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MIKKO HERRALA

DO ELECTROMAGNETIC FIELDS DAMAGE THE GENOME?

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ABSTRACT

Humans are ubiquitously exposed to natural and manmade electromagnetic fields (EMFs). New applications keep emerging, especially in the intermediate frequency (IF) range and, despite research conducted over many decades, the risks to human health are still partly unclear, particularly whether there are risks to human health under the current exposure limits. Extremely low frequency (ELF) magnetic fields (MFs) and radiofrequency (RF) EMFs have been classified as possibly carcinogenic to humans by the International Agency for Research on Cancer, mainly based on associations observed in epidemiological studies. However, the causality of the associations is still unclear, largely because there are no generally accepted mechanisms for explaining carcinogenic effects at exposure levels present in the environment. A common property of many environmental carcinogens is their ability to cause harmful changes in the genome. Consequently, many studies have been conducted to assess the possible genotoxicity of EMFs, with inconclusive results. Recent research has revealed that exposure to ionizing radiation and several other environmental agents can result in induced genomic instability (IGI), a phenomenon that differs from direct genotoxicity studied by conventional methods. Induced genomic instability can be defined as *de novo* appearance of delayed damage observed in the progeny of exposed cells many cell generations after exposure. Previous data on the ability of EMFs to induce genomic instability are very limited.

The general aim of this study is to investigate possible genome-damaging effects of EMFs and to increase understanding of the mechanisms of such effects. To this end, experiments were conducted to assess genotoxicity and IGI in cultured cells and animals exposed to ELF and IF MFs or RF EMFs. The aim of the ELF MF studies was to investigate genotoxicity and to test a mechanistic explanation for the effects of weak MFs (the radical pair mechanism) by studying interactions between ELF MFs and blue light. Experiments with IF MFs aimed at evaluating their genotoxicity, effects on DNA repair, and IGI. Genotoxicity and IGI were also studied in experiments with RF EMFs, and these experiments also aimed at testing

possible differences between modulated and non-modulated RF signals. A common aim at all frequencies was to study the effects of combined exposure to EMFs and known genotoxic chemicals.

The results indicated that exposure to 50 Hz 100 µT MFs for 24 h affected production of reactive oxygen species but did not increase micronuclei alone or in combination with menadione in human SH-SY5Y neuroblastoma cells. Combined exposure to blue light and ELF MFs was studied for the first time. The findings do not support the simple hypothesis that MF effects would be observed only in the presence of blue light, but interactions between blue light and ELF MFs were nevertheless observed. The finding that MF effects occurred without blue light indicates that MFs may affect light-independent radical reactions. These observations may be important for understanding the effects of weak MFs.

The IF MF studies revealed that exposure to 7.5 kHz MFs up to 300 µT for 24 h *in vitro* or *in vivo* did not cause genotoxicity alone or in combination with chemicals. There was some evidence that IF MFs might actually reduce the level of genetic damage, and rather strong evidence that the relative cell number was increased after exposure to IF MFs. Furthermore, exposure to vertical or horizontal 7.5 kHz MF at 300 µT did not induce genomic instability alone or in combination with chemicals in rat primary astrocytes. The results indicate that exposure to IF MFs may actually decrease genomic instability. However, this was the first time that the induction of genomic instability by IF MFs was studied.

Exposure of rat primary astrocytes to 872 MHz RF EMFs at 0.6 or 6 W/kg for 24 h did not cause genotoxicity alone and the results of combined exposure with chemicals were inconsistent. Modulation-dependent effects were not seen. Induction of genomic instability by RF EMFs was evaluated for the first time using 24-h exposure to 872 MHz GSM-modulated RF fields at 0.6 or 6 W/kg alone or in combination with menadione. No induction or enhancement of genomic instability in rat primary astrocytes was observed.

In conclusion, the present study produced new information that is likely to be important for understanding the mechanisms of the biological effects of weak MFs. The results did not support genotoxicity or co-genotoxicity of IF or RF EMFs. No evidence for induction of genomic instability by RF or IF EMFs was found in this study that assessed such effects for the first time.

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Medical Subject Headings: Electromagnetic Fields/adverse effects; Electromagnetic Radiation; Genome/radiation effects; DNA Damage; Genomic Instability; Reactive Oxygen Species; Free Radicals; Micronuclei, Chromosome-Defective; Cells, Cultured; Neuroblastoma; Astrocytes

TIIVISTELMÄ

Ihmiset altistuvat jatkuvasti erilaisille luonnollisille ja ihmisten aikaansaamille sähkömagneettisille kentille. Uusia sovelluksia kehitetään erityisesti välitaajuisille kentille ja huolimatta vuosikymmeniä kestäneestä tutkimuksesta riskit ihmisten terveydelle ovat yhä osittain epäselviä. Hyvin pientaajuiset ja radiotaajuiset sähkömagneettiset kentät on luokiteltu mahdollisesti syöpää aiheuttaviksi Kansainvälisen syöväntutkimuslaitoksen toimesta, perustuen pääasiassa epidemiologisiin tutkimuksiin. Kuitenkin kausaalisuus on epäselvä, koska ei ole olemassa tunnettua mekanismia, joka selittäisi sähkömagneettisten kenttien syöpävaarallisuuden. Tyypillistä syöpävaarallisille ympäristöaltisteille on niiden kyky aiheuttaa haitallisia muutoksia perimään. Näin ollen monet tutkimukset ovat selvittäneet sähkömagneettisten kenttien mahdollista perimämyrkyllisyyttä kuitenkin vailla yhtenäisiä tuloksia. Viimeaikaiset tutkimukset ovat paljastaneet, että ionisoiva säteily ja useat muut ympäristöaltisteet voivat aikaansaada perimän epävakautta, ilmiöitä, joka eroaa suorasta perimämyrkyllisyydestä, jota tutkitaan perinteisillä menetelmillä. Lisääntynyt perimän epävakaus voidaan määritellä uusien viivästyneiden vaurioiden ilmestymiseksi altistuneiden solujen, altistumattomissa jälkeläissoluissa, monta solusukupolvea altistumisen jälkeen. Aiempi tutkimustieto sähkömagneettisten kenttien kyvystä aikaansaada perimän epävakautta on hyvin vähäistä.

Tämän tutkimuksen tavoitteena oli tutkia sähkömagneettisten kenttien mahdollisia perimää vaurioittavia vaikutuksia ja lisätä ymmärrystä näiden vaikutusten mekanismeista. Tavoitteen saavuttamiseksi suoritettiin tutkimuksia perimämyrkyllisyydestä ja indusoidusta perimän epävakaudesta soluviljelmillä ja eläimillä, jotka altistettiin hyvin pientaajuisille, välitaajuisille tai radiotaajuisille sähkömagneettisille kentille. Hyvin pientaajuisilla kentillä tehtyjen kokeiden tavoitteena oli tutkia perimämyrkyllisyyttä ja testata mekanistista selitystä heikkojen magneettikenttien vaikutuksille (ns. radikaaliparimekanismi) tutkimalla hyvin pientaajuisten magneettikenttien ja sinisen valon vuorovaikutuksia. Kokeet välitaajuisilla magneettikentillä tutkivat niiden vaikutuksia perimämyrkyllisyyteen, DNA vaurioiden korjaukseen ja indusoituneeseen perimän epävakauteen. Perimämyrkyllisyyttä ja indusoitua perimän epävakautta tutkittiin myös radiotaajuisilla sähkömagneettisilla kentillä, joiden lisäksi selvitettiin, onko signaalin moduloinnilla vaikutuksia. Yhteinen tavoite kaikilla taajuusalueilla oli tutkia yhteisvaikutuksia sähkömagneettisten kenttien ja tunnettujen perimämyrkyllisten kemikaalien kanssa.

Tutkimuksen tulokset osoittivat, että altistuminen 50 Hz, 100 µT magneettikentälle 24 tunnin ajan vaikutti happiradikaalien tuotantoon, mutta ei lisännyt mikrotumien määrä yksin, eikä yhdessä menadionin kanssa ihmisten SH-SY5Y neuroblastooma soluissa. Yhteisaltistusta hyvin pientaajuisen magneettikentän ja sinisen valon kanssa tutkittiin ensimmäistä kertaa. Tulokset eivät tukeneet yksinkertaista hypoteesia, että magneettikentän vaikutuksia havaittaisiin ainoastaan sinisen valon läsnä ollessa, mutta yhteisvaikutuksia sinisen valon ja hyvin pientaajuisen

magneettikentän välillä kuitenkin havaittiin. Havainto, että magneettikenttä aiheutti vaikutuksia ilman sinistä valoa indikoi, että magneettikentät saattavat vaikuttaa myös valosta riippumattomiin radikaali reaktioihin. Nämä löydökset voivat olla tärkeitä heikkojen magneettikenttien aiheuttamien vaikutusten ymmärtämiseksi.

