-term low-level exposure of rats to RF electromagnetic fields. These studies were used in the development of Russian exposure standards, but only published in Russian. Therefore the basis of the current Russian standards was difficult to evaluate. Replications of the major findings of these studies were performed in a concerted action in Russian and French laboratories, using the exact same protocols, but slightly different rat strains. Exposure was to 2450 MHz continuous wave RF fields for 7 h per day, 5 days per week for a total of 30 days, with a whole-body SAR of 0.16 W/kg. The authors of the paper presenting the Russian data concluded that effects on both the immune system and reproduction had been observed (Grigoriev et al., 2010), while the French researchers did not find any effects (Poullietier de Gannes et al., 2011). This seeming discrepancy was discussed by the International Oversight Committee of the study, that concluded that the Russian study had not presented convincing evidence of effects and that it was not likely that the different rat strains used could explain the differences between the Russian and French studies (Repacholi et al., 2011).

Logani et al. (2012) studied in mice the protective effect of millimetre waves from the toxic side effects of an anticancer drug, cyclophosphamide, on certain immune functions and the role of endogenous opioids in this process. Mice were exposed on the nose to 42.2 GHz fields for 30 min per day and 3 days, at peak SAR of 681 W/kg. This resulted in a temperature increase of 1.55 °C. Treatment with cyclophosphamide suppressed the formation of certain cytokines and shifted the overall cytokine balance. Exposure to the RF field counteracted this suppression and restored the balance. Additional experiments with specific opioid receptor antagonists showed that endogenous opioids are involved in immunomodulation by millimetre waves.

Jin et al. (2012) studied the effects on the rat immune system of exposure to a combination of two types of mobile telecommunication signals: single code division multiple access (CDMA, 849 MHz) and wideband code division multiple access (WCDMA, 1.95 GHz) for 45 min per day, 5 days per week and 8 weeks, at a total SAR of 4.0 W/kg. No effects on a large number of different immune parameters were found.

Sambucci et al. (2010) prenatally exposed mice to a Wi-Fi signal of 2.45 GHz at a SAR of 4 W/kg for 2 h per day and 14 days. At 5 and 26 weeks of age no effects on the immune system were found. In a follow-up study, Sambucci et al. (2011) exposed new-born mice to a Wi-Fi signal of 2.45 GHz at a SAR of 0.08 or 4 W/kg for 2 h per day, 5 days per week, and 5 consecutive weeks. Also in the new-born mice these treatments did not result in any effects on immunological parameters.

Cardiovascular system

The only animal study on cardiovascular effects cannot be used due to missing dosimetry.

Colak et al. (2012) investigated the effects of exposure to RF fields from a 3G mobile phone operating at 1800-1900 MHz, on heart rate, blood pressure and ECG parameters in rats. Exposure took place during 20 days, for 40 min per day, of which 20 min active (in speech mode) and 20 min passive (in listening mode). The results did not show any effect on blood pressure, heart rate and ECG parameters. Administration of melatonin did not change these results. However, since actual exposure levels are not provided, this study cannot be properly interpreted.

The results of the studies on hearing, the immune system and the cardiovascular system are summarized in the table.

Studies on auditory, immune, cardiovascular system

Reference	Exposure type, schedule	Exposure level	Effect	Response
Kayabasoglu et al (2011)	900, 1800 MHz mobile phone 6 h/d, 30 d	Not provided	Inner ear function	- but not interpretable
Kaprana et al (2011)	900 MHz GSM 1 h	0.22 W output power	Auditory brainstem responses	+
Grigoriev et al 2010 Pouletier de Gannes et al 2009	2450 MHz 7 h/d, 5 d/wk, 30 d	SAR = 0.16 W/kg	Immune system, reproduction	+ (Russian studies) - (French studies)
Logani et al (2012)	42.2 GHz	Local peak SAR = 681 W/kg	Immune functions	+ might be thermal effect
Jin et al (2012)	CDMA, 849 MHz + WCDMA, 1.95 GHz 45 min/d, 5 d/wk, 8 wk	SAR = 4.0 W/kg	Immune functions	-
Sambucci et al (2010)	2.45 GHz WiFi 2 h/d, 14 d	SAR = 4 W/kg	Immune functions	-
Sambucci et al (2011)	2.45 GHz WiFi 2 h/d, 5 d/wk, 5 wk	SAR = 0.08, 4 W/kg	Immune functions	-
Colak et al (2012)	1800-1900 MHz 40 min/d, 20 d	Not provided	Blood pressure, heart rate, ECG	- but not interpretable

Conclusion on auditory, immune, cardiovascular system

An indication for an effect on the inner ear was found, but no effect on the immune system.

Overall conclusion on animal studies

Animal studies show that effects of RF EMF on brain function are possible and that in a number of tissues, including the brain, an increased oxidative stress may be induced by RF EMF exposure. This may enhance the risk for health effects. The mixed effects in the carcinogenicity studies provide some, but unreplicated and not very reliable indications of increased DNA damage after RF EMF exposure. No increased cancer risks were observed, however. The results of those fertility studies that have sufficient quality did not show any

effect from RF EMF exposure. Finally, an indication for an effect on the inner ear was found, but no effects on the immune system. Most of these findings are from single studies that need replications.

The Council notes that still a considerable number of studies could not be evaluated because of design problems. Especially noteworthy is that often proper information on exposure is lacking. This is a waste of effort and resources. Animal studies really have to use better designs in order to be useful for health risk analysis.

Human studies

The previous Council report (SSM, 2010:44) concluded that the effects of GSM EMF on the alpha-band in sleep EEG should be further studied, and preferably also in animal models in order to reveal the nature and mechanisms of this phenomenon. Imaging studies (e.g., PET) should be continued since they seemed to offer a promising way to evaluate the brain functions possibly vulnerable to RF EMF and there still is a standing order for studies on long-term exposure effects and studies on children. The studies published in peer-review journals since the last SSM report cover some of these issues.

Reviews and methodological issues

Three different reviews have appeared since the last SSM report. Regel and Achermann (2011) evaluate the results from studies on RF EMF effects on cognitive functions. In this thorough analysis they go through various confounding effects from experimental designs to dosimetry, and conclude with a critical evaluation of the previous literature and recommendations for future research. They again bring up the important issues of studying the long-term effects, children, and the new issue in literature, the “responders” and “non-responders”, originally demonstrated by Hinrikus et al. (2008a). They do not, however, touch the one very important factor contributing to the paradoxical variability of the results reported so far – statistics. These issues are evaluated in both cognitive, electrophysiological and imaging studies by Kwon and Hämäläinen (2011) whose main message is the requirement of proper statistical analyses in the reports.

Juutilainen et al. (2011) published an important review with the idea of exploring what impact the pulsing vs. continuous field has on the effects seen in reports. Pulsing of the EMF seems to have an effect of its own, but it seems to disappear due to the new technology (3G, UMTS) with very high pulsing frequency (see e.g. (Hinrikus et al., 2008b); on the effects of modulation pulsing to 450 MHz EMF effects). The final conclusion by Juutilainen et al. (2011) is that of the 18 studies on nervous system effects in human volunteers, only 6 reported modulation specific effects. Increased power in alpha EEG band (8-12 Hz) has been seen in some studies, most of which have used GSM-type modulation. The consistency of the positive findings indicates that there may be reproducible modulation-specific effects on the human central nervous system. The interpretation of the EEG findings is complicated by the presence of conducting EEG electrodes and leads, as they have been shown to enhance the local electromagnetic fields during RF exposure (Angelone et al., 2010; in Juutilainen et al., (2011)). However, in some sleep studies these effects have been obtained not during but after the exposure to GSM EMF. The more crucial question is whether these effects have any true meaning to the functioning and well-being of the organisms. As stated in previous Council reports, the presence and the type of these effects have to be tested in simpler preparations, e.g. cell cultures.

Cognition

Barth et al. (Barth et al., 2011) published a meta-analysis of short-term exposure to mobile phone EMF on human cognitive performance. Seventeen studies fulfilling the criteria (study design, documentation of means and standard deviations) were included in the analysis. No effects of either GSM or UMTS exposure were found. The authors conclude that "substantial short-term impact of mobile phones on cognitive performance can essentially be ruled out".

Sauter et al. (2011) published a study in which both GSM and WCDMA long-term (7h 15 min) EMF exposure was applied to 30 healthy male subjects (25.3 ± 2.6 years of average age). Three exposure conditions (sham, GSM 900 and WCDMA) were used during the nine study days for each subject in a randomly assigned and balanced order. All cognitive tests were presented twice (morning and afternoon) on each study day within a fixed timeframe. The cognitive functions were evaluated with well documented and widely used tests for divided attention, selective attention and vigilance, and working memory. After correction for multiple testing, only time-of-day effects remained significant in two tests. No effects of long-term exposure of either GSM or UMTS were obtained.

Could the cognitive effects claimed to be due to mobile phone EMF be due to some other factors in the experimental setup, known to affect performance? Hareuveny et al. (Hareuveny et al., 2011) "exposed" 29 right-handed male subjects with mobile phones attached to the right and left side of the head (only sham) performing a spatial working memory task with either the right or left hand. The results were exactly the same as reported previously in their two studies (Eliyahu et al., 2006, Luria et al., 2009); in Hareuveny et al. (2011) with real exposures. The conclusion is that the experimental setup itself may affect the results significantly (see also Kwon et al. (2008)) without any true exposure to EMF.

Electrophysiology

In many of the studies presented below, also cognitive tasks have been applied. As a general conclusion, no effects of EMF on cognitive functions could be seen. This is the same general finding as in the previous section.

Leung et al. (2011) studied the effects of GSM and 3G mobile phone exposures on cognitive functions and brain electrophysiology (event-related-potentials, ERPs, which are averaged EEG responses related to sensory stimuli or responses of the subject, and event-related-desynchronization/synchronization, ERD/ERS responses) in a double-blind cross-over study in 41 adolescents (13-15 year of age), young adults (42; 19-40 years of age) and older adults (20, 55-70 years of age), both sexes. The key issue in this study was that the tasks were tailored to each individual's ability level. The exposures were the same as applied in their previous studies and SAR was well taken care of. The first cognitive task was an auditory 3-stimulus oddball (go/no-go) task, and ERPs were determined as an electrophysiological measure. The second task was a commonly used visual working memory task (N-back task), where the cognitive load is controlled by instructing the subject to keep in mind an increasing number of consonants presented before the present one on the screen. ERD/ERS responses were determined here as an electrophysiological measure. The two dummy mobile phones were attached on both sides of the head comparable to normal ("touch") use. The results of the 3-stimulus oddball-task did not show any behavioural effects by either GSM or 3G exposure, whereas in electrophysiological responses augmented N1 components were found during GSM exposure independent of the age group. In the N-back task the adolescents performed less accurately during the 3G exposure compared to sham, and delayed ERD/ERS responses of the alpha power were found in both GSM and 3G conditions compared to sham

and independent of age group. The authors cannot propose any reasonable explanation to the inconsistency within their results and the inconsistency with other studies (see e.g. (SSM, 2009:36, SSM, 2010:44); (Kwon and Hamalainen, 2011)). They underline the importance to fit the difficulty level of the tasks individually to the subjects. This indeed seems to produce a non-significant difference in behavioural results in the 3-stimulus oddball task. No individual assessment of the difficulty level is described for the N-back task. Effect sizes, which seemingly are very small, are lacking in the report.

Evidence that the EEG modulations seen during exposure to GSM EMF is due to pulse modulation of the signal comes from a recent study by Trunk et al. (2013), who applied UMTS (3G) exposure. They first measured spontaneous EEG in 17 subjects, and then determined auditory evoked potentials (ERPs) and automatic deviance detection processes (mismatch negativity, MMN) in 26 subjects while they were exposed (double blind) to either genuine or sham EMF. The 30 min UMTS exposure did not induce any changes in any EEG spectral band, or in latency or amplitude of any ERP components.

Vecchio et al. (2012) describe faster reaction times in a go/no-go task for 11 healthy adults, with also less power decrease (indexing lower cortical activity) in high-frequency (10-12 Hz) alpha rhythms after a 45 min GSM exposure compared to that determined before the exposure. No statistically significant changes were obtained after the sham session.

Colletti et al. (2011) determined changes in cochlear nerve action potentials during operation (retrosigmoid vestibular neurectomy involving craniotomy exposing the nerve) while exposed to EMF emitted by a 900MHz GSM mobile phone known to have a maximum SAR of 0.82 W/kg. No SAR was determined during the experiment. The acoustically evoked cochlear compound nerve action potentials (CNAPs) were directly recorded from the exposed nerve of seven patients during the phone in stand-by mode (2 min) and then during the cochlear nerve exposure (5 min) to the EMF. Five patients formed the control group with sham exposure. After the exposure to the mobile phone, the potentials were recorded for 10 more minutes. All patients in the experimental group showed a substantial decrease in amplitude and a significant increase of latency on CNAPs during the 5 min exposure to EMF, and lasting for a period of around 5 min after the exposure. No changes in amplitudes or latencies of CNAPs were obtained in the control group. Simultaneously measured auditory brainstem responses (ABRs) from the vertex as normal EEG recording did not show any changes of the components analysed. Authors discuss various possibilities for these findings, and end up with EMF affecting either the cochlea or the exposed cochlear nerve. They speculate that the cochlea and the hair cells could be the core size of the effects. Finally they underline that the experimental setup includes the exposed auditory nerve, which in real life is under skin, skull, fat, muscle blood, grey and white matter of the brain tissue), and therefore no effects of EMF have been found.

Sleep and EEG

Schmid et al. (2012) studied whether pulse-modulation frequency components in the range of sleep spindles may be involved in mediating the increases in EEG power during sleep in this frequency range (11-15 Hz) seen in their previous studies. Thirty young men (20-26 years of age) were exposed at weekly intervals to 30 min prior to an 8-hour sleep to 900 MHz RF EMF pulse-modulated at 14 Hz or 217 Hz, and a sham condition. Three cognitive tasks measuring attention (2-choice reaction time task), reaction speed (simple reaction time task) and working memory (n-back task) were performed by the subjects during the 30 min exposure period. No exposure-related effects were found in cognitive tasks. In EEG the power

in spindle frequency range was increased during non-REM sleep (only in the 2nd episode which is a rather late sleep cycle) following the 14-Hz pulse modulated condition, whereas statistically significant effects after 217 Hz pulse modulation were not found. The authors claim that this is in line with previous studies, "even though the time course remains variable across studies". The time course indeed is different, and the only effects were obtained in the 14-Hz pulse modulated condition, and only after 1.5-2 hours after onset of sleep. No similar effect was seen in the first similar sleep episode. There is not any reasonable explanation for this finding. However, there is one important finding in the paper which is the very large interindividual variability in spindle peak power (see their Fig. 4). This figure demonstrates the interindividual differences, also pointed out by Loughran et al. (2012) (see below; see also (Hinrikus et al., 2008a)), and may be the reason for this finding being by chance.