Tutkimukset välitaajuisilla magneettikentillä osoittivat, että 7.5 kHz magneettikenttäaltistus 300 µT tasolle asti ei aiheuttanut perimämyrkyllisyyttä yksin tai yhdessä kemikaalialtistuksen kanssa soluviljelmissä tai eläimissä. Tulokset viittaavat siihen suuntaan, että välitaajuiset magneettikentät itse asiassa vähentävät perimään kohdistuneita vaurioita, ja tulokset osoittavat melko vahvasti, että suhteellinen solumäärä lisääntyi välitaajuisen sähkömagneettikenttäaltistuksen jälkeen. Altistumisen vertikaaliselle tai horisontaaliselle 7.5 kHz 300 µT magneettikentälle ei todettu aikaan saavan perimän epävakautta yksin tai yhdessä kemikaalien kanssa rotan primääriastrosyyteissä. Sen sijaan tulokset antoivat viitteitä siitä, että altistuminen välitaajuisille magneettikentille saattaa vähentää perimän epävakautta. Tämä oli kuitenkin vasta ensimmäinen kerta, kun indusoitua perimän epävakautta tutkittiin välitaajuisilla magneettikentillä.

Altistuminen 872 MHz radiotaajuiselle sähkömagneettiselle kentälle 0.6 tai 6 W/kg tasolla 24 tunnin ajan ei aiheuttanut perimämyrkyllisyyttä rotan primääriastrosyyteissä ja yhteisaltistus kemikaaleille aiheutti epäyhtenäisiä tuloksia. Signaalimodulaatiolla ei todettu vaikutuksia. Indusoitunutta perimän epävakautta tutkittiin ensimmäistä kertaa radiotaajuisilla sähkömagneettisilla kentillä käyttäen 24 tunnin altistusta 872 MHz GSM-moduloidulle radiotaajuiselle kentälle 0.6 ja 6 W/kg tasoilla yksin tai yhdessä menadionin kanssa. Indusoitunutta tai lisääntynyttä perimän epävakautta ei havaittu rotan primääriastrosyyteissä.

Kokonaisuutena tämä tutkimus tuotti uutta tietoa, joka on todennäköisesti tärkeää heikkojen sähkömagneettisten kenttien aiheuttamien biologisten vaikutusten ymmärtämiseksi. Tulokset eivät osoittaneet välitaajuisten tai radiotaajuisten sähkömagneettisten kenttien aiheuttavan perimämyrkyllisyyttä tai lisäävän kemikaalien aiheuttamaan perimämyrkyllisyyttä. Ensimmäistä kertaa välitaajuisilla ja radiotaajuisilla sähkömagneettisilla kentillä tutkitusta indusoidusta perimän epävakaudesta ei satu viitteitä.

Yleinen suomalainen asiasanasto: sähkömagneettiset kentät; sähkömagneettinen säteily; haitat; perimä; geenit; DNA; happiradikaalit; soluviljely; neuroblastooma; astrosyytit

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Kuopio, November 2018

Mikko Herrala

LIST OF ABBREVIATIONS

AM	Amplitude modulation
BLM	Bleomycin
CW	Continuous wave
DNA	Deoxyribonucleic acid
ELF	Extremely low frequency (0-300 Hz)
EMF	Electromagnetic field
FM	Frequency modulation
GSM	Global system for mobile communications
Gy	Gray, the unit of absorbed dose of ionizing radiation
Hz	Hertz, the unit of frequency
IARC	International Agency for Research on Cancer
ICNIRP	International Commission on Non-Ionizing Radiation Protection
IF	Intermediate frequency (300 Hz - 100 kHz)
IGI	Induced genomic instability
LCD	Liquid crystal display
LED	Light-emitting diode
LTE	Long term evolution
MF	Magnetic field
MMS	Methyl methanesulfonate
RF	Radiofrequency (100 kHz-300 GHz)
ROS	Reactive oxygen species
RPM	Radical pair mechanism
SAR	Specific absorption rate
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks (European Commission)
T	Tesla, unit of magnetic flux density
WCDMA	Wide band code division multiple access
WHO	World Health Organization
WLAN	Wireless local area networks
UMTS	Universal mobile telecommunications system
UV	Ultraviolet (radiation)

LIST OF ORIGINAL PUBLICATIONS

Chapter 2 Höytö A, Herrala M, Luukkonen J, Juutilainen J, Naarala J. (2017). Cellular detection of 50 Hz magnetic fields and weak blue light: effects on superoxide levels and genotoxicity. *International Journal of Radiation Biology 93(6):646-652. doi: 10.1080/09553002.2017.1294275*

Chapter 3 Herrala M, Kumari K, Koivisto H, Luukkonen J, Tanila H, Naarala J, Juutilainen J. (2018). Genotoxicity of intermediate frequency magnetic fields *in vitro* and *in vivo*. *Environmental Research 167:759-769. https://doi.org/10.1016/j.envres.2018.09.009*

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AUTHOR'S CONTRIBUTION

Chapter 2 Anne Höytö, Jonne Naarala and Jukka Juutilainen conceived and designed the study. The author and Anne Höytö undertook the experiments. Jukka Luukkonen contributed to the methods. Anne Höytö analysed the data and drafted the first manuscript. All of the authors contributed to manuscript revisions.

Chapter 3 The author in co-operation with Jonne Naarala and Jukka Juutilainen planned the *in vitro* experiments. The author in co-operation with Jonne Naarala and Jukka Juutilainen designed the *in vitro* exposure system and the author built the exposure system. The author performed the practical *in vitro* work in a laboratory. Kajal Kumari, Jonne Naarala, Heikki Tanila and Jukka Juutilainen planned *in vivo* experiments. Hennariikka Koivisto and Kajal Kumari were responsible for animal care and blood sampling. Kajal Kumari performed the practical *in vivo* work. Jukka Luukkonen contributed to the methods. The author drafted the first version of the manuscript with Kajal Kumari. All of the authors contributed to manuscript revisions.

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Chapter 5 The author in co-operation with Jonne Naarala and Jukka Juutilainen planned the experiments. The author and Ehab Mustafa performed the practical work in a laboratory. The author drafted the first version of the manuscript. All of the authors contributed to manuscript revisions.

CONTENTS

Chapter 1.

General introduction to electromagnetic fields, genotoxicity and genomic instability

1 LITERATURE REVIEW

1.1 ELECTROMAGNETIC FIELDS

Humans are ubiquitously exposed to natural and manmade electromagnetic fields (EMFs). Exposure to EMFs increased rapidly after the electrification of society and in recent decades numerous new applications using EMFs have been invented and put into operation for everyday usage. Electromagnetic fields have two different components, namely electric fields (E) and magnetic fields (H). Stationary charge generates an electric field while moving charge (current) creates both an electric field and a magnetic field. These two fields are separate in the near field (within a distance of approximately one wavelength from the source), but become coupled in the far field and can be called electromagnetic radiation. Electromagnetic radiation refers to electromagnetic waves, which consist of photons, propagating through space and time. Photon energy is directly proportional to the frequency and inversely proportional to the wavelength of electromagnetic radiation.

Electromagnetic fields are conventionally classified based on frequency and wavelength, as illustrated in the electromagnetic spectrum in Figure 1. Division into ionizing and non-ionizing radiation is the most fundamental classification. Ionizing radiations such as X-rays, gamma rays and ultraviolet (UVC) radiation have sufficient photon energy to ionize atoms or molecules and thereby cause, for example, direct DNA damage. However, static, extremely low frequency (ELF), intermediate frequency (IF) and radiofrequency (RF) electromagnetic fields, infrared radiation, visible light, and UVA and B radiation do not have enough photon energy to cause ionization of matter and are therefore called non-ionizing radiations. Static fields, such as the geomagnetic field, do not vary over time, in contrast to other types of EMFs, which oscillate as a result of an alternating current or voltage. This study focuses on ELF, IF and RF fields, which are described in more detail below.

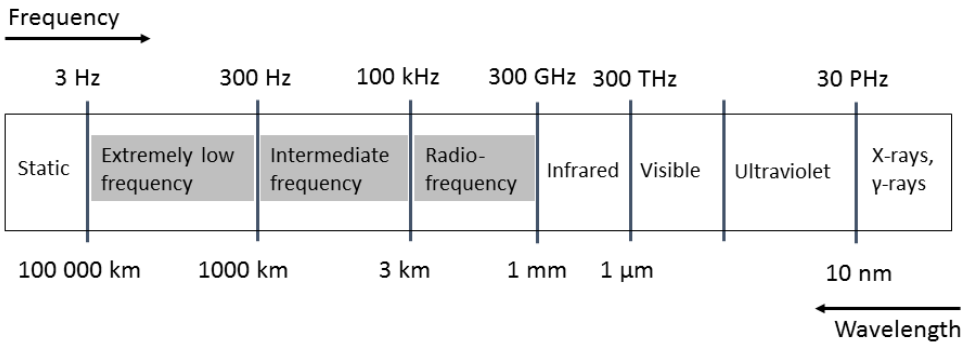

Figure 1. The electromagnetic spectrum. The frequency ranges used in the present study are highlighted in grey.

1.1.1 Extremely low frequency magnetic fields (ELF MFs)

Alternating magnetic fields (MFs) with frequencies less than 300 Hz are called ELF MFs. The electrical grid and different electronic applications operate normally at 50 or 60 Hz. Thus, ELF MFs exist whenever electricity is generated, distributed or utilized. The main sources of ELF MF exposure to the public are in-house installations, household appliances, power lines and electric power transformers installed inside residential buildings (Scientific Committee on Emerging and Newly Identified Health Risk (SCENIHR) 2015). However, the public exposure levels to ELF MFs are generally low and the magnetic flux density decreases rapidly with increasing distance to the source. Occupational exposure can be higher when working close to appliances using high currents, such as welding machines (Canova et al. 2018). The intensity of a MF is expressed as magnetic flux density (B) in teslas (T) or as magnetic field strength (H) in amperes per meter (A/m) (The International Commission on Non-Ionizing Radiation Protection (ICNIRP) 1998). The reference levels (which are obtained from the basic restrictions by mathematical modelling) for the general public and for occupational exposure are at 50 Hz 100 and 500 µT, respectively (EC 1999, 2004). Normal background ELF MF in households is less than 0.2 µT (SCENIHR 2009).