Loughran et al. (2012) investigated an important point in their study, i.e. individual variability in the effects of EMF on sleep EEG. They retested a subset of participants (20; 7 males, 20-51 years of age) from their previous study with 50 participants (Loughran et al., 2005) in order to see whether there is again an enhancement of EEG power in the 11.5-12.25 Hz frequency range, but also to determine the interindividual differences in sleep EEG and sleep quality. The participants received 30 min of either active or sham exposure by an ordinary GSM handset (SAR determined as in the previous study) before sleeping. The first 30 min of each participant's initial non-REM sleep period was analysed. There was an overall increase in power in the 11.5-12.25 Hz frequency range, and even more of an increase in the EEG power in the "Increasers" group than in the "Decreasers" group (groups were formed on the basis of their EEG changes in the previous study). No changes in power were observed in adjacent frequency ranges. There was no effect of active or sham exposure conditions on either sleep latency, REM latency, sleep duration, sleep efficiency, number of arousals, or KSS score (Karolinska Sleepiness Scale, applied in the morning following the experimental night), and there were no differences between the two groups of participants. This is a true replication study with important implications concerning the variability of individuals in EEG responses to GSM EMF.

Brain imaging with NIRS and PET tomography

There are two new studies where NIRS (near-infrared spectroscopy) has been applied to children and adults. Lindholm et al. (2011) examined the thermal and local blood flow responses in the head area of 26 pre-adolescent boys (aged 14-15 years) during 15 min exposure to GSM mobile phone (the exposure equipment and SAR measurements were the same as applied by Kwon et al. (Kwon et al., 2012, Kwon et al., 2011) in their PET (positron emission tomography) measurements, see below). The measurements were made in a climatic chamber in controlled thermoneutral conditions. No effects of exposure of this duration were obtained in either local cerebral blood flow (NIRS), the ear canal temperature, and autonomic nervous system arousal (measured by electrocardiography, ECG). Thus, no effects by GSM exposure of 15 min duration were found in this age group.

The effect of exposure duration on blood circulation in the adult head (auditory region) was targeted by Spichtig et al. (2012). They applied NIRS while exposing sixteen male subjects (26.8 ± 3.9 years average age, non-smokers) to UMTS EMF for 80 s (short-term) and 80 s to 30 min (medium-term). Also two different exposures, 0.18 W/kg and 1.8 W/kg (besides sham) were applied. The results showed a significant decrease (cf. Kwon et al., (2011)) in the medium-term response to both exposure levels, which, however, according to the authors is within the range of physiological fluctuations. Of other physiological measures, the medium-range change in heart rate was significantly higher at 1.8 W/kg compared to sham exposure,

whereas the other parameters (subjective well-being, tiredness and counting speed) showed no change. This study demonstrates the importance of exposure duration for detection of the physiological changes in the central nervous system.

There are two PET-studies focusing for the first time on glucose metabolism in the brain tissue. The first one was by Volkow et al. (2011) with 47 participants, which is a remarkable number considering the costs and effort in these studies. The exposure (GSM) on and off condition duration was 50 min, separated by 5 days, on the average. Whole-brain metabolism did not differ between on- and off-conditions, whereas metabolism in the region closest to the antenna (orbitofrontal cortex and temporal pole) was found to be significantly higher for on- than off-conditions. The increases were significantly correlated with the estimated EMF amplitudes. The problem is that no SAR was determined (it was only checked that the phone was in active mode). Also the vigilance level, well known to have large effects on brain activity, was controlled via "participants sat...with their eyes open, with a nurse present to ensure that they kept their eyes open and did not fall asleep". The design and data analyses including statistics have been heavily criticized (e.g. (Kosowsky et al., 2011)).

In contrast to Volkow et al. (2011), Kwon et al. (2011) reported decrement of glucose metabolism in the head region ipsilateral to the exposure (temporoparietal junction and anterior temporal lobe of the right hemisphere in a group of 13 participants due to the 33 min exposure by a carefully determined SAR for the GSM EMF (see Fig. 3 in the report). A very small temperature rise was also documented on the exposed side of the head. The attentional state of the participants was controlled by a simple visual vigilance task. No effect of the exposure on the task performance was observed. The authors conclude that short-term GSM mobile phone exposure can locally suppress brain energy metabolism in humans (cf ((Spichtig et al., 2012)).

Kwon et al. (2012) exposed fifteen young men to GSM EMF at three different locations (right and left ears and forehead) plus sham in order to determine the exact effect of exposure location on the possible changes in local blood circulation, their previous results having been rather obscure regarding the changes in activation seen in the brain. Subjects were exposed for 5 min in each scan, 3 scans for each condition, while performing a simple visual vigilance task. The exposure induced a slight temperature rise in the ear canals but did not affect brain hemodynamics and task performance. The authors conclude that there is no evidence that short-term exposure has any effect on cerebral blood flow.

General conclusions on human studies

The new issue not previously discussed (see, however (Hinrikus et al., 2008a)) is the interindividual variation in the possible reactivity of the human brain to RF EMF. This was pointed out in the studies of both Schmid et al. (2012) and Loughran et al. (2012). Whether this variability is related to cognitive functions and subjective sensitivity remains to be seen. In any case it now seems to be a well-established fact that there is no demonstrable effect by RF EMF on cognitive functions. This may of course be due to the non-existence of the effects or the coarseness of the measures to reveal any more subtle effects.

The brain imaging methods are the most suitable method for studying the EMF effects on the human central nervous system. Based on the imaging studies during the last 10 years, an interesting question arises. Studies with very short-term exposures have not shown any effects in adults (e.g. (Kwon et al., 2012)) or in children (Lindholm et al., 2011), whereas studies with longer exposures (at least 30 min) have demonstrated local decrement of glucose

metabolism (Kwon et al., 2011) or haemoglobin concentration (Spichtig et al., 2012) in the adult human brain. Therefore, we may conclude that the exposure duration, as well as cumulative exposure, should be more carefully studied, even though even also long exposures do not have any effect on cognitive functions (Sauter et al., 2011).

Epidemiological studies

Introduction

In the previous Council report (SSM, 2010:44) no health hazard could be identified regarding exposure from RF fields below international guideline levels. Nevertheless, for the tumours under study, that are invariably slow growing and rare tumours, the report emphasised the fact that it was still too early to draw firm conclusions.

Epidemiological studies can be conducted with different methods, where case-control studies, cohort studies and cross-sectional studies are the most common study designs. In addition, over the last few years, a range of incidence studies have been published that evaluated changes in the occurrence of brain tumours over time.

For all case-control studies listed below, numbers in brackets pertain to the response rate.

Exposure from mobile phones and cordless phones

Cordless house telephones (DECT) operate in a similar way as mobile phones by using radio signals to communicate between a handset and a base station. Cordless phones use a frequency band around 1900 MHz, whereas mobile phones use frequencies around 900, 1800 or 2100 MHz. The base-station for cordless phones is usually relatively close to the handset compared to the distance of a mobile phone and their base stations. More power is required for radio communications over greater distances. Accordingly, maximum output power of DECT cordless phones is 10 milliwatts (mW), but mobile phones operate at a maximum average output power of 250 mW. The emission power of almost all current cordless phone models is constant. In contrast, when a mobile phone is used in an area with good coverage, the emitted power is considerably reduced by the adaptive power control of the mobile phone. This is especially relevant for UMTS (Universal Mobile Telecommunications System) phones because of their effective power control (e.g. Gati et al., 2009; Persson et al., 2012; Vrijheid et al., 2009; Baliatsas et al., 2012). This means that in most situations, the exposure from cordless house telephones would be lower compared to GSM (Global System of Mobile Communication) mobile phones and UMTS mobile phones would be expected to emit even less compared to cordless phones, unless the connection quality is very bad. For the exposure assessment, this means that use of cordless phones has become more relevant since the introduction of UMTS phones and continues to become even more important, given that many people are switching from GSM to UMTS phones.

Childhood cancer

In 2011, Aydin et al. (2011) published the first study to date addressing the association between mobile phone use and the risk of brain tumours among children and adolescents. All children aged 7 to 19 years living in Denmark, Norway, Sweden or Switzerland and diagnosed with a brain tumour during the years 2004–2008 were eligible for the study. Two controls per case were randomly selected from population registries and matched by age, sex and geographical region. Exposure data were collected by means of face-to-face interviews with the subjects and their parents. For a subset of the participants, additional information regarding mobile phone use was obtained from mobile phone operator records. The study

included 352 (83.2%) cases and 646 (71.1%) controls. The odds ratio for regular use, defined as an average of at least one call per week for at least 6 months, was 1.36 (95% CI 0.92-2.02) compared to study participants who had never been regular users. All exposure categories yielded slightly elevated, but statistically non-significant risk estimates compared to non-users. Analyses of ipsi- and contra-lateral use as well as the location of the brain tumours showed no indication for increased risk of brain tumours in those areas of the brain that had likely received the highest amount of exposure.

For the subset of the study participants for whom mobile phone operator records were available, a statistically significant increased risk (OR 2.15, 95% CI 1.07-4.29) was found among the users with the longest period since first subscription, > 2.8 years, with a significant trend in risk with time since first subscription ($P < 0.001$). However, no such trend was found across categories of cumulative number of calls, or cumulative duration of calls. The absence of an exposure-response relationship either in terms of the amount of mobile phone use or by localization of the brain tumour argues against a causal association.

The risk estimates from the study were additionally compared with the observed time trends of brain tumour incidence in Sweden for the same age group for the period 1990 to 2008. For this step, the authors used their own reported risk estimates and evaluated if these were compatible with reported time trends of incidence data, using data from all Swedish children and adolescents. For this assessment, risk estimates from regular use (OR 1.36) and the operator records (OR 2.15) were used. An incidence rate for a risk of 2.15 did not correspond to the observed rate, thus did not provide evidence for a substantially increased brain tumour risk from the use of mobile phones in children and adolescents.

In an accompanying commentary, Söderqvist et al. (2011) raised objections against this study, stating that both increased ORs as well as heterogeneous ORs between the participating countries, indicating methodological differences or bias, were trivialized. In addition, they criticized that exposure from cordless phones was analysed separately from exposure from mobile phones. They further questioned the validity of using incidence time-trend data from Sweden only to evaluate the results, but not from the other countries that participated in the study. They pointed out that there were relatively large differences in time-trend incidence rates across participating countries. In an answer, Aydin et al. (2012) presented incidence time-trends for all Nordic countries, indicating relatively stable rates over the last twenty years in the age group 5-19 years. The authors also pointed out that the amount of heterogeneity between countries was in line with the expected random variability ($p = 0.20$).

Similar temporal stable incidence rates for the same age group were also shown for the USA (Boice and Tarone, 2011), indicating that substantial risk increase from use of mobile phone is not in line with the general incidence trends for brain tumours.

In Taiwan, Li et al. (2012a) performed a case-control study of radiofrequency exposure from mobile phone base stations in relation to childhood cancer. A total of 2606 cancer patients including 939 leukaemia cases and 394 brain cancer cases aged 15 years or less were selected from a national database, the "Inpatient Expenditures by Admissions (IEA)", during the period 2003 to 2007. 30 controls per case were randomly selected from the national "Registry for Beneficiaries", which covers all Taiwanese citizens. Ambient RF exposure for individuals was not measured, but the authors created a new exposure metric by calculating the emitted power (Watt) and duration of operation (Years) of mobile phone base stations per area in km² of a township, thus calculating WY/km². The total WY/km² was then estimated for each

township. Since the exposure was not validated, it is unclear in how far the calculated WY/km² translates into exposure of persons in the respective townships. Among other factors, the authors also adjusted for proximity to power lines, which was considered as a potential risk factor for some neoplasms. For all cancers combined, an OR of 1.13 (95% CI 1.01- 1.28) was observed for persons who lived in townships with exposure levels above the median, compared to those exposed below the median. For the other exposure parameters, all ORs were close to unity. In the analyses for leukaemia and brain tumours, the ORs were slightly elevated, but this was not statistically significant. It is likely that unmeasured factors associated with urbanity acted as a confounder in the analysis. Even though studies like this have reliable information from population-based databases reducing the possibility of selection bias and recall bias, the lack of real reliable individual exposure data makes interpretation of the results difficult.

Adult brain tumour studies

Incidence trend studies

There have been increasing numbers of studies assessing time trends of the incidence of brain or other central nervous system tumours over the last years. In general, incidence trend studies are difficult to interpret, given the number of factors that might influence the numbers. For example, improved detection methods, or changes in registration practice of affected persons can have profound effects on the trend estimates. However, in this special situation, with a steep increase in exposure prevalence (the usage of mobile phones in the population), the availability of virtually complete cancer registry data in many countries, and the limited number of known other environmental co-risk factors especially for brain tumours, the analysis of incidence time trends is considered to be highly informative. With the very high penetration of mobile phone use nearly globally, any true risk from mobile phones should be eventually visible in the incidence data. For an association with mobile phones to be plausible, the increase must occur after the implementation of mobile phone technology in the respective country. There is, however, uncertainty about the relevant induction and latency time and thus, it is not entirely clear at what time period after the start of the exposure a potential risk has to be detectable in the incidence data.

Little et al. (2012) compared risk estimates of two epidemiological studies: Hardell et al. (2011a) and INTERPHONE (discussed in the SSM, 2010:44; Interphone, 2010) with the incidence trends for gliomas in the United States. Data for almost 25 000 persons aged 18 years or older, for the period 1992 -2008 was collected from the National Cancer Institute's Surveillance, Epidemiology and End Results programme (SEER). No increase of the incidence rates of the last decade was observed, and Little et al. concluded that the predicted incidence rates based on the results from the study by Hardell et al. were substantially higher than the observed true rates. A modest increased risk, however, as reported among heavy users in the INTERPHONE study, would still be within the uncertainty range of the observed American glioma incidence rates.

A similar study as by Little et al. was performed by Deltour et al. (2012). Age-standardized incidence rates in the Nordic countries, based on 35,250 glioma cases, were analysed for men and women aged 20-79 years, covering the period between 1979 and 2008. This study is an update of a previous publication from 2009 (Deltour et al., 2009) which had data included up to 2003. A relatively stable annual percentage increase in incidence rates was observed, 0.4% (95% CI 0.1-0.6) among men and 0.3% (95% CI 0.1-0.5) among women. There was no obvious change in the glioma incidence after the introduction of the mobile phone technology. In men, the increase was restricted to older people (60-79 years) but not observed among

middle-aged men (40-59 years), who were most likely the earliest and heaviest mobile phone users in the past. The authors concluded that a relative risk of 2.0 for an induction period (here: time between the start of exposure and cancer to be detected) of up to 15 years, a risk of 1.5 for up to 10 years, and a relative risk of 1.2 for up to 5 years were incompatible with observed incidence time trends. Any risk of 2.0 or higher for up to 5 years' induction period restricted to heavy mobile phone users would also be incompatible.

In England, de Vocht et al. (2011) investigated the time trends in brain cancer incidence rates. Incidence data of unspecified malignant brain tumours from the UK Office of National Statistics (ONS) between 1998 and 2007 was used for the analysis. Because the data lacks tumour morphology, the authors assumed the majority to be gliomas, which represent the most common malignant brain tumour. For all tumour localisations together, no significant change in the incidence of brain cancers was found for men or women. When the analyses were restricted to those tumours located in the temporal lobe, the area that receives the highest exposure from mobile phones, a small systematic increase was observed. According to the authors, this slight increase would contribute approximately 1 new case per decade if it was truly caused by mobile phone use.

In Shanghai, Ding and Wang (2011) analysed the incidence trend of brain and nervous system tumours to evaluate changes in trends during the period 1983 to 2007, well covering the whole period of the introduction of mobile phones. The age-adjusted incidence rates for men increased from 3.7/100,000 in 1983 to 6.1 per 100,000 in 2007, giving an annual increase of 1.2 percent (95% CI 0.4-1.9). For females, the age-adjusted incidence was 2.9/100,000 in 1983 and 6.9/100,000 in 2007, giving an annual percentage change of 2.8 (95% CI 2.1-3.4). The incidence rates increased gradually during the whole period, and the annual percentage change did not increase after the introduction of cell phones.

Case-control studies

Spinelli et al. (2010) conducted an explorative case-control study to evaluate the risk of a range of environmental exposures on malignant brain tumours, including the exposure from mobile phones, self-reported distance to mobile phone base stations and the use of computers. The study included 122 adult cases, diagnosed between January and December 2005, and 122 controls hospitalised for other reasons than cancer and matched on age and sex. For mobile phone use, the subscription-hours of the contract with the mobile phone provider were used as an exposure proxy, as well as the number of years of mobile phone usage. For computers, the average weekly hours of usage over the last 5 years were inquired and for mobile phone base stations, the exposure assessment was based on self-reported distance to the transmitter of more or less than 500 m to the home residence. There were neither statistically significantly elevated ORs for mobile phone usage, nor an exposure-response relationship. Statistically significantly reduced risk estimates were found for persons living within 500 m of a mobile phone base station. Lack of a validated exposure assessment and the small sample size render the study largely uninformative. For example, it is well known that self-reported exposure from mobile base stations is not related to objectively measured field-strengths at the place of residence (Frei et al., 2010).

Based on the material from the INTERPHONE study, Cardis et al. (2011a) conducted a case-control study with data from the participating countries Australia, Canada, France, Israel and New Zealand to examine the risk of brain tumours in relation to the actual exposure that is received from mobile phones. The study included 809 glioma cases and 842 meningioma cases and their controls. Estimation of the total absorbed energy was based on type of telephone, network properties, frequency bands, communication systems and self-reported

amount of use. This information was available for 553 glioma and 676 meningioma cases and 1762 and 1911 controls, respectively. An algorithm was developed to evaluate total RF exposure at specific locations in the brain and applied to the subjects to estimate RF exposure at the tumour location. The estimation of exposure is described in detail in a separate publication (Cardis et al., 2011b). The correlation between the estimated exposure and the self-reported amount of mobile phone use was found to be high (weighted Kappa 0.68).

The odds ratio for regular phone use was 0.92 (95% CI 0.75-1.13) for gliomas and statistically significantly below unity for meningiomas with 0.80 (95% CI 0.66-0.96). There was no exposure-response relationship across exposure quintiles of cumulative call duration for gliomas or meningiomas. When analysing the total cumulative exposure, the ORs for gliomas were slightly, but statistically non-significantly, raised in the highest exposure category only, with an OR of 1.35 (95% CI 0.96-1.90). Analyses of total cumulative exposure for different lag-time intervals before diagnosis were also performed, with a significantly increased OR in the highest exposure category in the group exposed 7+ years before diagnosis for glioma (OR 1.91 95% CI 1.05-3.47) and meningioma (OR 2.01 95% CI 1.03 -3.93). The results when using exposure estimations were very similar to the results based on self-reported amount of mobile phone use. This is not surprising given the high correlation between these two metrics. For interpretation of causal inference the same methodological questions are relevant as it was for the main glioma and meningioma analyses in INTERPHONE 2010 (see SSM report from 2010 for more details).

Larjavaara et al. (2011b) conducted a study with a case-only analysis to evaluate whether gliomas occur preferentially in the areas of the brain that had received the highest amount of radio-frequency exposure. This study was also based on material from countries participating in the INTERPHONE study, but this time, 873 glioma cases were included from Denmark, Finland, Germany, Italy, Norway, Sweden and the United Kingdom. The localization assessment of the tumours was performed by neuroradiologists, based on radiological images. Two analyses were performed. In the case-case analysis, occurrence of tumours relative to the most exposed area of the head was compared between exposed and unexposed cases. In the case-specular analysis the actual location of the tumour was contrasted with a hypothetical location that was mirrored to the observed location. The assumption for both analyses is that if RF EMF exposure is a carcinogen, tumours of exposed cases should occur more often in exposed areas of the brain. This association may be more reliably estimated than analyses based on self-reported mobile phone use, which may be subject to recall bias. A case-only analysis also eliminates potential bias caused by non-participating controls.

The results for the case-case analysis showed non-significant ORs below unity for regular users compared to never-regular and to contralateral users. The results from the case-specular analysis showed that the distance between the tumour and mobile phone did not vary with the use of mobile phone. For long term users (≥ 10 years), the OR for having a glioma midpoint within 5 cm of the most exposed area was slightly, but statistically non-significantly, increased compared to the other study participants. In conclusion, the results of this study do not provide firm evidence that gliomas are preferentially located in those parts of the brain that receive the highest radio-frequency field exposure.

These two new INTERPHONE papers addressing methodological weaknesses of case-control studies discussed in the SSM report of 2010 are an important contribution to obtain a better understanding of the previously published results (Interphone Study Group, 2010). Overall, the two papers did not strengthen the evidence for an association between RF EMF exposure from the use of mobile phone and brain tumour. Thus, any risk, if present, cannot be substantial and must be related to long latency types, specific subtypes of tumours, and/or to extensive mobile phone use.

Cohort studies

A third publication of the Danish cohort study evaluating the association between brain tumours and mobile phone usage was published by Frei et al., 2011, including a follow up period from 1990 to 2007. This study is based on a cohort of mobile phone subscribers which was first published by Johansen et al. in 2001, and is described in detail in the first SSI report (SSI, 2005:01). The first publication had a follow-up until 1996. The first update of this study was performed by Schüz et al. (2006) and included a follow-up period until 2002. Neither Johansen nor Schüz found any evidence of an increased risk of brain, nervous system tumours or any other type of cancer among the subscribers. The longer follow-up period presented in the study by Frei et al. increased the numbers of person-years considerably, and a large number of long-term subscribers with more than 10 years exposure time could be included in the analysis.

From 1990 to 2007, 358,403 holders accrued a total of 3.8 million person-years. In the previous follow-ups, information on socio-economic factors was not available at the individual level. Frei et al. were able to link a subset of the subscriber cohort to another already existing national cohort, CANULI, from the Institute of Cancer Epidemiology on social inequality and cancer, which added information on proxies of socio-economic position, in particular education and income.

Relative risks for all cancers, central nervous system tumours, gliomas, meningiomas as well as other or unspecified intracranial tumours were close to unity in all exposure categories for both genders. In further stratified analyses in men by site of the tumour location, risk estimates for gliomas were highest for the occipital lobe (1.47, 95% CI 0.87 to 2.48) and for others/unspecific locations (1.35, 95% CI 1.05 to 1.75). For the temporal lobe, the part of the brain that is expected to absorb the highest amount of energy emitted from mobile phones, IRR was 1.13 (95% CI 0.89-1.45). When the data were analysed according to duration of follow-up, the highest risk estimates were found in the low- and middle exposure category, but not in the persons with the longest exposure duration.

This study is the second update of this cohort study. Most results of the present study are in line with the results of the previous studies of the subscriber cohort, with no indications of increased risks of central nervous system tumours.

In an accompanying editorial, Ahlbom and Feychting (2011) presented glioma incidence data from Sweden for the age groups 20-39, 40-59 and ≥ 60 years for the period 1970-2009, confirming the results of the cohort study. The authors also emphasised the importance of taking all studies on mobile phones and cancer into account before firm conclusions could be drawn. Because of the methodological problems for case-control studies in this field, the authors recommended the use of prospective cohort studies and continued monitoring of health registers in future research.

Söderqvist et al. (2012a) criticized in particular that of more than 700,000 subscribers initially identified in the cohort, more than 300,000 users were excluded, mainly because individual information about corporate subscribers not were available. These 300,000 were included in the comparison group. Similar objections have also been raised by (Khurana, 2011, Philips and Lamburn, 2011). An evaluation of the consequences of the exclusion of approximately 40% of the initial subscribers shows that the error in the risk estimation, if there is any, would be marginal. As an example, if one assumes a true relative risk of 2.5, and that 300,000 subscribers are erroneously included in the unexposed population, the relative risk as assessed in this study would be reduced from 2.5 to 2.2 (Ahlbom, 2012). This small underestimation is explained by the fact that diluting approx. 4 million non-subscribers with 300,000 subscribers does not substantially change estimated cancer rates in this group. Most importantly, the

subscriber group is not diluted by non-subscribers, and therefore, the hypothetical increased cancer rate in this group is estimated in an unbiased way. As a consequence, the relative risk is also only marginally biased.

In addition, Söderqvist et al. (2012a) criticized the exclusion of 50,000 subscribers which could not be linked to another national cohort to derive socioeconomic factors such as income and education. However, the same applies as mentioned above: this does not result in a substantially biased risk estimate and is justified by the advances of adjusting for socioeconomic factors in the analyses. An additional criticism of the commentary by Ahlbom and Feychting (2011) pertained to using glioma incidence trends of Swedish and not Danish data, although the subscriber cohort originates from Denmark. Söderqvist et al. presented a figure and a table from Denmark with percentage change in incidence rates per year, with the highest percentage changes during the period 2000-2009.

Regarding exposure assessment, Söderqvist et al. are concerned with the lack of individual exposure data regarding the amount of use and laterality, and that cordless phone users without mobile subscription are regarded as unexposed. Lack of individual data on the amount of use is a limitation of this study also acknowledged by the authors. However, the evaluation of all three Danish Cohort study publications (Johansen et al., 2001; Schuz et al., 2006 and Frei et al., 2011) is helpful for evaluating this aspect. In the first paper with follow-up until 1996, the cumulative amount of mobile phone use must have been much larger in subscribers compared to non-subscribers because non-subscribers could have used a mobile phone only for a maximum of 1 year. There was, however, no difference in risk between these two groups. This study was, however, limited for assessing the risk of duration of exposure. In contrast, the last paper is more informative for assessing the role of exposure duration (because subscribers will always be several years ahead in mobile phone use compared to non-subscribers) but less so for the cumulative use of mobile phones, since non-subscribers may have caught up in exposure in the meanwhile.

All in all, Ahlbom and Feychting (2011) highlight the advantages of the subscriber cohort compared to case-control studies, while Söderqvist et al. (2012a) highlight the limitations. It is well known that interview-based case-control studies have advantages. E.g. individual exposure can be assessed, but limitations such as recall bias are unavoidable for this type of study. The Danish cohort studies make an important contribution to the total assessment in the field. This is due to the long period of follow-up, which allows addressing long term exposure effects. Cohort studies provide added value to the overall evidence by using objective exposure data that is not biased by different recall between cases and controls about past exposures.

Hardell and Carlberg (2012) conducted a survival analysis of the glioma patients of their previous case-control studies in relation to the use of mobile- and cordless phones (summarised as "wireless phones"). Thus, conceptually this corresponds to a cohort study with retrospectively self-reported data on wireless phone use. They included all 1,251 cases diagnosed between 1997 and 2003 with a malignant brain tumour and followed them from the date of diagnosis until death or until May 30, 2012. The participants were aged 20-80 years at the time of diagnosis. In addition to all gliomas, the astrocytoma patients (a subgroup of gliomas) were divided into three groups according to malignancy, grade I-II, grade III and grade IV, where grade IV is regarded as most malignant. The analyses included three latency time periods, >1-5, >5-10 and >10 years of mobile phone use, cumulative use in hours cut into three groups. Adjustment was made for gender, age, year of diagnosis, socioeconomic position and whether a case or a proxy was interviewed. For glioma, the overall hazard ratio (HR) for wireless phone use was 1.1 (95% CI 0.9-1.2) for any duration of exposure and 1.2 (1.002-1.05) when considering a latency of 10 years. Heavy wireless phone users (>2,000 h

lifetime use) had an increased risk for dying with a HR of 1.3 (1.04-1.7). When the analyses were stratified by grade of astrocytoma, a prolonged survival time was observed for wireless phone users compared to non-users in the low-grade group, but no such effect was observed for grade III and grade IV astrocytoma cases. Within grade IV astrocytoma cases, an increased risk for long-term (>10 years) wireless phone users was observed. This analysis presents a creative way of investigating whether mobile phone use affects the survival rate of brain tumour patients. However, the use of proxy interviews with next-of-kin for deceased patients is a severe limitation of this study: If proxies tend to overestimate the wireless phone use of their relatives, the results are biased. No validation data on this aspect are presented in the paper.