1.1.2 Intermediate frequency magnetic fields (IF MFs)

Magnetic fields, which cannot be categorized as ELF MFs or RF EMFs and are between their frequencies, are called IF MFs. There are different classifications for IF MFs but typically fields at frequencies from 300 Hz to 100 kHz are classified IF MFs (Ahlbom et al. 2008). Many properties of IF MFs are similar to those of ELF MFs and the same units (T or A/m) are used to express the MF intensity. Sources of IF

MFs in households are, e.g., induction heating cookers, LCD screens, compact fluorescent lighting, laundry machines and different power tools (Aerts et al. 2017). Typical occupational sources of IF MFs are industrial induction and plasma heaters, electronic article surveillance systems and different medical equipment (Litvak et al. 2002, Roivainen et al. 2014). Also the induction loop pad of a hearing aid systems is a source of IF MFs (Hansson Mild et al. 2017). The reference levels for IF MFs are 6.25-16.6 µT for the general public and 20-83.3 µT for occupational exposure, depending on frequency (EC 1999, 2004). Generally, people are exposed only to low levels of IF MFs, but exposure to IF MFs is increasing due the new applications being developed and commercialized.

1.1.3 Radiofrequency (RF) fields

Radiofrequency fields includes frequencies from 100 kHz to 300 GHz. It is used in Radiofrequencies include frequencies from 100 kHz to 300 GHz. Radiofrequency fields are used in numerous applications, including various forms of telecommunication, radar technologies and heating. Radio and TV broadcasts use RF fields, as well as mobile phones and wireless local area networks (WLANs). Use of RF fields has increased rapidly in recent decades when mobile phones and the internet have become an essential part of everyday life. Radiofrequency field exposure can be near- or far-field exposure. The typical exposure situation for a mobile phone is near-field exposure, while exposure from mobile phone base stations or TV and radio broadcasting antennas can be defined as far-field exposure. In the near field, there is no clear connection between the electric and magnetic fields, while in the far field the E and H components are perpendicular to each other and to the direction of propagation of the electromagnetic wave. The intensity of an RF field is commonly expressed as power density in units of watts per square meter (W/m^2) (ICNIRP, 1998). The measure used to determine how much RF power is actually absorbed by the body or tissue is called the specific absorption rate (SAR), which is expressed in units of watts per kilogram (W/kg). The exposure limits for RF field exposure for the general public are 0.08 W/kg for whole-body average SAR, and 2 W/kg (head and trunk) or 4 W/kg (limbs) for localized SAR (local SAR is determined over 10 g of tissue) (EC, 1999). For occupational exposure, the corresponding basic restrictions are 0.4 W/kg for whole-body average SAR and 10 W/kg (head and trunk) or 20 W/kg (limbs) for localized SAR (EC, 2004).

Radiofrequency fields can be modulated to make them carry information. Typical modulations are, for example, frequency modulation (FM) and amplitude modulation (AM) used in radio broadcasting. Complex modulations are used in mobile communication systems, including Global System for Mobile communications (GSM), Universal Mobile Telecommunications System (UMTS), Wideband Code Division Multiple Access (WCDMA) and Long-Term Evolution (LTE). In addition

to telecommunication, RF fields can be used in radars and heating (for example, in microwave ovens) and in various medical applications such as magnetic resonance imaging (IARC, 2013). Non-modulated RF fields are commonly described as continuous waves (CW).

1.2 GENOTOXICITY

All life on earth is based on the ability of living cells and organisms to reproduce themselves with almost perfect fidelity to form new generations. Key to this process is the genome, which contains all genetic material. The genome consists of molecules called deoxyribonucleic acid (DNA), which contains the instructions to an organism on how to develop, live and reproduce. The DNA consists of nucleotides, which contain a phosphate group, a sugar group and a nitrogenous base. These nucleotides are attached together with hydrogen bonds to form two long strands, which are twisted around each other forming the DNA double helix. In DNA replication, these two strands separate and two new strands are synthesized, each with a sequence complementary to one of the original strands, creating two double-helical molecules, which are identical to the original DNA. To fit inside the cell´s nucleus, DNA is coiled tightly to form structures called chromosomes. Humans have 23 pairs of chromosomes and each chromosome contains a single DNA molecule.

The DNA has a special need for metabolic stability because its information content must be transmitted virtually intact from one cell to another during cell replication or during the reproduction of an organism. Stability is maintained in two ways. First, there are mechanisms that ensure high replication accuracy. Second, there are mechanisms for repairing genetic information when DNA suffers damage. This damage may be caused by replication errors that are not corrected or by environmental damage. A chemical or physical agent´s ability to cause damage to DNA or to the genetic processes of living cells is called genotoxicity (Klaassen et al., 2013).

Genotoxicity can lead to mutagenicity or carcinogenicity (the development of malignant tumours) if the damage to the genetic material is not repaired correctly. Genotoxicity, unlike mutagenicity, which refers to transmissible genetic alterations, covers also other endpoints, which are not themselves transmissible from cell to cell or from generation to generation. Typical genotoxic events are, for example, unscheduled DNA synthesis, sister chromatid exchanges, DNA strand breaks, micronuclei (chromosome fragments and/or whole chromosomes that are not incorporated into the nucleus after cell division) and gene mutations. Genotoxicity can be caused by direct damage to DNA (caused by radiation or chemicals) or indirectly by the production of reactive oxygen species (ROS).

Genotoxicity can be measured as direct interaction with DNA or more indirectly through the assessment of DNA repair, or the production of gene mutations or

chromosome alterations. Several methods can be used to measure genotoxicity, including the Comet assay (OECD, 2016a) and micronucleus scoring (OECD, 2016b), which are used in the present study. The Comet assay can be used to measure immediate DNA damage and DNA repair while the micronucleus assay measures chromosomal damage after the repair processes.

1.3 INDUCED GENOMIC INSTABILITY

Cells need to maintain stability of the genome to prevent errors from DNA replication, endogenous genotoxic stress such as ROS from cellular metabolism, and environmental exposures (Yao & Dai, 2014). If the mechanisms maintaining genomic stability are compromised, the genome can become unstable. Such genomic instability is common in cancer cells, and can result from defective genes (Huang et al., 2003; Yao & Dai, 2014). Genomic instability induced by exposure to external agents is called induced genomic instability (IGI) (Huumonen et al., 2014).

Induced genomic instability can be defined as the *de novo* appearance of delayed damage (for example, chromosomal aberrations, mutations, micronuclei or apoptosis) observed in the progeny of exposed cells many cell generations after exposure (Morgan et al., 1996; Baverstock, 2000). Induced genomic instability was originally found in cells exposed to ionizing radiation, but several other agents, for example many chemicals or ultraviolet (UV) radiation, have been reported to induce genomic instability (O'Reilly & Mothersill, 1997; Brennan & Schiestl, 2001; Li et al., 2001; Coen et al., 2001; Phillipson et al., 2002; Korkalainen et al., 2012). Induced genomic instability can be assessed using traditional genotoxicity assays, but it is distinct from direct genotoxicity and appears to be induced and transmitted epigenetically (Baverstock, 2000; Huumonen et al., 2014). Different epigenetic mechanisms for IGI have been proposed, such as DNA methylation, DNA methyltransferases, histone modifications and micro-ribonucleic acids (micro-RNAs) (Ilnytskyy & Kovalchuck, 2011; Huumonen et al., 2014).

It has been suggested that IGI could result from increased ROS production. This is justified by the fact that agents that are known to cause IGI also induce ROS production (Lorimore et al., 2003).

As the development of cancer requires the accumulation of multiple genetic changes, IGI is potentially highly relevant to cancer and genomic instability is a characteristic of most cancer cells (Streffer, 2010; Shen, 2011; Yao & Dai, 2014). However, understanding of IGI in cancer is still limited (Negrini et al., 2010).

1.4 HEALTH EFFECTS OF ELECTROMAGNETIC FIELDS AND MECHANISMS BEHIND THE EFFECTS

Exposure to EMFs is common and possible adverse effects of such exposure could therefore be important at the population level even if the individual risk is small. Normally humans are only exposed to low levels of EMFs but the exposure can be continuous or long lasting. Electromagnetic fields have some well-known biological effects depending on the frequency and field strength. These effects generally occur at such high field intensities that they are very rare in the human environment, and are mainly relevant to a limited number of workers. Most of the recent research and discussion on the health effects of EMFs focuses on the possible effects of weak environmental fields that would affect a large proportion of the population. However, the mechanisms of the possible health effects of weak EMFs are still unclear and various hypotheses have been suggested.

ELF and IF MFs

Extremely low frequency and IF MFs induce electric fields and currents in the human body and, if strong enough, stimulate nerve and muscle cells. High levels of induced currents can paralyze breathing or cause ventricular fibrillation and death. Strong MFs can also cause a phenomenon called phosphene, which is characterized by the experience of seeing light without light actually entering the eye. These established effects (ICNIRP, 2010) require magnetic flux densities higher than 1 mT. The basic restrictions and reference levels in the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines for ELF and IF MF exposure are based on these well-known effects.