Since the last Council report (SSM, 2010:44), two reviews regarding mobile phones and tumours in different sites of the head have been published (Swerdlow et al., 2011), (Repacholi et al., 2012). The objective of Swerdlow et al. was to review the evidence on whether mobile phone use increases the risk of glioma and meningioma, with a particular focus on the INTERPHONE study. They concluded that the combination of results from biological and animal studies, other epidemiological studies and incidence trend studies, do not suggest an increased risk for brain tumours within 10-15 years of exposure among adults.

In addition to mobile phone use, Repacholi et al. also reviewed RF EMF exposure applied in in-vivo studies. Meta-analysis of the epidemiology studies did not provide evidence of an increased risk of mobile phone use on tumours of the head (gliomas, meningiomas, vestibular schwannomas or parotid gland tumours). They also concluded that in-vivo studies did not identify consistent relationships between mobile-phone exposure and brain tumour risks. Similar as in Swerdlow et al., the authors point out uncertainties related to long term use (≥ 10 years) among adults and potential risks in children.

Other tumours

Salivary gland tumours

In Sweden, a case control study of wireless phone use and risk of salivary gland tumours was performed by Söderqvist et al. (2012b), using a self-administered postal questionnaire. In contrast to most other studies investigating mobile phone use and risk of neoplasms, exposure from cordless phones was also taken into account and combined with mobile phone use to the combined exposure measure 'wireless phone use'. 69 cases (88%) and 262 controls (83%) were recruited from a regional oncology centre between the years 2000 and 2003. The analyses included three latency time periods, >1-5, >5-10 and >10 years of use, and total use. In addition, the authors present an analysis based on cumulative hours of mobile phone use. The overall odds ratio for wireless phones use was 0.8 (95% CI 0.4-1.5). The lowest ORs were seen in the highest exposure groups both for duration and cumulative hours of use. The incidence of parotid gland tumours in Sweden between 1970 and 2009 was also presented in this study, showing a decreased incidence in the last 30 years, which make it unlikely to be associated with the use of mobile phones.

A Chinese hospital-based case-control study was performed by Duan et al. (2011), evaluating the risk of parotid gland tumours and use of mobile phones. Cases and controls were recruited from the authors' hospital during the period 1993-2010. Cases had confirmed malignant epithelial parotid gland tumours, controls were individuals without any oral maxillofacial malignancies. 136 (62%) cases and 2051 (78%) controls were still alive and agreed to participate. Analyses were also performed for mucoepidermoid carcinoma, but it is unclear

whether these tumours are included in the main analyses of the malignant epithelial parotid gland tumours. Data was collected by personal or telephone interviews. No significant increased risk was observed among regular users compared to non-regular users with an OR of 1.14 (95% CI 0.72-1.81) after adjustment for gender, age, residential area, marital status, education, monthly income and smoking status. In the sub analyses, “duration in years since first use to the time of diagnosis”, “calculated duration of use” and “average daily use in hours” showed significantly increased ORs. Results were strongly affected by adjusting for potential confounders, and results were not consistent with results from previous case-controls studies addressing the association between mobile phone use and parotid gland tumours (Repacholi et al., 2012).

Vestibular schwannoma (also called acoustic neuroma)

Similar as for the analysis of brain tumours by Frei et al (2011), an update from the Danish mobile phone cohort study regarding risk for vestibular schwannoma was performed by Schutz et al. (2011). Also for this update they gained information on highest educational level attained, income and marital status for the subscriber cohort by matching data to another national cohort study enabling adjustment for potential confounding by socioeconomic position. Data from 404 men and 402 women diagnosed with vestibular schwannoma was ascertained from the main clinical treatment centre and the Danish cancer registry. By linkage of the two cohorts, each of the subjects was classified as long time mobile phone users (> 11 years use) with short time/non-subscribers as comparison group. The study was based on approximately 2, 9 million people and 23 million person-years. In women, no case was observed among long-term users (versus 1.6 expected), and the analyses were performed for men only. The age-adjusted incidence rate for long-term male subscribers was 0.87 (95% CI 0.52-1.46), similar to that of short time/non-subscribers. The effect estimate changed only marginally when analyses were adjusted for the socioeconomic factors.

By use of national data from an international prospective cohort study in which Denmark participates (Cosmos), the authors were able to obtain information on self-reported laterality of mobile phone use from the (non-diseased) participants. The Cosmos study showed that among Danish mobile phone users, 53% preferred the right ear, 35% preferred the left and 13% had no preferred ear when using mobile phones. In the subscriber cohort 47% of the long-time subscribers and 48% of the short-time/non-subscribers had the vestibular schwannoma on the right side. This indicates that the vestibular schwannomas not are more common on the right side of the head despite a majority of the population prefers the right ear when using mobile phones.

In addition to glioma and meningioma (see details in SSM report 2010), INTERPHONE also evaluated the risk of vestibular schwannoma in mobile phone users (Interphone Study Group, 2011). The same study protocol as for glioma and meningioma was used, and overall, 1105 (82%) cases and 2145 (53%) controls were included. The odds ratio for regular mobile phone users compared to non-regular users was 0.85 (95% CI 0.69-1.04) when censoring the year before inclusion into the study. There were no statistically significant increased risks or exposure-response relationship for time since start of mobile phone use (up to >10 years), cumulative call time or cumulative number of calls. When censoring five years before inclusion into the study the overall risk estimate for regular users was 0.95 (95% CI 0.77-1.17). In the group with the highest cumulative call time (10th decile), there was a statistically significant increased odds ratio of 2.79 (95% CI 1.51-5.16) although the odds ratio in the 9th decile was 0.60 (95% CI 0.34-1.06). For both 1 and 5-year time lags, most of the odds ratios were below unity in most of the exposure groups.

Regarding laterality and telephone use, the overall odds ratios were approximately the same for ipsi- and contra-lateral use. For the highest cumulative use category of ipsilateral use, ORs were higher than for contralateral use. But also for this analysis a lack of exposure-response pattern weakens the confidence in the results. The risk estimates of this analysis are surprisingly similar to the INTERPHONE results on glioma risk (Interphone Study Group, 2010) and essentially the same reservations on conclusions on causal inference remain. Risk estimates below unity from use of mobile phones may be the consequence of participation bias in the case when mobile phone users among the controls are more likely to participate in the study compared to non-users. Such risk estimates are therefore not indicative of a protective effect from use of mobile phones. At the same time, isolated increased risk estimates among heavy users may at least partly be due to recall bias, meaning that cases may tend to overestimate their exposure more than controls (or controls underestimate more than cases). Such a recall bias would produce increased risk estimates. For example, in the present analysis, the authors noted that 16 cases (1.4%) and 22 controls (1.0%) reported 5 h or more of mobile phone use per day, an implausible amount, most of them contributing to the highest exposure category.

In Japan, a case-case study of mobile phone use and the risk of vestibular schwannoma was performed by Sato et al. (2011), using a self-administered postal questionnaire. 787 (51%) vestibular schwannoma patients from 22 different hospitals in Japan, diagnosed between 2000 and 2006 participated in the study. Exposure until one and five years before diagnosis was analysed separately. 180 participants provided information on laterality. The overall risk ratio for regular mobile phone use compared to non-use was 1.08 (95 % CI 0.93-1.28) for regular use until one year before diagnosis and 1.14 (95% CI 0.96-1.14) a 5-year exposure lag. Among “heavy users”, defined as average use >20 minutes/day, increased risks were identified for both exposure lags, with ORs of 2.74 (95 % CI 1.18-7.85) and 3.08 (95 % CI 1.47-7.41), respectively. Tumour diameter tended to be smaller in cases with ipsilateral use (when the tumour occurred on the side of the usual phone use). Hearing loss is a symptom for vestibular schwannoma, and heavy users with hearing loss might consult a doctor at an early stage of the disease, which might be an explanation for this finding.

Larjavaara et al. (2011a) conducted a study with incidence trends for vestibular schwannomas in the Nordic countries Denmark, Finland, Norway and Sweden. Data of 5133 vestibular schwannoma patients for the period 1987-2007 was collected from the national cancer registries. For all countries combined, the average annual increase was 3.0 percent (95% CI 2.1-3.9), with most of the increase occurring before 1990. Average age-standardized incidence rates per 1,000,000 person-years showed substantial differences between the countries, with the highest rates in Denmark (11.6/ 1,000,000 person-years for both genders) and lowest among Finnish men (6.1/1,000,000 person-years). The annual increase in percentages differed also between the countries, with – 0.7% for Finnish women to 5.5% for Norwegian men. The differences between the countries are difficult to interpret, but they also do not provide an indication of an increased risk for vestibular schwannoma related to the use of mobile phones.

Leukaemia

In South East England Cooke et al. (2010) performed a case control study to evaluate the risk of leukaemia (except chronic lymphocytic leukaemia) in relation to mobile phone use. During the period 2003-2007 (in some areas 2003-2009) 806 (50%) cases and 589 (75%) controls in the age group 18-59 years participated in the study. Data was obtained by face-to-face

interviews. The cases were ascertained via the haematology and oncology units and from the Thames Cancer Registry. As controls, non-blood relatives of the cases were recruited. No increased risk among regular mobile phone users was observed (OR 1.06, 95% CI 0.76-1.46). Further, no increasing trend or significant risk in relation to years since first use, lifetime years of use, cumulative number of calls and cumulative hours of use was observed. A statistically non-significant increase was observed in the longest categories (≥ 15 years) of years since first use and lifetime years of use, with ORs of 1.87 (95% CI 0.96-3.63) and 1.63 (95% CI 0.81-3.28), respectively. Stratifying the analyses by the use of analogue and digital mobile phones showed no evidence for an increased risk. Overall, the results do not suggest that use of mobile phones increases the risk of leukaemia, but the authors acknowledge a possible risk in long-term users.

Malignant melanoma

Hardell et al. (2011b) conducted a case-control study of mobile and cordless phone use and risk of malignant melanoma in the head and neck region, using a self-administered postal questionnaire. 347 cases (82%) were obtained from the Swedish Cancer registry and 1184 controls (80%) were recruited from the Swedish Population Registry. The participants were aged 20-77 years at the time of diagnosis during 2000-2003. The analyses included three exposure lags in time periods of >1-5, >5-10 and >10 years of use, and total use, adjusted for gender, age, and year of diagnosis. In addition, cumulative numbers of hours of mobile and cordless phone were analysed. The overall odds ratio for wireless phone (mobile and/or cordless phone) use was 0.9 (95% CI 0.7-1.2). The highest ORs was found in the lowest latency group, >1-5 years of use for exposure in the temporal area, cheek and ear, but not in persons with longer exposure duration. No interaction was detected between mobile phone use and malignant melanoma risk across categories of different hair and eye colours, skin types or number of sunburns.

All types of cancer

On the background of local residents' concerns about their exposure to radio and cellular transmitters in an Israeli village, Atzmon et al. (2012) conducted an interview-based case-control study to determine a number of possible reasons of cancer, and whether there were an elevated cancer risk for inhabitants living close to the transmitters. Cancer cases were defined as eligible for inclusion on the basis of medical documents and histopathology diagnosis of cancer. The study included 307 subjects, of whom 47 were diagnosed with cancer. Individual exposure from the mobile phone base stations was estimated based on the distance between the residence and the closest transmitter. Mobile phone, cordless phone use and Wi-Fi was reported to be asked for, but those results were not included in the paper. ORs of several cancer types were all around unity for distance of the place of residence and mobile phone base stations, except for breast cancer, for which a decreased OR was reported and colorectal cancer, for which a very slight increase in risk was reported. It is unclear in which time frame exactly cases was included in the analysis and how controls were selected. The authors comment that they were limited in their exposure assessment, given that many of the antennas did not exist anymore by the time of the assessment. In addition, the sample size was very small and distance to the next mobile phone base station has been shown to correlate poorly to true exposure levels (Frei et al., 2010), which renders this exposure proxy rather uninformative.

In a Brazilian ecological study performed in Belo Horizonte (Dode et al. 2011), over 7000 deaths from cancer occurring between 1996 and 2006 were analysed in association with distance to the next mobile phone base station. The mortality rate ratio was 1.35 for people

who had had their place of residence within 100 meters of a mobile phone base station (compared to mortality in the total population of Belo Horizonte) and declined with larger distances. No statistical test was applied to assess statistical significance of the mortality rates or for a trend over increasing distance categories.

A particular problem of this study was that addresses of persons who had died were available, but addresses of persons still alive were only available on a census tract resolution (about 2500 census tracts for about 2.2 million inhabitants). The authors calculated deaths occurring within 100 m of a base station, crudely divided by the population of all census tracts that were touched by the 100 m distance buffers around the mobile phone base stations. This means that the areas of the numerators did not match the areas of the denominators. In a next step, the crude mortality rate was calculated over increasing distance buffers, so that the first calculation was the mortality rate over 0-100 m and the second 0-200m and so on, until a final buffer of 1km was reached, which included 96% of the population of Belo Horizonte. Since the smaller buffers were included in all consecutive distance buffers and ended with nearly the full population of Belo Horizonte, accordingly, the calculated relative risks seem to follow an exposure-response relationship, because they were forced to unity over the largest distance buffer. A problem of the approach by Dode et al. (2011) is that if areas of higher base station density are more urban areas, the population density is higher. Thus, the number of inhabitants in the buffers around the base station is likely to be underestimated and the calculated mortality rates overestimated. In addition, even though the authors had information available regarding age and sex distribution of the areas, this was not taken into account in their calculation. Urban areas may differ in many ways from less urban areas with lower base station density: Affluence, age distribution, received medical care and so on, which may also affect mortality and was not considered in the analysis.

Information about locations of base stations was only available for 2003 and 2006 and it is not clear how this information was used for deaths that occurred before 2003. It has to be further emphasized that distance to mobile-phone base station is scarcely correlated with RF-EMF exposure (Frei et al., 2010). The authors presented some electric field measurements but did not consider them for exposure assessment. Neither did they describe a measurement protocol or reported the correlation between distance and their measurement values. In summary, this study is uninformative.

Child development

The Danish Birth Cohort study provided an update (Divan et al., 2012) of a study published by Divan et al. (2008), summarised in (SSM, 2009:36). The first paper included about 13,000 children born between 1997 and 1999, in the second paper about 29,000 children born in the years 1998-2002 were added. At age seven of the children, mothers were asked how often they had used a mobile phone during pregnancy, as well as about behaviour problems of their children. Children's behavioural problems were assessed with the Strength and Difficulties Questionnaire (SDQ) that measures emotional symptoms, conduct problems, hyperactivity and peer problems.

Mobile phone use of mothers had increased in the time between the first and the second study, 12% of mothers reported to have used a mobile phone during pregnancy in the first publication, compared to 23% in the second study. As in the first publication, mobile phone use was associated with an increase of behavioural problems of the children. After adjustment for a range of potential confounders, there still remained an increased risk with an exposure-response relationship across the number of times mothers used the mobile phone per day:

maternal mobile phone use of 4 calls or more per day resulted in an adjusted OR of 1.4 (95% CI 1.2-1.7) for the child to have behavioural problems, compared to children whose mothers had used mobile phones maximally once per day. In the second publication, the authors addressed the hypothesis that mother's inattention in rearing the child was responsible for the observed association. However, the elevated risk estimates remained also after that the authors accounted for breastfeeding, time the mother spent with the child each day, or childcare; factors seen as proxies for mother-child interactions. Exposure levels to the foetus from maternal mobile phone use would be extremely low, and the authors additionally assessed postnatal exposure to mobile phones. Children whose mothers had been using a mobile phone during pregnancy and who were using one themselves had somewhat higher OR than observed for prenatal exposure only. Mother's use of cordless phones was not assessed.

Given that behavioural problems and mobile phone use was assessed based on self-report and at the same time point and from the same person, the study has some potential for recall bias. Especially in the new study, the OR decreased slightly per each birth year. This could point to a cohort effect, where early adopters of mobile phone technology differed in several aspects from the other persons in the cohort, not only in their mobile phone usage.

In a third publication by Divan et al., the authors analysed the full Danish National Birth Cohort data set of 41,541 children (Divan et al., 2011). The exposure assessment was the same as in the two publications on childhood behaviour. When the children were 6 and 18 months old, a telephone interview was performed with the mothers that included questions regarding the child's cognitive, language and motor development. There was no evidence of an impact of mothers mobile phone use on their children's development, with ORs all close to unity. This is in line with a previous study by Vrijheid et al. (2010) (discussed in the previous Council report).

In a fourth paper of the Danish Birth Cohort, the same exposure as in the previous publications was evaluated, this time in association with migraine as well as headache-related symptoms. Data from 52,680 children from women who were enrolled during their pregnancy between 1996 and 2002 was used in the analysis (Sudan et al., 2012). When the children were seven years old, mothers were asked whether their child was suffering from migraines. They also responded to the statement whether their child "often complained of headaches, stomach-aches, or sickness". This was considered as headache-related symptoms if parents reported this was "partly true" or "very true". Statistical analysis were adjusted for numerous confounders: Mother's age, mother's history of migraines, mother's feelings of worry, burden, and stress during pregnancy, social-occupational status, child's exposure to tobacco smoke, and child's sex. Children with prenatal and postnatal mobile phone exposure were 1.30-fold (95%: 1.01-1.68) more likely to get migraine and 1.32-fold (95% CI: 1.23-1.40) to have headache-related symptoms. These symptoms showed a statistically significant exposure-response relationship with number of daily mobile phone calls during pregnancy. The authors indicate that the results should be interpreted with caution because of the potential for uncontrolled confounding and exposure misclassification. A further limitation is that the outcome (like the exposure estimate) is self-reported by the mothers and that the question on headache was unspecific including stomach-aches and sickness. In line with the first two publications of the Danish Birth Cohort study by Divan et al, because exposure and outcome were reported at the same time point, also this publication has some potential for recall bias. Since the exposure to the foetus during the mothers' use of a mobile phone would be extremely low, the mechanism of how prenatal exposure could induce migraines and

headaches in the children remains essentially unclear. Regarding postnatal exposure, the observed association may be due to reverse causality, because children with migraine and other symptoms may be offered a mobile phone to get in touch with the parents in case of emergency.

Reproductive health

Effects of RF EMF exposure on male infertility have been previously assessed either in experimental studies on exposed sperm (in vitro), or in epidemiological studies on sperm from exposed or unexposed men. These studies were recently reviewed in (Agarwal et al., 2011, Gye and Park, 2012, La Vignera et al., 2012, Merhi, 2012). In studies on exposed sperm, a range of parameters has been evaluated, including motility, viability, normal sperm concentration, morphology, increase in radical oxygen species production, total antioxidant capacity score, DNA fragmentation, sperm mitochondrial membrane potential and sperm competence to bind the zona pellucida. Epidemiological studies have evaluated primarily sperm concentration, motility, morphology and viability (Agarwal et al., 2011, La Vignera et al., 2012). Overall, the reviews concluded that in the majority of studies, mobile phone exposure was associated with altered sperm parameters in experimental sperm studies as well as in epidemiological studies. Sperm motility and morphology seemed to be the most affected parameters. A somewhat more critical view was expressed by Merhi, who stated that studies have been diverse and inconsistent in conduct (Merhi, 2012). In particular, it was highlighted that the most important outcome would be to demonstrate increased infertility in an exposure-dependent manner, in order to be able to assess whether mobile phone use does or does not negatively impact reproduction. However, no such analysis has been reported (yet). Certain methodological characteristics of these epidemiological studies, such as the selection of participants from fertility clinics and the self-reported exposure assessment are of concern regarding the interpretability of their results. It is also highly questionable if the amount of mobile phone use is relevant for exposure of the testis, given that the exposure is rapidly decreasing with increasing distance from the device. Exposure to the testis might be more relevant when the phone is carried in the pocket during travelling (Urbanello and Roosli, 2012) but a systematic exposure evaluation of this context is still missing.

Gutschi et al. (2011) used a consecutive sample of 2110 men attending a fertility clinic in the time period between 1993 and 2007, and compared cell phone users to non-users. Sperm count, motility and morphology were compared as well as hormonal profiles. Except for sperm count, all assessed parameters were reported to be negatively affected in cell phone users. Given that mobile phone use was assessed based on self-report, the study has potential for recall or reporting bias. The exposure assessment was rather crude and only based on users versus non-users of mobile phones. The statistical analysis was not adjusted for potential confounders (e.g. age), which could have affected the results. There could be many more characteristics that correlate with both mobile phone use and factors that affect sperm quality in men that were not taken into account in this study.

Pregnancy outcomes

In a Norwegian cohort study by Baste et al. (2012), the authors analysed paternal exposure to RF EMF. 28,337 men were included in the study, which corresponds to the complete Royal Norwegian Navy officers employed between 1950 and 2004. Fathers were linked to the medical birth registry of Norway and 37,920 pregnancies were included in the analysis. The authors analysed risks of congenital malformation, perinatal mortality including stillbirth, low birth weight, preterm birth, small for gestational age, pregnancy with preeclampsia and the sex ratio. Exposure assessment was based on measurements on those spots where the crew

was most likely to be located (e.g. foredeck, afterdeck, officer's mess) and concerned exposure in the frequencies around 2.1 and 4 MHz (used for communication), as well as 9.1 and 9.6 GHz (radar), which is described in more detail in a separate publication (Baste et al., 2010). Exposure was differentiated between "acute", occurring in the 3 months preceding conception, and "non-acute" exposure which had occurred more than 3 months prior to conception. The authors report an increased risk of perinatal mortality as well as for pregnancies complicated by preeclampsia for those with acute exposure. There was no clear exposure-response-relationship. All RRs for non-acute exposure were around unity. A strength of the study is the completeness of the population from the registry, while covering a long time period, as well as the exposure assessment based on measurements and not self-reports. Interestingly, acute high exposed fathers but not non-acute exposed were somewhat more likely to become fathers of boys, with a RR of 1.38 (95% CI 0.99-1.93). This is in contrast to what was reported in a previous publication by the same authors on self-reported exposure in navy personnel that identified higher exposed persons as more likely to become fathers of girls (Baste et al., 2008).

Other health endpoints

In the Danish mobile phone subscriber cohort study, diagnosis and symptoms of multiple sclerosis (MS) were investigated in relation to mobile phone use among all 405,971 Danish residents who had a mobile phone subscription before 1996 (Harbo Poulsen et al., 2012). Both the year of diagnosis as well as the type of the first symptoms was assessed from medical records between 1987 and 2004. Mortality Rate Ratios (MRR) and Incident Rate Ratios (IRR) were calculated using Poisson models adjusted for age, sex, and calendar year in comparison to the rest of the Danish population who were not holding a mobile phone subscription prior to 1996. For female subscribers the risk (incidence rate ratio) for a MS diagnosis was 1.02 (95% CI: 0.83–1.24) and for men 1.11 (95% CI: 0.98–1.26). For female long-term subscribers (>10 years of subscription) the MS risk was 2.08 (95% CI: 1.08–4.01), based on 9 cases. For both genders combined no increased risk for long-term mobile phone users was observed (IRR: 1.09, 95% CI: 0.77–1.53). Presenting symptoms of MS differed between mobile phone subscribers and non-subscribers ($p = 0.03$), with slightly increased risk of diplopia (double vision) in both genders (IRR: 1.38, 95% CI: 1.02–1.86), an increased risk of fatigue among women (IRR: 3.02, 95% CI: 1.45–6.28), and of optic neuritis among men (IRR: 1.38, 95% CI: 1.03–1.86). Risk of death among MS-patients was not increased for subscribers compared to non-subscribers (MRR: 0.91, 95% CI: 0.70–1.19), but women with the longest subscription period (7-9 years) had an increased risk (MRR: 2.44, 95% CI: 1.20–4.98), which was not observed in males. The likelihood of getting a subscription after diagnosis or first symptoms was also analysed but not found to be significantly elevated (IRR: 1.07, 95% CI: 0.95–1.21 and IRR: 1.04, 95% CI: 0.88–1.22, respectively). The authors concluded that they found little evidence for a pronounced association between mobile phone use and risk of MS or mortality rate among MS patients. They note that the difference of MS symptoms corresponds to the symptom pattern that has been previously suggested to be associated with mobile phone use and that this deserves further attention, although small numbers and lack of consistency between genders prevent a causal interpretation. The strength of this Danish study is the objective assessment of exposure and outcome, which prevents from bias. A weakness, however, is the lack of information regarding the amount of mobile phone use: as in the other two analyses of the Danish subscriber cohort discussed in this report, the study adds to the evaluation whether duration of mobile phone use is a risk factor rather than the evaluation of the actual cumulative exposure. Information about possibly relevant confounding factors (e.g. socio-demographic characteristics) was lacking and was not considered in the analyses.

Cognitive decline of mobile phone users aged 55 years and older was investigated in 871 non-demented Chinese participants of the Singapore Longitudinal Ageing Studies (SLAS) cohort (Ng et al., 2012). Baseline examination took place between 2004 and 2005 and included the conduct of a Mini-Mental State Examination (MMSE) and a face-to-face interview. The frequency of mobile phone use was inquired on a three-point Likert scale (ranging from “never or rarely, i.e. less than one call per week”; to “often, i.e., daily”). Follow-up examination of the MMSE was conducted 4 years after baseline. In cross-sectional analyses at baseline, adjusted for relevant confounding factors, primarily higher global MMSE scores were found among mobile phone users. In longitudinal analyses, the change of MMSE between follow-up and baseline was not related to extent of self-reported mobile phone use at baseline. Risk of cognitive decline was also not associated with mobile phone use. The cross-sectional analyses suggest that mobile phone use among elderly is a self-selecting process. People with better cognitive functioning are apparently more likely to use mobile phones. The longitudinal analyses indicate that mobile phone use among older people does not result in deleterious effects on cognitive functioning. The crude exposure assessment, based on self-reports only, is a limitation for this otherwise well conducted longitudinal study. The mobile phone users differed substantially from the non-user groups in terms of various characteristics such as age, sex, education and physical activity. Although these factors are included in the statistical analysis, residual confounding is of concern.

Auditory functions of 112 mobile phone users aged between 18 and 45 years were compared to a control group of 50 subjects with similar mean age and sex distribution (Panda et al., 2010). The subjects were recruited from hospital visitors and among people who responded to a general notice about an awareness campaign regarding mobile phone use between July 2005 and November 2006. The audiologic parameters did not differ between the two groups. Only self-reported amount of mobile phone use was available in this study and the analyses were not adjusted for potential confounding factors.

In a subsequent study of the same research group (Panda et al., 2011), 125 mobile phone users and 58 control persons were recruited between July 2008 and December 2009 in the Department of Otolaryngology, Postgraduate Institute of Medical Education and Research, Chandigarh, India using the same recruitment strategy as in the first study. Personal interviews were conducted to obtain data on mobile phone usage such as the preferred ear used when calling, total cumulative usage in years, and average daily use in minutes. Hearing thresholds at speech frequency were found to be higher in mobile phone users compared to controls, although the difference was only significant for GSM but not for CDMA users. Middle latency responses were lower in GSM and CDMA mobile phone users compared to controls. The authors concluded that long-term and intensive GSM and CDMA mobile phone use may cause damage to the cochlea as well as the auditory cortex. Again, a lack of objective exposure data and confounding information is a limitation of this study. Further, the recruitment process of both studies in the context of an awareness campaign may have produced a selection bias because mobile phone users with hearing problems may have preferentially volunteered for the study.

In a cross-sectional study Saravi (2011) compared bone mineralisation of 24 male adult non-mobile phone users with 24 mobile phone users who had been carrying the phone close to the right hip for at least 1 year. Volunteers were recruited by word of mouth and were mainly faculty members and students from the Faculty of Medical Sciences. Total right and left hip bone mineral density (BMD) and bone mineral content (BMC), as determined by dual-energy x-ray absorptiometry, did not differ between the two groups. Within the mobile phone user

group, the bone mineralisation of the right hip was statistically reduced compared to the left hip for three out of six parameters. The difference was correlated to the amount of self-reported mobile phone use. In the control group, a difference between the left and the right hip was found for only one parameter. This first study on the association between mobile phone use and bone mineralisation is limited due to the cross-sectional design, a volunteer recruitment strategy which is vulnerable to bias and self-reported exposure assessment. Additional studies are needed before firm conclusions in terms of causality can be drawn.