Low field effects at magnetic flux densities less than 1 mT are more controversial. The International Agency for Research on Cancer (IARC) (2002) has classified ELF MFs as possibly carcinogenic for humans. This decision was based on epidemiological studies indicating an association between MF exposure and childhood leukaemia. The first of these epidemiological studies was published by Wertheimer and Leeper as early as 1979, and many other studies have produced similar findings, as demonstrated in two pooled analyses (Ahlbom et al., 2000; Greenland et al., 2000). In these epidemiological studies, childhood leukaemia was associated with exposure levels exceeding 0.3-0.4 μT. Such exposure levels are not common, as the typical background level of ELF MFs in households is less than 0.1 μT, and less than 1% of the estimated geometric mean exposures of the European population exceed 0.3 μT (Grellier et al., 2014).

A recent pooled analysis by Amoon et al. (2018) did not find an increased risk of leukaemia among children who lived within any distance (including < 50 m) from power lines of all voltages combined. A small but imprecise increase in risk of leukaemia was found among children who lived in homes < 50 m from higher voltage (≥ 200kV) power lines.

Overall, causality of these epidemiological findings remains unclear as numerous animal and *in vitro* studies have been performed, mainly failing to provide support for carcinogenicity (IARC, 2002; WHO, 2007). However, many *in vitro* studies have revealed effects of ELF MF exposure alone or in combination with some other chemical or physical agent on different cellular endpoints. For example, ELF MF effects on ROS production have been observed in many studies (Mattsson & Simko, 2014; Wang & Zhang, 2017). Moreover, it seems that co-exposure to other chemical or physical agents may be relevant in the case of ELF MFs (Juutilainen et al., 2000, 2006; IARC, 2002; WHO, 2007; SCENIHR, 2015). Together, the results are not consistent and highly dependent on experimental set-ups, cell lines or animal strains, exposure levels and the quality of the studies. A review of genotoxicity studies on ELF MFs is provided in section 1.5 and a review of IF MF genotoxicity studies in section 1.6.

A major problem in explaining the effects of weak ELF MFs is the lack of a known mechanism. One of the challenges is to explain how a 0.3-0.4 µT ELF MF (as suggested by the epidemiological studies) could lead to significant biological effects in the presence of the much stronger (25-65 µT) geomagnetic field. A plausible hypothesis for explaining biological responses to weak MFs is the so-called radical pair mechanism (RPM) (WHO, 2007; Juutilainen et al., 2018). According to the RPM, chemical reactions involving radical pairs as transient intermediates are sensitive to a variety of weak magnetic interactions (Steiner & Ulrich, 1989; Brocklehurst, 2002; Timmel & Henbest, 2004; Rodgers & Hore, 2009; Hore & Mouritsen, 2016). In low fields (< 1 mT), the RPM generally increases the concentration of free radicals (Brocklehurst & McLauchlan, 1996; Timmel et al., 1998). Radicals are also a part of normal cell physiology, including intracellular signal transduction (Finkel, 2003). Therefore, MF effects on radical levels could potentially have multiple biological consequences if they occur in cellular organelles or molecules that are key components in biological regulatory networks. A known biological effect based on the RPM is magnetoreception: several animal species are able to detect weak magnetic fields at microtesla levels for the purposes of orientation and navigation in the geomagnetic field (Rodgers & Hore, 2009; Liedvogel & Mouritsen, 2010; Ritz et al., 2010).

Although the detection mechanisms involved in animal magnetoreception are still to be fully determined, magnetically sensitive reactions of radical pairs in cryptochromes (a class of blue-light-sensitive flavoproteins involved in the circadian rhythms) seem to be involved, at least in birds (Hore & Mouritsen, 2016). It has been confirmed that also human cryptochromes are capable of functioning as light-sensitive magnetosensors or as part of a magnetosensing pathway (Foley et al., 2011). As the circadian clock is connected to DNA damage responses and the regulation of ROS levels (Wilking et al., 2013; Patel et al., 2014), Juutilainen et al. (2018) have hypothesized that the primary interaction mechanism behind the carcinogenic effects of weak ELF fields is MF effects on radical reactions in cryptochromes. This

primary interaction could lead to dysregulation of ROS signalling, impaired DNA damage responses, genomic instability and finally to cancer.

Although the RPM is a plausible mechanism for the biological effects of weak ELF fields, explaining the suspected health effects of very weak ELF MFs continues to be challenging within the framework of this hypothesis as the present geomagnetic field is much stronger (Juutilainen et al., 2018). In addition to RPM, other mechanisms have been suggested to explain the biological effects of weak ELF fields (Zhadin & Barnes, 2005; Shaw et al., 2015; Binhi & Prato, 2017), but there is only limited support for these suggestions.

In addition to its relationship to cancer, ELF MF effects on neurodegenerative diseases (Mattsson & Simko, 2012; Jalilian et al., 2017), cardiovascular diseases, the immune system, reproduction and development have also been studied (WHO, 2007; SCENIHR, 2015). Although some positive findings have been reported, evidence for these effects is generally weaker than that for carcinogenic effects.

Data concerning the health effects of IF MFs are insufficient (Ahlbom et al., 2008; SCENIHR, 2015), even though the earliest studies were carried out decades ago (e.g. Juutilainen & Saali, 1986; Huuskonen et al., 1998). Recently, however, the effects on reproduction (Kim et al., 2004; Lee et al., 2009; Kumari et al., 2017a), pregnancy outcomes (Khan et al., 2018), behaviour (Win-Shwe et al., 2013; Kumari et al., 2017b) and development (Nishimura et al., 2011, 2012; Kumari et al., 2018) have been studied. These studies have generally not detected adverse effects of IF MFs.

RF fields

Strong RF fields have well-known thermal effects when they heat tissues. Heating of tissues by more than 1-2 °C (whole body) can cause adverse health effects, such as heat exhaustion and heat stroke (ICNIRP, 1998). In addition, alterations in neural and neuromuscular functions, increased blood-brain barrier permeability, ocular impairment, stress-associated changes in the immune system, haematological changes, reproductive changes, teratogenicity and changes in cell morphology have been detected in cellular and animal systems (ICNIRP, 1998). The ICNIRP (1998, 2009) guidelines are based on these well-known effects. However, human exposure to RF fields rarely causes temperature increases of more than 1 °C. Non-thermal effects at low exposure levels have been suggested but the findings are controversial. The mechanisms of non-thermal RF field effects are still not known after more than 30 years of research and the RPM hypothesis that could explain the effects of low frequency MFs would not be applicable with higher frequencies (Sheppard et al., 2008; Hore & Mouritsen, 2016). Other mechanisms have also been proposed to explain the non-thermal effects of RF fields but none of them is generally supported (Sheppard et al., 2008; IARC, 2013). It has been proposed that the effects of low-level RF radiation would depend on modulation of the RF signal. Juutilainen et al. (2011a) did not find consistent evidence for modulation-dependent effects on carcinogenesis or genotoxicity in their review of possible modulation-dependent

biological effects of RF fields, although there was suggestive evidence of some other modulation-specific effects.

Despite the lack of a known mechanism, the IARC (2013) has classified RF fields as possibly carcinogenic based on limited epidemiological evidence of increased numbers of gliomas among mobile phone users and limited evidence of carcinogenicity in animal studies. However, there was a minority view in the IARC Working Group that evidence for cancer in humans was inadequate. Furthermore, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (2015) has concluded that epidemiological studies on mobile phone RF field exposure do not indicate an increased risk of brain tumours and they do not indicate an increased risk of other cancers of the head and neck region. The SCENIHR (2015) has also stated that the results of cohort and incidence time trend studies do not support an increased risk of glioma, while the possibility of an association with acoustic neuroma remains open. Juutilainen et al. (2011b) have reviewed animal carcinogenicity studies and concluded that the results are rather consistent, and do not indicate carcinogenic effects of RF fields at exposure levels relevant to human exposure from mobile phones.

In addition to carcinogenicity, other health effects have been investigated, including the effects on genotoxicity, reproduction, development, the nervous system, cognitive functions and brain activity (Juutilainen, 2005; van Rongen et al., 2009; Verschaeve et al., 2010; IARC, 2013; SCENHIR, 2015). However, the evidence is weak for such adverse effects induced by RF fields (SCENHIR, 2015).

1.5 SUMMARY OF GENOTOXICITY AND CARCINOGENICITY FINDINGS WITH REGARD TO ELF MFs

In his dissertation, Luukkonen (2011) reviewed ELF MF studies relevant to mechanisms of cancer published between 2006 and 2011. Luukkonen reviewed 15 studies addressing ELF MF effects on genotoxicity and observed that the majority of those studies (11/15) found effects on various genotoxicity endpoints. Furthermore, all of the negative studies had been conducted without co-exposure, which means that all studies performed with co-exposure had been positive. In this section recent studies (published in 2011 or later) related to the genotoxicity or carcinogenicity of ELF MFs are reviewed.