In a cross-sectional study of 21,135 adults aged ≥ 18 years who participated in the 2008 U.S. National Health Interview Survey, self-reported physician-diagnosed hypertension was analysed regarding the type of phone use (Suresh et al., 2011). Based on in-person interviews, participants were categorized as mobile phone non-users (weighted prevalence: 33%), predominantly landline phone users (43%), dual users of mobile phone and landline (29%), and predominantly mobile phone users (22%). In multivariable regression models adjusted for sex, ethnicity, smoking, alcohol intake, body mass index, landline phone use, and physical activity, the participants who predominantly used mobile phones were less likely to report a physician-diagnosed hypertension compared to non-users (OR=0.86; 95%-CI: 0.75–0.98). The inverse association between mobile phone use and hypertension was more pronounced in women, in participants aged < 60 years, in whites, and in those with a BMI < 25 kg/m². This is a large population-based analysis. A limitation is that the assessment outcome and exposure was based on self-reports. Moreover, the socio-demographic characteristics differed substantially across the four exposure groups. Among other differences, the mobile phone user group was younger, less likely to smoke, more likely to be a light alcohol drinker and more likely to be higher educated. Although these factors are included in the statistical analysis residual confounding is a strong concern for this study.

Overall conclusions on epidemiology

Since the last Council report numerous epidemiological studies on mobile phone use and risk of brain tumours and other tumours of the head (vestibular schwannomas, salivary gland) have been published. No convincing evidence links mobile phone use to the occurrence of glioma or other tumours of the head region among adults. Recent studies have covered longer exposure periods. There is still only limited data regarding risks of long term use of mobile phones, but compared to the previous report, the evaluated exposure duration has increased to approximately 13-15 years of use. Thus, current scientific uncertainty remains for regular mobile phone use for more than 13-15 years, rare tumour subtypes (e.g. salivary gland tumours), specific brain regions or for slow-growing tumours (such as vestibular schwannoma). It is also too early to draw firm conclusions regarding children and adolescents and risk for brain tumours, but the available literature to date does not indicate an increased risk.

The available incidence data do not indicate a substantial increase in brain tumours that could be associated with the use of mobile phones. However, small to modest risks restricted to heavy mobile phone use, to rare histological subtypes or to longer latency periods (> 15 years) may still be undetectable in the currently available data.

The amount of published studies regarding leukaemia and malignant melanomas is very limited, but the published studies so far do not suggest that mobile phone use increases the risk of these diseases.

Apart from cancer, new epidemiological studies have also addressed child development, reproductive health, multiple sclerosis, cognitive decline in elderly, auditory functions, bone mineralisation and hypertension. Some protective and adverse effects have been observed, but methodological limitations prevent firm conclusions in terms of causal associations. In addition, the number of studies per outcome is relatively small, and consistency between various studies cannot be addressed.

Most intriguing are studies on child development and mobile phone use. However, to differentiate between effects from relevant exposure and effects from mobile phone use per se (e.g. social interaction, cognitive training) is a challenge and needs particularly well-designed studies. Studies might even suffer from reverse causality if behavioural problems result in an increased mobile phone use and not the other way round. Given the strong increase of mobile phone usage worldwide and therefore the potential of a large public health impact, effects of mobile phone use on child development should be followed up. Preferably, this should be addressed in prospective studies with the capability to disentangle effects from RF fields and other effects of mobile phone use.

Self-reported electromagnetic hypersensitivity (EHS) and symptoms

Introduction

Different types of human and epidemiological studies have addressed the association between various sources of EMF and symptoms or health-related quality of life. Many of these studies have also focussed on individuals who state to react to EMF at lower levels than the general population (electromagnetic hypersensitivity). In order to give a comprehensive review of these studies, they are summarised separately in the following chapter.

Electromagnetic hypersensitivity (EHS) is an unclear phenomenon without a well-established definition. The phenomenon is sometimes also called idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF), since a causal relation with EMF exposure has not been established so far. According to the World Health Organization (WHO, 2005), EHS is characterized by a variety of non-specific symptoms, which afflicted individuals attribute to various sources of EMF. Unspecific symptoms such as sleep disturbances, fatigue, tiredness, concentration difficulties, dizziness, nausea or skin symptoms are the most common reported symptoms. The combination of symptoms is not part of any recognized syndrome. There is a lack of validated criteria for defining and assessing EHS and previous studies have applied different criteria. Baliatsas et al. (2011) conducted a systematic review to evaluate EHS criteria of studies published up to June 2011. In the 63 identified studies “hypersensitivity to EMF” was the most frequently used descriptive term. The predominantly applied criteria to identify EHS were: 1. Self-report of being sensitive or hypersensitive to EMF. 2. Attribution of at least one non-specific symptom to at least one EMF source. 3. Absence of medical or psychiatric/psychological disorder that would explain the presence of these symptoms. 4. Occurrence of the symptoms is temporally, usually within 24 hours, related to perceived EMF exposure. Experimental studies used a larger number of criteria than those of observational design and performed more frequently a medical examination or interview as prerequisite for inclusion.

Surveys

In a Taiwanese survey conducted with 1251 adults selected from a nationwide computer-assisted telephone interview system, the prevalence of EHS was estimated to be 13.3 % (95% CI: 11.2-15.3%) (Meg Tseng et al., 2011). An additional finding from the survey was that people who were aged 65 years or older were less likely to report EHS, whereas people with a very poor self-reported health status, those who were unable to work, and those who had a psychiatric disease were more likely to report to suffer from EHS. This prevalence estimate may not be representative for Taiwan because the participation rate was very low (11.6%). Thus, it is conceivable that concerned people were more likely to participate.

Kato and Johansson conducted a postal questionnaire survey of 75 EHS persons (95% women) recruited via EHS self-help groups in Japan (Kato and Johansson, 2012). Similar to other surveys, participants mainly reported fatigue/tiredness, headache, concentration difficulties and memory difficulties (Röösli and Hug, 2011, Röösli et al., 2010a). These complaints were mostly attributed to exposure from a mobile phone base station or a mobile phone handset. Interestingly, 65% of the participants reported to experience health problems due to the exposure from other passengers' mobile phones in trains or buses, and 12% reported that they could not use public transportation at all.

Extremely Low Frequency (ELF) fields

Human laboratory studies

McCarty and colleagues reported about three experiments which were carried out with a 35 year old medical doctor, who reported to have EHS (McCarty et al., 2011). During testing she was sitting on a chair with closed eyes. On both sides of her head a metal plate was fixed at a distance of 36 cm which produced a sinusoid 60 Hz electric field with an average field strength at the head of 300 V/m, with a spatial maximum of 1000 V/m. The average exposure of the body was calculated to be 50 V/m. In the first experiments, sham conditions and pulsed field conditions (50 ms on and 50 ms off) were applied ten times for 100 s intervals in a randomized and double blind manner. After all 10 true exposure conditions the subject reported to experience moderate to strong symptoms such as headache or muscle pains. After the 10 sham conditions she complained 5 times about slight symptoms and 5 times she did not report symptoms at all. In the second experiment, a third exposure condition with a continuous field was added and each condition was applied 5 times. Symptoms occurred more often during the pulsed field compared to sham but not during the continuous field condition. According to the authors this indicates that transients, which are occurring when the field is switched on and off, are more relevant to health than continuous field conditions. The ability to perceive the exposure was tested in a third experiment. Eight sequences with 30 to 50 tests, consisting of 2 s true/sham field conditions followed by a 10 s break were applied. The carrier frequency was set to 60 Hz in three sequences, to 1 kHz in two sequences and to 10, 100, 500 kHz in the further three sequences. In addition, four control sequences were applied without any true exposure. The person correctly detected presence of the EMF in 11% of the exposure conditions, but also reported sensing fields in 10% of the control conditions without exposure. According to the authors, this indicates that field rating was not better than what would be expected by chance.

The article was criticized in several letters to the editor because it was not described how symptoms were recorded and it was suggested that posterior, data driven, categorization could have resulted in a statistical artefact (Marino et al., 2012; Rubin et al., 2012b; Rubin et al., 2012a).

In a human laboratory study, physiological changes, subjective symptoms and perception of a magnetic field were investigated in two volunteer groups of 15 self-reported EHS and 16 non-EHS individuals (Kim et al., 2012a). Subjects were recruited through advertisement in the Yonsei University Health System (YUHS) in Seoul, Korea, and both groups were on average 26 years old. To identify EHS persons, the symptom score list of Eltiti et al. (2007) was used. To be eligible for the study, symptoms had to be attributed to ELF EMF and not to be explained by the presence of a chronic illness. During the experiment, sham and true magnetic field exposure conditions were applied for 30 min using a randomized, counterbalanced, double blind, cross-over design, and study participants were asked to fill in the Eltiti symptom scale (Eltiti et al., 2007) before and after each experiment. During the experiment the volunteers were sitting on a chair and a coil was placed about 20 cm above their head producing a 60 Hz magnetic field of approximately 12.5 μ T at the top of their head. Before the experiment, the average symptom score was 32.5 in the EHS group and 5.9 in the non-EHS group. Neither physiological reactions (heart rate, respiration rate, and heart rate variability), symptoms (throbbing, itching, warmth, fatigue, headache, dizziness, nausea, and palpitations), nor field perception were related to the actual applied exposure condition. The

authors concluded that the subjective symptoms of the EHS-group did not result from the magnetic field exposure but from other non-physiological factors. This is a well-designed and conducted study but the sample size is relatively small.

In another provocation study, 29 EHS individuals and 42 control persons were exposed to either a sham or a 50 Hz 500 μ T magnetic field, which was applied to their right arm in 20 subsequent 1 min sessions in a quasi-random way (ten times on and ten times off) (Koteles et al., 2012). The study participants had to guess the presence or absence of the field. Compared to the expected number of 5 correct hits per person, the average number of correct hits was 5.97 for the EHS group and 4.45 for the control group. However, also the number of false alarms (reporting being exposed when in reality there was no magnetic field applied) were higher in the EHS group (4.90) compared to the control group (3.90). The authors concluded from the higher proportion of correct hits and false alarms in the EHS group that EHS individuals compared to the control group showed a higher than expected detection performance, and they used a significantly lower criterion when deciding about the presence of the magnetic field. It is noteworthy that one individual was excluded from the control group, because he was able to detect the magnetic field almost perfectly and this performance was replicated in a second session. In addition to field perception, heart rate variability was measured before, and symptoms were assessed before and after the experiment. No differences in heart rate variability between the two groups were found. Further, after the experiment the EHS group reported a considerably higher number of symptoms than the control group but the study design did not allow evaluating whether the symptoms were caused by the magnetic field exposure because a control condition was lacking. It is not clear from the paper whether the differences between the two groups really represent a better field rating of the EHS group or whether these differences were produced when EHS persons reported more often being exposed and thus also produced the higher percentage of false positive alarms compared to the control group. No information on the level of the exposure condition is provided in the paper and thus, it cannot be assessed whether a perfect field rating as observed for one person is unexpected or not, for the applied exposure conditions.

Radiofrequency (RF) fields

Human Laboratory studies

In a double blind provocation study, cognitive and physiological responses of EHS and non-EHS persons exposed to a 420 MHz Terrestrial Trunked Radio (TETRA) base station signal were investigated (Wallace et al., 2012). 51 EHS individuals and 132 controls were included in the study and invited for three sessions spaced one week apart. The first session was an “open provocation”, meaning that study participants were aware that they were exposed to a TETRA signal with a power flux density of 10 mW/m². In session two and three, each participant was exposed to a sham and a real exposure condition in a randomized way during 50 minutes. In both groups, no differences in cognitive performance between sham and TETRA exposure were observed. Physiological responses, which were blood volume pulse, heart rate and skin conductance, also did not differ between the exposure conditions. This is a well conducted provocation study with a relatively large sample size. However, application of a Bonferroni correction for multiple testing considerably reduces the statistical power of the study.

A double-blind provocation study with Iranian students aged 18 to 28 years reporting EHS was reported by Mortazavi et al. (2011). 20 persons were exposed to real and sham GSM 900

mobile phone signals during 10 minutes each. No further information about the transmitting mode or exposure level of the mobile phone was reported in the paper. The students were not able to discriminate between real and sham exposure better than expected by chance. No exposure effects on heart rate, respiration, and blood pressure were observed. The EHS subjects were identified through a survey where 700 Iranian students participated. In this survey, the extent of concentration problems and low back pain was investigated and both outcomes were associated with self-reported mobile phone use, but potential confounding factors were not taken into account. The authors conclude that their findings confirm the results of other provocation studies and that they indicate the possible role of psychological factors in EHS. The results of the survey have to be interpreted with caution since they are based on self-reports and no confounding factors were considered in the analysis. Moreover, the directions of the observed associations are not presented and it seems that low back pain was more common in non-mobile phone users than mobile phone users.

Augner and colleagues conducted a meta-analysis on human laboratory studies addressing the association between GSM mobile phone exposure and well-being in self-reported sensitive or non-sensitive people (Augner et al., 2012). They identified 17 suitable studies which were published between 2001 and 2010, including a total of 1174 participants. Exposure duration in the individual studies ranged from 5 to 180 minutes. After pooling the effects of all studies, neither subjective (headache, nausea, fatigue, dizziness, skin irritation, exposure perception) nor objective parameters of well-being (blood pressure, heart rate, heart rate variability, skin resistance, respiration) were found to be related to short-term GSM mobile phone exposure. The authors concluded that there is no evidence for short term effects of electromagnetic fields emitted by mobile phones on well-being and recommend that future research should focus on possible long-term effects.

Epidemiological studies

In a Swedish study a self-report questionnaire was used to compare 45 persons with only mobile phone attributed symptoms and 71 with “general” EHS, recruited through newspaper advertisement with a population-based sample (n=106) and a healthy control group (n=63) matched with respect to age and sex (Johansson et al., 2010). The control group was a subsample of the population-based sample where participants reporting EMF-related symptoms were excluded. Most symptoms were reported by the EHS group, followed by the group with mobile phone-related symptoms. The population-based sample and the control group reported fewer symptoms. The mobile phone group reported a high prevalence of somatosensory symptoms related to the head such as warmth at the ear, burning skin or tingling/tightness whereas the other EHS group was more likely to report symptoms such as fatigue, concentration difficulties or dizziness. In comparison to the reference groups, the mobile phone group showed increased levels of exhaustion and depression but not of anxiety, somatisation or stress; the EHS group showed increased levels for all of the conditions except for stress. The authors conclude that the findings support the idea of a difference between people with symptoms related to specific EMF sources and people with general EHS. This may indicate that other factors than EMF exposure play a role when attributing symptoms to specific EMF sources. Whether symptoms are associated with EMF exposure cannot be answered with this cross-sectional study.