In vitro studies

After the review by Luukkonen (2011), 22 *in vitro* studies assessing ELF MFs and genotoxicity have been published (Table 1). These studies typically assessed DNA damage, micronuclei, or other genotoxicity-relevant endpoints using different methods. All studies were performed using 50 or 60 Hz MFs, except for the study by Mihai et al. (2014) who used 100 Hz MF. Co-exposure to other chemical or phys-

ical agents was included in 12 out of 22 studies. Typical co-exposures were various genotoxic or oxidative chemicals and ionizing radiation.

Ten of these 22 studies presented in Table 1 reported ELF MF effects. The majority (7/10) of the studies reporting positive findings found that ELF MFs induced or increased genotoxicity, while two studies observed protective or damage-decreasing effects of ELF MFs. In addition, the study of Buldak et al. (2012) observed that 1 mT MF exposure for 16 min increased DNA damage alone but pre-exposure to MF decreased the chemically induced damage compared to mere chemical treatment. Six out of ten studies reported MF effects alone, while co-exposure was required in four studies. Interestingly, all four of these studies (Luukkonen et al., 2011, 2017; Kesari et al., 2016; Nakayama et al., 2016) were performed using magnetic flux densities of <1 mT. Overall, studies reporting ELF MF effects were mainly performed with high magnetic flux densities. Nine studies were conducted with an exposure level of <1 mT, and four of these (Luukkonen et al., 2011, 2017; Kesari et al., 2016; Nakayama et al., 2016) reported MF effects. All these studies involved co-exposure, that is, none of the studies using MFs of <1 mT reported MF effects without co-exposure. Among the studies reporting no MF effects (all exposure levels), half of the studies (6/12) also included co-exposures. Of all the studies, only three (Huang et al., 2014b; Srdjenovic et al., 2014; Su et al., 2017) were performed with primary cells, while the other studies used secondary cells. None of these studies reported MF effects and none of them included co-exposure.

In conclusion, it seems that co-exposure increases the likelihood of finding MF effects in fields of <1 mT. This finding is in line with earlier reviews (Juutilainen et al., 2006; IARC, 2002; WHO, 2007; Luukkonen, 2011). In stronger fields, there is more evidence that MFs may induce genotoxicity without co-exposure in some experimental conditions.

Table 1. *In vitro* studies assessing genotoxicity of ELF MFs published in 2011 or later.

Assay	MF Exposure	Co-exposure	Response	Response direction	Reference
MN, DNA damage and repair in human neuroblastoma SH-SY5Y cells.	50 Hz, 0.1 mT for 24 h.	Menadione 0.1-20 µM or MMS 10-35 µg/ml for 3 h after MF exposure.	Pre-exposure to MF enhanced menadione-induced DNA damage, DNA repair rate, and MN formation.	↑	Luukkonen et al. 2011
DNA damage and repair in murine squamous cell carcinoma AT478 cells.	50 Hz, 1 mT for 16 min.	Cisplatin 2.56 µg/ml after MF exposure for 24 h. H_2O_2 100 µM 24 h after other exposures for 5 min.	MF exposure increased DNA damage. Pre-exposure to MF decreased DNA damage compared to mere cisplatin or H_2O_2 exposure.	↑↓	Buldak et al. 2012
DNA damage in human neuroblastoma BE(2)C cells.	50 Hz (bipolar pulsed-square wave), 1 mT for 48 h.	None.	MF exposure decreased DNA doublestrand breaks.	↓	Del Re et al. 2012
MN in mouse embryonic fibroblast NIH3T3 cells and in human lung fibroblast WI-38 cells.	60 Hz, 0.01, 0.5 or 1 mT for 4 h.	Ionizing radiation 2 Gy, H_2O_2 100 µM and cellular myelocytomatosis oncogene activation.	No effects.		Jin et al. 2012
DNA damage in human lung fibroblast IMR90 cells and in human cervical carcinoma HeLa cells.	60 Hz, 7 mT for 10, 20, 30 or 60 min.	None.	MF exposure induced DNA doublestrand breaks and activated the DNA damage checkpoint pathway in both cell lines.	↑	Kim et al 2012
DNA damage and repair in human neuroblastoma BE(2)C cells.	50 Hz (bipolar pulsed-square wave), 1 mT for 48 h.	H_2O_2 300 µM for 1 h after MF exposure.	No effects.		Giorgi et al. 2014

Table 1. Continued

Assay	MF Exposure	Co-exposure	Response	Response direction	Reference
Expression of the ATM-Chk2-p21 pathway proteins and cell cycle distribution in human HaCaT keratinocytes.	60 Hz, 1.5 mT for 24, 48, 72, 96, 120 or 144 h.	None.	MF exposure (96, 72 and 144 h) altered mRNA expression of cell cycle-related genes, increased levels of phospho-ATM, phospho-Chk2 and p21. 144 h MF exposure caused an increase in G0/G1 and a decrease in S cells.	↑	Huang et al. 2014a
Expression of the ATM-Chk2-p21 pathway proteins and cell cycle distribution in primary NHEK cells from neonatal foreskin (PCS-200-010).	60 Hz, 1.5 mT for 24, 48, 72, 96, 120 or 144 h.	None.	No effects.		Huang et al. 2014b
DNA damage in mouse fibroblast NIH3T3 cells, human lung fibroblast WI-38 cells, human lung epithelial L132 cells and in human mammary gland epithelial MCF10A cells.	60 Hz, 1 mT for 4 or 16 h.	Ionizing radiation 1 Gy, H_2O_2 50 µM and cellular myelocytomatosis oncogene activation.	No effects.		Jin et al. 2014
DNA damage in Vero cells (ECACC 88020401).	100 Hz, 5.6 mT for 45 min continuously or intermittently (1 sec on and 3 sec off).	None.	MF exposure increased DNA damage measured 48 h after exposure.	↑	Mihai et al. 2014

Table 1. Continued

Assay	MF Exposure	Co-exposure	Response	Response direction	Reference
DNA damage and repair in human embryo lung-derived SV40 virus transformed WI38VA13 subcloned 2RA cells and in human xeroderma pigmentosum (A type) skin-derived XP2OS (SV) cells.	60 Hz, 5 mT for 1, 3, or 24 h.	UV-B 0, 20, 40, 60 or 80 J/m^2 before MF exposure.	No effects.		Mizuno et al. 2014
MN in normal human lymphocytes.	50 Hz, 0.1 mT for 24 or 48 h.	None.	No effects.		Srdjenovic et al. 2014
DNA damage in human lung fibroblast WI-38 cells and human lung epithelial L132 cells.	60 Hz, 1 or 2 mT for 6 h.	Ionizing radiation 1 Gy and H_2O_2 0.05 mM (L132 cells) or 1 mM (WI-38 cells) during MF exposure.	MF exposure at 2 mT increased DNA double-strand breaks. Exposure to 2 mT MF potentiated the expression of γ -H2AX and γ -H2AX foci production compared to mere ionizing radiation.	↑	Yoon et al. 2014
DNA damage and aneuploidy in mouse hippocampus neuronal HT22 cells.	60 Hz, 2 mT for 4 or 16 h.	None.	No effects.		Mun et al. 2015

Table 1. Continued

Assay	MF Exposure	Co-exposure	Response	Response direction	Reference
MN in human neuroblastoma SH-SY5Y cells and in rat glioma C6cell line.	50 Hz, 0.01 or 0.03 mT for 24 h.	Menadione 1, 5, 10 and 20 µM for SH-SY5Y cells and 1, 5, 10, 15, 20 and 50 µM for C6 cells for 3 h after MF exposure.	MF exposure increased MN in SH-SY5Y cells at 30 µT. This effect was largest at the highest menadione dose used.	↑	Kesari et al. 2016
DNA single-strand breaks in macrophage RAW264 cells.	50 Hz, 0.5 mT for 24 h.	LPS 10 ng/ml for 1 h before MF exposure.	MF exposure increased LPS-induced DNA single-strand breaks compared to mere LPS-exposure.	↑	Nakayama et al. 2016
DNA damage in Chinese hamster lung cells.	50 Hz, 0.4 mT for 0.5 or 24 h.	None.	No effects.		Shen et al. 2016
DNA damage in *Salmonella typhimurium.*	50 Hz, 0.1 mT for 1 h.	MMS 0.1 mM and 1 mM, cis-platinum 0.01 and 0.1 mM, AFB1 0.1 and 1 g/ml and 2-AA 0.25 and 2.5 g/ml during MF exposure.	No effects.		Verschaeve et al. 2016
DNA damage in human lens epithelial SRA01/04 cells.	50 Hz, 0.4 mT for 2, 6, 12, 24 or 48 h.	None.	No effects.		Zhu et al. 2016

Table 1. Continued

Assay	MF Exposure	Co-exposure	Response	Response direction	Reference
DNA damage and expression of proteins involved in DNA damage responses in human neuroblastoma SH-SY5Y cells.	50 Hz, 0.1 mT for 24 h.	Menadione 1-25 µM for 1 or 3 h after MF exposure.	Pre-exposure to MF decreased p21 protein level and DNA damage after 1-h menadione treatment compared to mere menadione treatment.	↓	Luukkonen et al. 2017
DNA damage in neurogenic tumour cell lines (U251, A172, SH-SY5Y) and in primary cultured neurogenic cells from rats (astrocytes, microglia, cortical neurons).	50 Hz, 2 mT for 1, 6 or 24 h.	None.	No effects.		Su et al. 2017a
DNA damage in human neuroblastoma SH-SY5Y and SK-N-BE-2 cells.	50 Hz, 0.01, 0.1 or 1 mT for 1 h continuously or 5 h intermittently (15 min on and 15 min off).	$AlCl_3$ 4 or 40 µM during MF exposure.	No effects.		Villarini et al. 2017

2-amino-anthracene (2-AA), Aflatoxine B1 (AFB1), Aluminium chloride ($AlCl_3$), deoxyribonucleic acid (DNA), extremely low frequency (ELF), hydrogen peroxide (H_2O_2), Lipopolysaccharide (LPS), messenger ribonucleic acid (mRNA), methyl methanesulphonate (MMS), micronuclei (MN) ultraviolet B (UV-B)

Animal studies

After the review by Luukkonen (2011), 13 animal studies have assessed the genotoxicity or carcinogenicity of ELF MFs (Table 2). These studies typically assessed DNA damage, micronuclei, mutations or tumour incidence. All studies were performed at 50 or 60 Hz in rodents using magnetic flux densities between 0.0002 and 10 mT. Nine out of these 13 studies reported effects of ELF MFs, while four studies (Korr et al., 2014; Saha et al., 2015; Wilson et al., 2015; Woodbine et al., 2015) found no effects.