In a prospective cohort study of young adults (20-24 years) the association between mental health outcomes and use of mobile phones was investigated based on questionnaires at baseline and one year follow-up (Thomee et al., 2011). From 10,000 women and 10,000 men who were invited, 4,347 women and 2,778 men participated in the baseline survey

(participation rate: 36%) and 2701 women and 1455 participated in the follow-up (21%). In a cross-sectional analysis at baseline adjusted for relationship status, educational level and occupation, persons reporting a high amount of mobile phone use were more likely to also report stress, sleep disturbances, and symptoms of depression. In the prospective analysis, persons were excluded that reported symptoms at baseline, in order to assess who developed symptoms during the study period. In this analysis, a high amount of mobile phone use at baseline was associated with sleep disturbances in men only and with symptoms of depression in men and women. An increased occurrence of mental health outcomes was also observed in people with heavy use of mobile phones and people who experienced accessibility via mobile phones to be stressful. The low participation rate may have introduced selection bias, which is of particular concern for the cross-sectional analysis but to some extent also for the longitudinal analysis because the drop-out rate was relatively high. Exposure assessment was based on self-reports and only a limited number of possibly relevant confounders have been considered in the analysis. In addition, it was not possible to differentiate between effects that are associated with using a mobile phone as such, and the exposure to EMF from a mobile phone.

In a Korean cross-sectional study 214 medical students (participation rate: 87%) were asked about headaches attributed to mobile phone use with a 14-item questionnaire (Chu et al., 2011b). Forty (19%) of the students reported to have experienced headache more than 10 times within one hour after mobile phone use during the last year. According to an in-depth evaluation, the headache was triggered by prolonged mobile phone use. Headache attributed to mobile phone use was usually of dull or pressing pain quality, localised ipsilateral at the side of mobile phone use, and associated with a burning sensation.

In a German cross-sectional study on 1,025 adolescents aged between 13 and 17 years, the occurrence of various types of headache in relation to media use was investigated (Milde-Busch et al., 2010). An association between any type of headache and extent of listening to music was observed but no associations with other types of media use such as mobile phone use, computer use or watching TV. RF EMF exposure from mobile phone use was not specifically considered in this study.

A large Japanese cross-sectional study investigated mobile phone use behaviour of adolescents after lights out (Munezawa et al., 2011). A total of 95,680 adolescents participated in the questionnaire survey (participation rate 63%). About 8% reported to use their mobile phone for calling and about 18% for text messaging after lights out every day. Frequency of mobile phone use for calling and for sending text messages after lights out was associated with sleep disturbances (short sleep duration, subjective poor sleep quality, excessive daytime sleepiness, and insomnia symptoms) independent of covariates and independent of each other. This study did not focus on RF EMF exposure but showed that the use of mobile phones for calling and for sending text messages after lights out is relatively common among Japanese adolescents and is associated with sleep disturbances.

In a cross-sectional study, 3611 Dutch adults (response rate: 37%) completed a questionnaire about non-specific physical symptoms as well as environmental and psychological characteristics (Baliatsas et al., 2011). Various significant associations between occurrence of symptoms and psychological characteristics were observed. Most importantly, after adjustment for demographic and residential characteristics, the symptom score was positively correlated to self-reported proximity to base stations and power lines but not to calculated distance between household addresses and location of base stations or power lines. A

limitation of the study is the cross-sectional design and the fact that the survey was conducted in 2006 whereas data on the locations of transmitters were obtained for the year 2008. This is expected to result in erroneous distance assignment when new base stations have been built between 2006 and 2008. Since distance to mobile phone base station is not correlated to RF EMF exposure (Frei et al., 2010), the observed absence of an association must not be considered as evidence for an absence of effect. However, the study demonstrates that studies relying on self-reported distance to mobile phone bases stations are likely to be prone to bias.

A Polish cross-sectional study addressed subjective complaints of people living near mobile phone base stations (Bortkiewicz et al., 2012). Suitable flats with a total of 1154 inhabitants from five regions of Łódź were selected for the study according to the transmitting characteristics of base stations in the vicinity. 181 men and 319 women participated and were interviewed about their demographics, occupational and environmental exposure to EMF, health conditions and subjective complaints. Electric field measurements were performed in the buildings located closest to the azimuth of the antennas and distance was obtained from the housing estate plan. Electric fields above 0.8 V/m were recorded in 12% of the flats. Electric field strength was not correlated to the distance between flats and base stations. After adjusting for age, sex, occupational ELF- and RF EMF exposure and EMF-emitting household equipment, the prevalence of headache and impaired memory was related to the distance to the next base station, although the highest prevalence was not found closest to the base station but in the distance category of 101-150 m for headache and beyond 150 m for impaired memory. No data about the association between symptoms and measured EMF exposure were presented but the authors concluded that they did not find a correlation between the electric field strength and the frequency of subjective symptoms. The cross-sectional design is a limitation for assessing causality. In addition, only a few possibly relevant confounding factors were considered.

In a German population-based cross-sectional study 24-hour exposure profiles of 1484 children and 1508 adolescents were measured between 2006 and 2008 (Heinrich et al., 2010). The participation rate was 52%. Exposure levels were compared with acute symptoms that were assessed twice during the study day using a symptom diary. The inquired symptoms were headache, irritation, nervousness, dizziness, concentration problems and fatigue. Data were analysed by means of logistic regression models adjusted for age, sex, level of education of the parents, study town and environmental worries and stratified for children and adolescents. From a large number of investigated associations, only a few significant associations were found which did not show a consistent exposure-response pattern. The authors thus concluded that the few observed significant associations were not causal but rather occurred by chance.

In a Swiss cohort study on health-related quality of life, 1375 individuals took part in a baseline survey (participation rate 37%) in 2008, and of these, 1122 individuals (82%) completed a follow-up investigation one year later (Frei et al., 2012; Mohler et al., 2012). Exposure to fixed site transmitters at the place of residency was calculated with a geospatial computation model. Cordless and mobile phone use was obtained from the questionnaire, and 453 participants gave consent that their mobile phone connection data of the previous six months could be obtained from their operator. An exposure assessment model was used to calculate total RF EMF exposure of each study participant (Frei et al., 2009). After controlling for numerous potential confounders, exposure to environmental RF EMF at baseline was not consistently associated with symptoms, sleep disturbances, excessive daytime sleepiness, tinnitus or headache one year later. Similarly, an increase or decrease of the personal RF EMF

exposure between 2008 and 2009 was not accompanied with a respective change of health disturbances. With respect to RF EMF sources operating close to the body, self-reported use of mobile and cordless phones was not associated with health-related quality of life in a consistent manner. Also the operator-recorded mobile phone use, which was available for a subset of the study participants, was not related to health disturbances (Frei et al., 2012; Mohler et al., 2012). The authors concluded that the few observed statistical associations, which did not show a consistent pattern, most likely were due to chance given the high number of health effects and exposures that were analysed. About 8% of the study participants reported to have EHS and an additional 14% of the participants attributed symptoms to RF EMF exposure (attributers) without considering themselves as being hypersensitive to electromagnetic fields. The prevalence of symptoms was highest in the EHS persons. However, health disturbances of EHS individuals and attributers were neither associated with environmental RF EMF exposure levels nor with wireless phone use (Röögli et al., 2010b).

Reviews

Rubin et al. updated an earlier systematic review (Rubin et al., 2005) on 31 provocation studies which had exposed EHS volunteers to active or sham (no exposure) EMF and assessed whether volunteers could detect these fields or whether they reported more symptoms when being exposed to EMF (all frequency ranges). For the update, the authors identified 15 new experiments resulting in a total database of 46 provocation studies that had been performed under blind or double-blind exposure conditions with overall 1175 EHS volunteers (Rubin et al., 2011). They found no evidence for an association between exposure and health disturbances. There was also no evidence that EHS volunteers were able to perceive EMF exposure better than expected by chance. However, the studies supported the role of the nocebo effect in triggering acute symptoms in EHS individuals, meaning that people were more likely to have symptoms when they thought they were exposed. The authors concluded that despite the conviction of EHS sufferers that their symptoms are triggered by exposure to EMF, repeated experiments have been unable to replicate this phenomenon under controlled conditions.

Baliatsas et al. conducted a systematic review including a meta-analysis of observational studies about RF EMF exposure and non-specific physical symptoms in the general population (Baliatsas et al., 2012). In total, 22 studies were identified that were published between 2000 and 2011. According to a qualitative assessment, no or only inconsistent associations between symptoms and EMF exposure were found. Random effects meta-analyses did not reveal significantly elevated odds ratios (OR) for the severity of various symptoms in relation to RF EMF exposure: headache (OR=1.65; 95% confidence interval CI=0.88–3.08 based on 3 studies), concentration problems (1.28; 0.56–2.94, 3 studies), fatigue-related problems (1.15; 0.59–2.27, 3 studies) and dizziness-related problems (1.38; 95% CI=0.92–2.07, 2 studies). Also, no associations were observed between RF EMF exposure and the frequency of these symptoms.

Overall conclusions on Symptoms and self-reported electromagnetic hypersensitivity (EHS)

Since the last Council report, research on EHS and quality of life in the general population has progressed considerably. The EHS phenomenon has mainly been investigated in human laboratory studies applying extremely low frequency electric or magnetic fields or mobile phone-like exposure. Two studies on ELF exposure reported effects, but methods were not

adequately reported. Strikingly, in one study, a person had an almost perfect field perception. This deserves some attention and the exposure circumstances should be better described. Overall, however, new experimental EHS studies on mobile phone use did not indicate short-term effects.

Until the last Council report, only cross-sectional epidemiological research on symptoms and RF EMF was available. In the meanwhile, a few longitudinal studies have been published, which allow more reliable conclusions. A cohort study of mobile phone use in young adults with a follow-up of one year (Thomee et al., 2011) demonstrated that cross-sectional analysis are more likely to find associations which cannot be confirmed in longitudinal analyses. This may indicate the important role of confounding and reverse causality as discussed in the chapter “overall conclusions on epidemiology”. Nevertheless, also in the longitudinal analyses a few associations between mobile phone use and health-related quality of life were observed which deserve further attention. Since the study did not attempt to differentiate between exposure effects and non-exposure effects, the cause for this association cannot be resolved at this stage. Moreover, the possibility that quality of life status and use of mobile phone may be affected by some common latent variables cannot be excluded. In terms of exposure from fixed site transmitter, the Swiss cohort study (Röösli et al., 2010b); (Frei et al., 2012); (Mohler et al., 2012) did not consistently find effects after one year of exposure. Exposure gradients were relatively small in the study.

In conclusion, the new epidemiological studies on symptoms using an improved design rather indicate the absence of a risk from RF EMF exposure on health-related quality of life. Uncertainty concerns mainly high exposure levels from wireless phone use and longer follow-up times than one year.

Recent expert reports

IARC Monograph on Radiofrequency fields

In May 2011, the WHO/International Agency for Research on Cancer (IARC) convened a Working Group of 31 scientists from 14 countries to assess the potential carcinogenic hazards from exposure to radiofrequency electromagnetic fields. This assessment will be published as Volume 102 of the IARC Monographs, which follows Volume 80 on non-ionizing radiation (extremely low-frequency electromagnetic fields).

The IARC Monograph Working Group discussed and evaluated the available literature on the following exposure categories involving radiofrequency electromagnetic fields:

- personal exposures associated with the use of wireless telephones,
- environmental exposures associated with transmission of signals for radio, television and wireless telecommunication, and
- occupational exposures to radar and to microwaves.

The IARC Monograph Working Group reviewed the existing exposure data, the studies of cancer in humans, the studies of cancer in experimental animals, and the mechanistic and other relevant data. They discussed the possibility that these exposures might induce long-term health effects, in particular an increased risk for cancer.

Regarding personal exposures, the evidence was evaluated as being *limited* among users of wireless telephones for glioma and acoustic neuroma (vestibular schwannoma), and *inadequate* to draw conclusions for other types of cancers. For occupational and environmental exposures, the evidence was also judged to be inadequate. The Working Group did not quantitate the risk; however, one study of past cell phone use (up to the year 2004), showed a 40% increased risk for gliomas in the highest category of heavy users (reported average: 30 minutes per day over a 10-year period).

Overall, the Working Group classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B), based on an increased risk for glioma, a malignant type of brain cancer associated with wireless phone use.

A brief report summarizing the main conclusions of the IARC Working Group and the evaluations of the carcinogenic hazard from radiofrequency electromagnetic fields (including the use of mobile telephones) was published in The Lancet Oncology (Baan et al., 2011).

The following part of this Chapter briefly summarises some expert reports published since the last Council report. The summaries are directly edited from the executive summaries of these reports. The Council has not evaluated or commented any of the reports.

Report of the independent Advisory Group on Non-ionising Radiation (AGNIR) 2012

(Edited from the Executive Summary of the report (AGNIR, 2012))

Since the last AGNIR review on RF fields, in 2003, large research programs in the UK and across Europe have come to fruition. The amount of research published has greatly increased and much of it has been of higher quality than was previously available.

Exposure of the general public to low level RF fields from mobile phones, wireless networking, TV and radio broadcasting, and other communications technologies is now almost universal and continuous. Additional sources of exposure to RF fields are appearing from new technologies such as domestic smart meters and airport security scanners.

Current exposure guidelines are based on thermal effects of RF fields. Individual exposures and doses associated with many RF field sources are well documented, enabling predictions to be made of associated temperature rises in vivo.

Studies of the effect of RF field exposure on cells in vitro now include an increasing number that have re-tested findings from previous studies. No consistently replicable effects have been found from RF field exposure at levels below those that produce detectable heating. In particular, there has been no convincing evidence that RF fields cause genetic damage or increase the likelihood of cells becoming malignant.

Studies of animals have employed a wide range of biological models, exposure levels and signal modulations. Taken together, these studies provide no evidence of health effects of RF field exposures below internationally accepted guideline levels. In particular, well-performed large-scale studies have found no evidence that RF fields affect the initiation and development of cancer, and there has been no consistent evidence of effects on the brain, nervous system or the blood-brain barrier, on auditory function, or on fertility and reproduction.

The evidence suggests that RF field exposure below guideline levels does not cause acute symptoms in humans, and that people, including those who report being sensitive to RF fields, cannot detect the presence of RF fields. Similarly, well-conducted studies do not suggest that exposure to RF fields gives rise to acute cognitive effects. There is, however, some evidence that RF field exposure may affect EEG and other markers of brain function. However, these effects have not been consistent across studies. In addition, the size of these reported effects is often small relative to normal physiological changes, and it is unclear whether they have any implications for health.