Exposure levels were generally lower than those used in *in vitro* studies and only three studies (Miyakoshi et al., 2012; Villarini et al., 2013; Heredia-Rojas et al., 2017) used a magnetic flux density over 1 mT. All three these studies reported MF effects. When exposure time had been at least one week, almost all studies (8/9) reported MF effects. Among the studies lasting less than a week, three out of four studies did not produce positive findings, and the only study that detected effects (Miyakoshi et al., 2012) had used a 10 mT magnetic flux density. Five out of six studies using co-exposure reported positive findings. However, these findings included both increased and decreased genotoxicity/carcinogenicity in the groups exposed to ELF MFs.

Four studies (Qi et al., 2015; Soffriti et al., 2016a, 2016b; Bua et al., 2018) assessed the carcinogenicity of ELF MFs. However, no studies using the childhood leukaemia model were conducted. Qi et al. (2015) reported that 0.05 mT exposure (12 h/d) increased the incidence of chronic myeloid leukaemia in female mice. Soffriti et al. (2016a) observed that 0.02 or 1 mT MF exposure (19 h/d) combined with a single 0.1 Gy dose of ionizing radiation increased mammary adenocarcinomas in male and female rats and the incidence of malignant schwannomas of the heart in males, compared to mere ionizing radiation treatment. Furthermore, co-exposure to 1 mT MF increased the incidence of lymphomas/leukaemia in males, compared to mere ionizing radiation treatment. Another study by Soffriti et al. (2016b) reported that co-exposure to 1 mT MF decreased thyroid C-cell carcinomas plus adenomas in female rats, compared to mere formaldehyde treatment. By contrast, co-exposure to 1 mT MF led to a suggestive increase of carcinomas and adenomas in males but the results were not statistically significant, compared to mere formaldehyde exposure. Bua et al. (2018) detected that MF exposure at 0.1 mT (19 h/d) decreased the incidence of total malignant tumours in male rats.

In conclusion, the results of the carcinogenicity studies are inconsistent and the number of studies is low. Overall, the results from genotoxicity and carcinogenicity studies in animals suggest that a long exposure time (> 1 week) increases the likelihood of observing effects. This observation is similar to that of an earlier review by Juutilainen et al. (2000).

Table 2. Animal studies assessing genotoxicity or carcinogenicity of ELF MFs published in 2011 or later.

Assay	MF Exposure	Co-exposure	Response	Response direction	Reference
Genotoxicity					
MN in astrocytes of new-born male Sprague-Dawley rats.	50 Hz, 10 mT for 72 h.	Bleomycin 5 or 10 mg/kg,	MF exposure increased bleomycin (10 mg/kg) induced MN compared to mere bleomycin treatment.	↑	Miyakoshi et al. 2012
DNA damage and MN in the brain and bone marrow of newborn Wistar rats.	50 Hz, 0.5 mT for 30 d.	None.	MF exposure increased DNA damage in brain tissues and MN in bone marrow samples.	↑	Rageh et al. 2012
DNA damage and protein expression in male CD1 mice.	50 Hz, 0.1, 0.2, 1 or 2 mT for 7 d (15 h/d).	None.	MF exposure at 1 or 2 mT increased DNA strandbreaks in all the cerebral areas immediately after the exposure.	↑	Villarini et al. 2013
DNA damage in the brain, kidney, and liver of adult male mice.	50 Hz, 0.1 or 1 mT for 8 weeks.	None.	No effects.		Korr et al. 2014
DNA damage in embryonic C57BL/6 mouse brain.	50 Hz, 0.1 or 0.3 mT for 2 h (0.1 mT) or for 15 h (0.3 mT) continuously or intermittently (5 min on, 10 min off).	None.	No effects.		Saha et al. 2014
DNA damage and MN in the blood erythrocytes and male germ cells of CD-1 Swiss mice.	50 Hz, 0.065 mT for 30 d from day 11.5 post conception until weaning.	X-rays, 1 Gy before MF exposure.	MF exposure decreased X-ray induced DNA damage in sperm cells.	↓	Udroiu et al. 2015

Table 2. Continued

Assay	MF Exposure	Co-exposure	Response	Response direction	Reference
Mutations in sperm and blood samples of BALB/c × CBA/Ca F1 hybrid male mice.	50 Hz, 0.01, 0.1 or 0.3 mT for 2 or 15 h.	None.	No effects.		Wilson et al. 2015
DNA damage and repair in C57BL/6 mouse embryos.	50 Hz, 0.3 mT for 9 h.	Ionizing radiation 0.1 Gy after 3 h MF exposure.	No effects.		Woodbine et al. 2015
MN in male BALB/c mouse bone marrow.	60 Hz, 1, 1.5 or 2 mT for 72 h or for 10 d at 8 h/d.	MMC 5 mg/kg.	MF exposure at 1.5 and 2 mT increased MN. Co-exposure with 2 mT MF and MMC decreased MN compared to mere MMC or mere 2 mT MF exposure.	↑↓	Heredia-Rojas et al. 2017
Carcinogenicity					
Tumour incidence in different tissues of male and female B6C3F1 mice.	50 Hz, 0.05 mT for 15.5 months (12 h/d) from prenatal life.	None.	MF exposure increased the incidence of chronic myeloid leukaemia in female mice.	↑	Qi et al. 2015

Table 2. Continued

Assay	MF Exposure	Co-exposure	Response	Response direction	Reference
Tumour incidence in different tissues of male and female Sprague-Dawley rats.	50 Hz, 0.02 or 1 mT for 19 h/d from prenatal life until natural death.	Ionizing radiation 0.1 Gy	Co-exposure to MF (0.2 and 1 mT) increased mammary adenocarcinomas in males and females and incidence of malignant schwannomas of the heart in males compared to mere ionizing radiation treatment. Co-exposure to 1 mT MF increased incidence of lymphomas/leukaemia in males compared to mere ionizing radiation treatment.	↑	Soffritti et al. 2016a
Tumour incidence in different tissues of male and female Sprague-Dawley rats.	50 Hz, 1 mT for 19 h/d from prenatal life until natural death.	Formaldehyde 50 mg/l.	Co-exposure to MF decreased thyroid C-cell carcinomas plus adenomas in females compared to mere formaldehyde treatment. Co-exposure to MF led to non-significant increase of carcinomas and adenomas in males.	↑↓	Soffritti et al. 2016b
Tumour incidence in different tissues of male and female Sprague-Dawley rats.	50 Hz, 0.0002, 0.02, 0.1 or 1mT for 19 h/d from prenatal life until natural death.	None.	MF exposure at 0.1 mT decreased the incidence of total malignant tumours in male rats.	↓	Bua et al. 2018

deoxyribonucleic acid (DNA), extremely low frequency (ELF), magnetic field (MF), micronuclei (MN), Mitomycin-C (MMC)

1.6 SUMMARY OF GENOTOXICITY AND CARCINOGENICITY FINDINGS IN RESPECT OF IF MFs

In the available literature, only nine studies were found that assess the genotoxicity or carcinogenicity of IF MFs (Table 3). The frequencies used in these studies ranged from 2 to 90 kHz and the magnetic flux densities were between 0.00625 and 6.05 mT. The exposure times used in the *in vitro* studies were relatively short, from 2 to 4 h; in only one study, by Nakasone et al. (2008), the exposure time was longer, namely 48 h. These studies assessed DNA damage, micronuclei, mutagenicity or carcinogenicity in bacteria, mammalian cells or rodents.

None of these studies reported effects of IF MFs. Three studies (Svedenstål & Holmberg, 1993; Lee et al., 2007; Nakasono et al., 2008) combined exposure with chemicals or X-rays, but did not detect any IF MF effects. Of these, the studies by Svedenstål and Holmberg (1993) and Lee et al. (2007) were also the only carcinogenicity studies. Svedenstål and Holmberg (1993) studied lymphomas in CBA/S mice exposed to 20 kHz pulsed saw-tooth MF at 15 µT for lifetime, while Lee et al. (2007) assessed tumour incidence in female Sprague–Dawley rats and in newborn ICR mice exposed to 20 kHz MF at 0.00625 mT for six to 20 weeks (8 h/d).

In conclusion, the number of studies performed at the IF range is small. Also earlier reviews have stated that the number of studies on IF MFs is too small to draw decent conclusions (Ahlbom et al., 2008; SCENIHR, 2015). However, no genotoxic or carcinogenic effects of IF MFs have been detected thus far.

Table 3. Studies assessing genotoxicity and carcinogenicity of IF MFs published in the years 1993-2014.

Assay	MF Exposure	Co-exposure	Response	Reference
Genotoxicity				
MN in CBA/Ca mice bone marrow.	20 kHz, saw-tooth waveform, 15 µT, for 18 d.	None.	No effects.	Huuskonen et al. 1998
DNA damage in *Salmonella typhimurium*TA1353 (pSK1002).	20 kHz, 0.6 mT for 2h.	None.	No effects.	Haga et al. 2005
DNA damage in *Salmonella typhimurium*TA1353 (pSK1002).	20 kHz, 0.6 mT or 60 kHz 0.1 mT for 2h.	None.	No effects.	Igarashi et al. 2005
Mutagenicity, MN, DNA damage in Chinese hamster ovary K-1 (CHO-K1) cells, bacteria, Chinese hamster V-79 cells.	23 kHz, 0.532 mT for 2-4 h.	None.	No effects.	Miyakoshi et al. 2007
Mutagenicity, co-mutagenicity and gene conversion assays in bacteria and yeasts.	0.91mT at 2 kHz, 1.1mT at 20 kHz and 0.11mT at 60 kHz for 48 h.	BH, AF2, ENNG, BP and 2-AA.	No effects.	Nakasono et al. 2008
MN, DNA damage, mutagenicity in Chinese hamster-derived ovary cells, CHO-K1 cells, Chinese hamster-derived lung cells, V-79 cells, human-derived glioblastoma cells, A172.	23 kHz, 6.05 mT for 2 h.	None.	No effects.	Sakurai et al. 2009
DNA damage in human lens epithelial cell line (HLEC; SRA01/04).	90 kHz, 0.93 mT for 2-4 h.	None.	No effects.	Shi et al. 2014
Carcinogenicity				
Lymphomas in female CBA/S mice.	20 kHz, pulsed saw-tooth waveform, 15 µT for lifetime.	X-rays, total of 5.24 Gy, before MF exposure.	No effects.	Svedenstål & Holmberg 1993

Table 3. Continued

Tumour incidence in female Sprague–Dawley rats and in new-born ICR mice.	20 kHz, 0.00625 mT for 6 to 20 weeks (8 h/d).	DMBA 15 mg or BP 3 mg or DMBA 100 µg and TPA 4 µg to produce tumours.	No effects.	Lee et al. 2007

2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (AF2), 2-aminoanthracene (2-AA), benzo(a)pyrene (BP), deoxyribonucleic acid (DNA), intermediate frequency (IF), magnetic field (MF), micronuclei (MN), N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), t-butyl hydroperoxide (BH)

1.7 SUMMARY OF GENOTOXICITY AND CARCINOGENICITY FINDINGS IN RESPECT OF RF FIELDS

In their meta-analyses of genetic damage in mammalian cells, Vijayalaxmi and Prihoda (2008, 2012) found that there were statistically significant increases in some genotoxicity endpoints under certain RF field exposure conditions. However, the effects were observed mainly in studies with small sample sizes, and evidence of publication bias was found in the meta-analyses. In addition, Verschaeve et al. (2010) concluded in their review that the evidence for low-level genotoxic effects of RF fields was very weak and many of the positive studies may well have been due to thermal exposures. Luukkonen (2011) reviewed RF field studies relevant to mechanisms of cancer published between 2006 and 2011. Luukkonen reviewed 34 studies addressing RF field effects related to genotoxicity and found that the results were rather inconsistent, as effects of RF fields were found in 14 studies while 20 studies did not detect any RF field effects. This section reviews recent studies (published in 2010 or later) related to the genotoxicity or carcinogenicity of RF fields.

In vitro studies

After the review by Luukkonen (2011), 23 studies have addressed the genotoxicity of RF fields *in vitro* (Table 4). These studies typically assessed micronuclei or DNA damage using different methods. Most of the studies were performed using frequencies of 900 or 1800 MHz, but higher frequencies were used in a few studies, and Mizuno et al. (2015) applied a 12.5 MHz field. Typical modulations in the studies were CW, GSM and UMTS. The SAR levels in these studies varied between 0.15 and 21 W/kg. Two studies did not report the SARs, but expressed the exposure level as electric field strength or power density (Hintzsche et al., 2012; Xing et al., 2016). Co-exposure to other chemical or physical agents was used in nine studies. The exposure time varied between 0.3 and 144 h.

Over half of the studies (13/23) reported positive findings of RF field exposure, while no RF field effects were observed in ten studies. Of the studies reporting effects, 7/13 reported that RF fields had induced or increased genotoxicity, while 4/13 studies reported reduced genotoxicity in the cells exposed to RF fields. In addition, studies by Sun et al. (2016) and Sannino et al. (2017) reported both increased and decreased genotoxicity under different conditions. Interestingly, four of the total of six studies reporting 'protective' effects of RF fields were performed with co-exposure. Overall, the results do not seem to depend on exposure time, SAR level or modulation of the signal. As concluded earlier by Luukkonen (2011), the results of studies on the genotoxicity of RF fields are inconsistent and thus difficult to interpret. The statement of Verschaeve et al. (2010), that many of the positive studies may well be due to thermal effects, is still valid as it is often difficult to evaluate the

exposure systems and performance of their temperature controls, especially when high SARs are applied.

Table 4. *In vitro* studies assessing genotoxicity of RF fields published in 2011 or later.

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
Aneuploidy of chromosomes 11 and 17 in human amniotic cells.	900 MHz (GSM), SAR 0.25, 1, 2 or 4 W/kg for 24 h.	None.	No effects.		Bourthoumieu et al. 2011
MN in human peripheral blood lympho-cytes.	900 MHz (GSM), SAR 1.25 W/kg for 20 h.	MMC 100 ng/ml, 4 h after RF exposure for 14 h.	Pre-exposure to RF radiation in S-phase of the cell cycle decreased MN compared to mere MMC-treatment.	↓	Sannino et al. 2011
MN in HaCaT cells and in A_L cells.	900 MHz (GSM or CW), 5, 10, 30 or 90 V/m for 0.5 or 22 h.	None.	No effects.		Hintzsche et al. 2012
MN in primary mouse brain cells.	10.715 GHz, SAR 0.725 W/kg for 3 d (6 h/d).	None.	Increased MN.	↑	Karaca et al. 2012
MN in human blood lymphocytes.	1950 MHz (UMTS), SAR 0.15, 0.3, 0.6 or 1.25 W/kg for 20 h.	MMC 100 ng/ml, 4 h after RF exposure for 14 h.	Pre-exposure to RF radiation at SARs of 0.3 and 0.6 W/kg decreased MN compared to mere MMC-treatment.	↓	Zeni et al. 2012
DNA damage and oxidative DNA base damage in mouse spermatocyte-derived GC-2 cell line.	1800 MHz (GSM), SAR 1, 2 or 4 W/kg for 24 h intermittently (5 min on and 10 min off).	10 µM α - tocopherol for 24 h, before RF exposure.	RF exposure at a SAR of 4 W/kg increased extent of DNA migration and levels of the DNA adduct 8-oxoguanine.	↑	Liu et al. 2013

Table 4. Continued

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
DNA damage and MN in human lymphoblastoid cell line HL-60.	1800 MHz (CW), SAR 1.3 W/kg for 24 h intermittently (5 min on and 10 min off) or continuously.	None.	No effects.		Speit et al. 2013
DNA damage, chromosome aberrations, MN and sister chromatid exchanges in human peripheral lymphocytes.	1800 MHZ (GSM), SAR 0.2, 2 and 10 W/kg for 28 h intermittently (5 min on, 10 min off).	None.	No effects.		Waldmann et al. 2013
MN in human peripheral blood lymphocytes.	2450 MHz (WCDMA or CW), SAR 10.9 W/kg for 2 h.	2 mM melatonin, added 30 min prior to RF exposure.	No effects.		Vijayalaxmi et al. 2013
DNA damage in Chinese hamster lung cells, primary rat astrocytes, human amniotic epithelial cells, human lens epithelial cells SRA01/04, human skin fibroblasts and in Human umbilical vein endothelial cells.	1800 MHz (GSM), SAR 3 W/kg for 1 or 24 h intermittently (5 min on and 10 min off).	None.	RF exposure for 24 h increased DNA DSB in Chinese hamster lung cells and in human skin fibroblasts.	↑	Xu et al. 2013
DNA damage in mouse spermatocyte-derived GC-2 cell line.	1800 MHz (GSM), SAR 1, 2 or 4 W/kg for 24 h intermittently (5 min on and 10 min off).	None.	RF exposure at a SAR of 4 W/kg induced oxidative DNA base damage.	↑	Duan et al. 2015