Epidemiological studies on cancer risks in humans in relation to occupational RF field exposures and residential exposures from proximity to RF transmitters have had considerable methodological weaknesses, particularly in exposure assessment. They give no evidence of any causal effect but also give no strong evidence against it.

There is now a substantial body of epidemiological research published on cancer risks in relation to mobile phone use. Although some positive findings have been reported in a few

studies, overall the evidence does not suggest that use of mobile phones causes brain tumours or any other type of cancer. The data, however, are essentially restricted to periods of less than 15 years from first exposure.

Conclusions

The quantity, and in general quality, of research published on the potential health effects of RF field exposure has increased substantially since AGNIR last reviewed this subject. Population exposure to RF fields has become more widespread and heterogeneous. There are still limitations to the published research that preclude a definitive judgment, but the evidence considered overall has not demonstrated any adverse health effects of RF field exposure below internationally accepted guideline levels. There are possible effects on EEG patterns, but these have not been conclusively established, and it is unclear whether such effects would have any health consequences. There is increasing evidence that RF field exposure below guideline levels does not cause symptoms and cannot be detected by people, even by those who consider themselves sensitive to RF fields. The limited available data on other non-cancer outcomes show no effects of RF field exposure. The accumulating evidence on cancer risks, notably in relation to mobile phone use, is not definitive, but overall is increasingly in the direction of no material effect of exposure. There are few data, however, on risks beyond 15 years from first exposure.

In summary, although a substantial amount of research has been conducted in this area, there is no convincing evidence that RF field exposure below guideline levels causes health effects in adults or children.

Weak high-frequency electromagnetic fields - an evaluation of health risks and regulatory practice

(Edited from the English summary of the Norwegian report (Nasjonalt folkehelseinstitutt, 2012:3))

On the basis of the public concerns, the Ministry of Health requested the Norwegian Institute of Public Health to assemble a cross-disciplinary Expert Committee to summarize the scientific knowledge regarding exposure to weak high-frequency fields. The analysis should also include an assessment of the suitability of the threshold limit values, as well as an assessment of how the potential risks related to exposure from electromagnetic fields should be managed in Norway.

The Expert Committee was established in spring 2010 and was composed of individuals with expertise in environmental and occupational medicine, biology, physics, metrology, biophysics, biochemistry, epidemiology and philosophy, as well as expertise in administration and risk management. The Expert Committee has reviewed and evaluated recent research in the relevant fields. They have reviewed recent research reports and expert review reports by international and national expert groups. Based on this review and on available data about exposure to electromagnetic fields, the Committee has conducted a risk assessment and also evaluated the current regulatory practice.

An overall assessment of the health risks of exposure to radiofrequency fields has been implemented in the same way as is common for other types of environmental exposure. Health risks have been evaluated on the basis of internationally published research literature, which is very extensive for RF fields. Exposure to RF fields in the Norwegian population has

been considered primarily using measurements taken by the Norwegian authorities in the course of 2010. The Expert Committee has assessed the overall health risk based on these measurements.

There is a broad international consensus among experts that the ICNIRP reference values provide good protection against both the excitation of nerve tissue and harmful heating of body tissues. For exposure at levels below the ICNIRP reference values, the ICNIRP has found no documented adverse effects, despite extensive research. No mechanisms have been identified which could account for any such effect. The Expert Committee considers the increased risk reported in some case-control studies to be inconsistent with the results from studies of time trends based on cancer registry data in either the Nordic or other countries.

Overall, the available data show no association between exposure to RF fields from a mobile phone and fast-growing tumours, including gliomas in the brain which have a short induction period. For slow-growing tumours, including meningiomas and acoustic neuromas, the data available so far do not indicate an increased risk. However, it is too early to completely exclude the possibility that there may be an association with exposure to RF fields from mobile phones, because the period of use of mobile phones is still too short. Available epidemiological cohort and case-control studies provide no information about a possible effect after a long induction period. The longest induction period studied is 13 years, and no participants had used mobile phones for more than 20 years when the studies were conducted.

For leukaemia, lymphoma, salivary gland tumours and other tumours, there are insufficient data to draw conclusions, but the available studies do not suggest an increased risk. The only study that looked at exposure to RF fields from mobile phones and the possible risk of brain tumours among children and adolescents does not support an association, but a minor increase in risk cannot be excluded as a result of limited statistical power in the study. There are several registry-based studies that have examined the development of the incidence of brain tumours over time among children and adolescents. They show no indication of increased disease incidence in these groups after the introduction of mobile phones. Exposure from base stations and radio and television transmitters is significantly lower than from using a mobile phone and the available data do not suggest that such low exposure could increase the risk of cancer.

A number of studies of cancer in animals have been performed, and relevant mechanisms have also been studied using micro-organisms and cells. Overall, these studies provide further evidence that exposure to weak RF fields does not lead to cancer.

It is well known that exposure to RF fields at levels that provide thermal effects (dielectric heating), can damage sperm. Several studies of sperm samples from humans and animals have been carried out to investigate possible non-thermal effects of RF exposure on sperm. Since sperm cells are particularly sensitive to heating from RF fields, it is important that there is good control of exposure during the experiments. Most of the earlier studies were of too poor quality, particularly with regard to control of this aspect of exposure, for any conclusion to be drawn from them. Overall, there is little indication that exposure to weak RF fields adversely affects fertility. The few studies that do exist do not provide evidence that exposure to weak RF fields during pregnancy has adverse effects on the foetus.

Based on a large number of studies, many of which are of high quality, there is no evidence that weak RF fields cause symptoms such as headache, fatigue or concentration problems, either after short or long-term exposure.

There is also no evidence that individuals with health problems that they attribute to electromagnetic fields are able to detect such exposure. Blind trials show that symptoms also occur when subjects are not exposed. This means that electromagnetic fields do not need to be present for health problems attributed to electromagnetic fields to occur. Health problems can thus be due to other factors. The Expert Committee concludes that scientific studies indicate that electromagnetic fields are not the direct or contributing cause of the condition of health problems attributed to electromagnetic fields (electromagnetic hypersensitivity).

A large number of studies have examined the possible effects of exposure to weak RF fields (i.e. exposure within the ICNIRP's reference values). The studies have been performed on cells and tissues, and in animals and humans. The effects that have been studied apply to changes in organ systems, functions and other effects. There are also a large number of population studies with an emphasis on studies of cancer risk. The large total number of studies provides no evidence that exposure to weak RF fields causes adverse health effects. Some measurable biological / physiological effects cannot be ruled out.

Report from the Swedish Council for Working Life and Social Research

In 2003, the Swedish Council for Working Life and Social Research (FAS) was commissioned by the Government to evaluate research on possible health problems related to exposure to electromagnetic fields, primarily research on electromagnetic hypersensitivity. FAS, in turn, commissioned a working group, chaired by Professor Anders Ahlbom at Karolinska Institutet, to produce annual reports on the scientific developments in the field. The first report from the working group was published in the beginning of 2004. The mandate from the Government was discontinued in the beginning of 2012. FAS then tasked Professor Ahlbom with producing a summary of the annual reports. The title of the summary report, published in June 2012, is *Radiofrequency Electromagnetic Fields and Risk of Disease and Ill Health - Research during the last ten years* (Ahlbom, 2012). The executive summary of the report follows:

The focus of the FAS report is electromagnetic fields of the type that occur in connection with mobile telephony, so called radio frequency (RF) fields and the possibility that exposure to such fields poses a risk of disease or ill health. The purpose is to describe what was known ten years ago, what we have learned during the past decade, and where we stand today.

Ten years ago

The mechanism of interaction between RF fields and the human body was established long ago and is increased temperature of exposed tissue (compare microwave ovens). Methods for measurements of the fields in the air were developed early but the data on distribution of the absorbed energy in the human body was still restricted. Data regarding sources and levels of exposure to the population was limited because systematic measurements had not been conducted. A considerable number of provocation studies on exposure to fields of lower frequencies (related to electric power and computer screens) had already been conducted and had not found any evidence of an association to symptoms (headache, vertigo, dizziness, concentration difficulties, insomnia) but the corresponding information about RF fields and

occurrence of symptoms was scarce. Few and methodologically limited epidemiological studies had been conducted on RF field exposure and cancer.

What was learned during the past ten years

Extensive research on various aspects of RF fields has been conducted during the last ten years and the knowledge database has increased considerably. Simulation models have improved our knowledge about how the fields and the energy are distributed in the body. Mobile, so called exposimeters have been developed for use in epidemiological studies. Many more measurements have been conducted to increase our knowledge about sources and levels of exposure to the population.

More than 15 provocation studies (single or double blind) have been conducted on symptoms attributed to exposure to RF fields. These studies have not been able to demonstrate that people experience symptoms or sensations more often when the fields are turned on than when they are turned off. One longitudinal study has looked at frequency of symptoms in relation to environmental exposure and this study found no association between exposure and symptoms.

A considerable number of studies on cancer, and in particular brain tumour, were presented. As a consequence there exist now very useful data including methodological results that can be used in the interpretation of this research. With a small number of exceptions the available results are all negative and taken together with new methodological understandings the overall interpretation is that these do not provide support for an association between mobile telephony and brain tumour risk. In addition, national cancer statistics are very useful sources of information because mobile phone usage has increased so quickly. Had mobile phone use and brain cancer risk been associated it would have been visible as an increasing trend in national cancer statistics. But brain cancer rates are not increasing.

Where we stand today

We now know much more about measurements and absorption of RF fields and also about sources of exposure to the population and levels of exposure. A considerable number of provocation studies on RF exposure and symptoms have been unable to show any association. Overall, the data on brain tumour and mobile telephony do not support an effect of mobile phone use on tumour risk, in particular when taken together with national cancer trend statistics throughout the world.

Research on mobile telephony and health started without a biologically or epidemiologically based hypothesis about possible health risks. Instead the inducement was an unspecific concern related to a new and rapidly spreading technology. Extensive research for more than a decade has not detected anything new regarding interaction mechanisms between radiofrequency fields and the human body and has found no evidence for health risks below current exposure guidelines. While absolute certainty can never be achieved, nothing has appeared to suggest that the since long established interaction mechanism of heating would not suffice as basis for health protection.

The EFHRAN Project

European Health Risk Assessment Network on Electromagnetic Fields Exposure
(<http://efhran.polimi.it/dissemination.html>)

The general objective of the EFHRAN project (2009-2012) has been to establish a network for performing health risk assessments of exposure to electromagnetic fields. The project was funded by the European commission. Universities and research centres from seven European countries have participated together with 17 collaborating partners from a further ten countries including the World Health Organization (WHO) and three stakeholder associations.

The project was designed to achieve the following strategic objectives:

- To monitor and search for evidence of health risks related to EMF exposure
- Characterize and, where appropriate, quantify potential health risk posed by EMF exposure
- Enhance the ability of the European Commission to respond rapidly to health issues and concerns related to EMF, using scientifically sound advice and analyses
- Improve the compilation of knowledge and its dissemination on issues related to EMF and health

The project has issued six final reports on its website. The one most relevant for SSM:s Scientific Council on EMF is:

Risk analysis of human exposure to electromagnetic fields

(Report D2, October 2012)

(Edited from the overall summary and conclusions http://efhran.polimi.it/docs/D2_Final_version_oct2012.pdf)

EFHRAN aims to monitor and search for evidence of health risks associated with exposures to EMF at low, intermediate and high frequencies: low frequencies are defined as time-varying EMF with frequencies of up to 300 Hz and high frequencies as EMF with frequencies between 100 kHz and 300 GHz. In partial fulfilment of this objective, the present document reviews the latest research into possible health effects of EMF, and incorporates the results of these studies to the consensus opinions of both EMF-NET (2009) and SCENIHR (2009a) in order to construct an updated health risk assessment. Recent epidemiological and experimental studies have been included, as have both cancer and non-cancer endpoints. In order to evaluate the strength of evidence for any given endpoint, a four point classification scheme has been used that was based on the system devised by IARC to estimate the carcinogenic risk to humans from a wide range of agents. The four points are: a) sufficient evidence; b) limited evidence; c) inadequate evidence; and d) evidence suggesting a lack of effects.

Low frequencies (Extremely Low Frequency, ELF)

Inclusion of the recent data has not necessitated any revisions to the existing consensus opinions of EMF-NET (2009) or SCENIHR (2009a). For none of the diseases is there sufficient evidence for a causal association between exposure and the risk of the disease. There is limited evidence for an association between magnetic fields and the risk of leukaemia in children. However, it is possible that a combination of chance, bias and confounding may have produced this result.

There is inadequate evidence for Alzheimer's disease, childhood brain tumours, and amyotrophic lateral sclerosis. However the data suggest that some elevated risks may exist, particularly for Alzheimer's disease, which suggests that further studies on these outcomes would be useful. For all other cancers, other neurodegenerative diseases and for non-specific symptoms, evidence is also inadequate, but there appears to be no justification to conduct further studies. There is evidence suggesting a lack of effect for breast cancer, cardiovascular disease and for EHS.

High frequencies (Radiofrequency, RF)

Inclusion of recent data regarding adult brain tumours necessitates a revision to the original classification, and it is now considered to be best described as being *limited*. However, this classification is subject to uncertainty, because the evidence for an increased risk of brain tumours is restricted to two large-scale case-control studies, and there are unresolved questions relating to possible biases and errors inherent to retrospective epidemiological studies. Further, the time-trend analyses are also not compatible with a large increase in brain tumour incidence in relation to mobile phone use. This revision updates the existing consensus opinion of EMF-NET (2009) and SCENIHR (2009a) but is consistent with the more recent assessment performed by the IARC Working Group (Baan et al, 2011) regarding the carcinogenicity of RF fields.

Inclusion of recent data on other endpoints has not necessitated any revisions to the existing consensus opinions of EMF-NET (2009) or SCENIHR (2009a). For none of these diseases there is sufficient evidence for a causal association between exposure and the risk of the disease, and this includes all childhood cancers. Overall, the strength of evidence for these outcomes remains as *inadequate*. While increased responsiveness to RF fields has not been demonstrated in provocation studies, even in subjects that self-report hypersensitivity, the possibility remains that long-term mobile phone use may induce symptoms, such as migraine and vertigo, and further work is required to clarify this issue

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

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

The Authority reports to the Ministry of the Environment and has around 270 employees with competencies in the fields of engineering, natural and behavioural sciences, law, economics and communications. We have received quality, environmental and working environment certification.

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