Table 4. Continued

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
DNA damage in mouse peripheral blood leukocytes.	42.2 GHz (pulse-modulated modulation frequency of 1 and 16 Hz or CW), SAR 1.5 W/kg for 20 min.	X-ray radiation at a dose of 4 Gy or H_2O_2 20 μM for 10 min or MMS 2.5 mM for 10 min, after RF exposure.	Pre-exposure to pulse-modulated RF radiation decreased DNA damage, which was induced by co-exposures.	↓	Gapeyev and Lukyanova 2015
DNA damage in rat primary lymphoblasts.	900 MHz (CW), SAR 2 or 10 W/kg for 1.5 h or 1800 MHz (PM) SAR 2.5 or 12.4 W/kg for 2 h.	None.	No effects.		Kumar et al. 2015
DNA damage, MN and gene mutations in human embryo lung-derived SV40 virus transformed WI38VA13 subcloned 2RA cells.	12.5 MHz, SAR approximately 21 W/kg for 48, 96 or 144 h.	None.	No effects.		Mizuno et al. 2015
DNA damage in neuro-2a cells.	900 MHz (GSM), 0, 0.5, 1 or 2 W/kg for 24 h.	OGG1 siRNA.	RF exposure at a SAR of 2 W/kg induced oxidative DNA base damage. RF exposure at SARs of 1 and 2 W/kg with OGG1 siRNA caused DNA base damage.	↑	Wang et al. 2015

Table 4. Continued

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
DNA damage and repair in human promyelocytic leukaemia cell line HL-60 and in human hematopoietic stem cells (HSC).	900 MHz (GSM), 1950 MHz (UMTS) and 2535 MHz (LTE), SAR 0.5, 1, 2 or 4 W/kg for 4, 20 or 66 h.	None.	GSM-modulated RF exposure for 4 h decreased DNA damage in HSC at SARs of 0.5, 1 and 4 W/kg.	↓	Gläser et al. 2016
MN in *Vicia faba* root tips.	915 MHz (CW), SAR 0.4–1.6 W/kg for 72 h.	None.	RF radiation increased MN from 2.3 to 7-fold compared to sham, depending on exposure level.	↑	Gustavino et al. 2016
DNA damage and repair in mouse embryonic fibroblasts (MEF)s with proficient (Atm+/+) or deficient (Atm−/−) ataxia telangiectasia mutated (ATM).	1800 MHz (GSM), SAR 4.0 W/kg for 1, 12, 24 or 36 h intermittently (5 min on/10 min off).	None.	1 h RF exposure induced and 36 h exposure decreased DNA SSB in Atm+/+ MEFs. 12 h RF exposure induced and 24 and 36 h exposure decreased DNA SSB in Atm-/- MEFs. 12 and 24 h RF exposure induced and 36 h exposure decreased DNA DSB in Atm-/- MEFs. RF exposure activated the SSB repair pathway in Atm+/+ MEFs and both the SSB and DSB repair systems in Atm−/− MEFs.	↑↓	Sun et al. 2016
DNA damage in mouse NIH/3T3 and human U-87 MG cells.	1800 MHz, 1209 mW/m^2 for 0, 3, 6, 12, 24 or 48 h.	NAC.	RF exposure increased DNA damage, which restrained in the presence of NAC.	↑	Xing et al. 2016

Table 4. Continued

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
MN in human glioblastoma cell lines U87 (wild type) and U251 (mutated).	1950 MHz (UMTS), SAR 0.25, 0.5 or 1 W/kg for 16 h.	Simultaneously MMC 1.0 µg/ml.	No effects.		Al-Serori et al. 2017
MN in Chinese hamster lung fibroblast cell line (V79).	1950 MHz (UMTS), SAR 0.15, 0.3, 0.6 or 1.25 W/kg for 20 h.	MMC 1 or 5 ng/ml during RF exposure, and 300 or 500 ng/ml after RF exposure.	RF exposure increased MN at SARs of 0.15 and 0.3 W/kg. Pre-exposure to RF radiation at a SAR of 1.5 W/kg decreased MN compared to mere MMC-treatment.	↑↓	Sannino et al. 2017
DNA damage in neurogenic A172, U251, and SH-SY5Y cells.	1800 MHz (GSM), SAR 4.0 W/kg for 1, 6 or 24 h intermittently (5 min on/10 min off).	None.	No effects.		Su et al. 2017b
DNA damage in primary cultured astrocytes, microglia and cortical neurons.	1800 MHz (GSM), SAR 4.0 W/kg for 1, 6 or 24 h intermittently (5 min on and 10 min off).	None.	No effects.		Su et al. 2018

8-oxoguanine DNA glycosylase (OGG1 siRNA), continuous wave (CW), deoxyribonucleic acid (DNA), doublestrand breaks (DSB), Global System for Mobile Communications (GSM), hydrogen peroxide (H_2O_2), Long Term Evolution (LTE), methyl methanesulphonate (MMS), micronuclei (MN), Mitomycin C (MMC), N-acetyl-L-cysteine (NAC), pulse modulated (PM), radiofrequency (RF), singlestrand breaks (SSB), specific absorption rate (SAR), Universal Mobile Telecommunications System n(UMTS), Wide Band Code Division Multiple Access (WCDMA)

Animal studies

After the review by Luukkonen (2011), several animal studies have been performed to assess the genotoxicity or carcinogenicity of RF fields. However, the quality of the studies is sometimes questionable because of inadequate descriptions of the exposure systems and protocols. In addition, it is difficult to evaluate the reliability of the reported SAR levels, as the calculation or modelling of SARs in animals is challenging. A total of 16 studies using exposure systems that allow determining the exposure parameters were included in this review (Table 5). Studies performed with a mobile phone acting as an exposure system, with no adequate knowledge of the SAR level, were excluded. Rodents were typically used in these studies, but one study used rabbits (Güler et al., 2012) and one earthworms (Tkalec et al., 2013). All studies were conducted with frequencies between 900 and 2450 MHz and with relatively low exposure levels – the whole body SAR level was higher than 1 W/kg in four studies (Tillman et al., 2010; Güler et al., 2012; Furtado-Filho et al., 2015; Lerchl et al., 2015). In most of the studies, the exposed animals were allowed to move freely in the cages or the exposure was uniform for the whole body, but Gürler et al. (2014) used an exposure set-up where the animals were in fixed positions around the antenna, which resulted in higher exposure of the head than other parts of the body. The exposure times in the studies varied a great deal, from days to whole lifetime exposure, and the daily exposure time varied from minutes per day to continuous exposure.

Ten out of 12 studies reported RF field effects on genotoxicity and two studies did not find any RF field effects (Trošić et al., 2011; Furtado-Filho et al., 2015). Seven studies reported that RF fields had induced or increased genotoxicity, while two studies found decreased genotoxicity in the groups exposed to RF radiation. In addition, the study by Sahin et al. (2016) reported that 10 d exposure to 2100 MHz 3G RF fields (SAR 0.4 W/kg) had increased oxidative DNA damage in the brains of female rats, but increasing the exposure time to 40 d led to decreased damage. Two studies used co-exposure and found that exposure to RF fields had decreased genotoxicity induced by ionizing radiation (Jiang et al., 2013) or bleomycin (Zong et al., 2015).

Four studies since 2010 have assessed the carcinogenicity of RF fields. Tillman et al. (2010) studied tumour incidence in female mice exposed to 1966 MHz (UMTS) RF fields from prenatal to whole lifetime (20 h/d). The study included prenatal exposure to ethylnitrosourea (ENU, 40 mg/kg) and the results indicated that co-exposure to 4.8 W/m^2 RF fields increased lung tumours compared to ENU treatment only. Lerchl et al. (2015) repeated the cocarcinogenicity study of Tillman et al. (2010) with slight enhancements. They increased the number of animals, the RF field exposure groups (SAR 0.04, 0.4 and 2 W/kg) and used continuous exposure (24 h/d). Lerchl et al. (2015) observed that co-exposure to RF fields at all exposure levels increased the numbers of the tumours in lungs and liver compared to mere ENU treatment. However, Lerchl et al. (2015) did not find any dose-response effect

and the carcinogenicity of RF field exposure alone was not tested. Paulraj and Behari (2011) studied tumour incidence in male Swiss albino mice exposed to 112 MHz fields, amplitude modulated at 16 Hz at an SAR of 0.75 W/kg, or to 2450 MHz RF fields at an SAR of 0.1 W/kg for 16 weeks (2 h/d, 3 days a week). They used pre-exposure of 7,12-dimethylbenz(a)anthracene (100 µg) and observed no effects. Furthermore, no RF field effects were detected when ascites carcinoma cells were transplanted 14 d before RF field exposure. Falcioni et al. (2018) detected an increase in heart Schwannomas in male Sprague-Dawley rats exposed to 1800 MHz GSM-modulated RF fields at an SAR of 0.1 W/kg.

A recent large two-year animal carcinogenicity study detected an increased number of tumours (most clearly in heart Schwannomas) in male rats exposed to RF fields (900 MHz, GSM or CDMA modulated, at SAR 6 W/kg) (NTP, 2018a, 2018b), but not in female rats or mice. However, these results have not yet been published in a peer-reviewed journal.

Overall, it seems that recent animal RF field studies indicate more positive findings than earlier reviews (Verschaeve et al., 2010; Luukkonen, 2011). However, there is no clear consistency of the exposure parameters and the quality of some studies might be doubtful, causing bias to the results of the review.

Table 5. Animal studies assessing genotoxicity or carcinogenicity of RF fields published in 2010 or later.

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
Genotoxicity					
DNA damage in brain, liver and kidney of male Wistar rats.	915 MHz (GSM), SAR 0.6 W/kg for 14 d (1 h/d).	None.	No effects.		Trošić et al. 2011
Oxidative DNA damage in liver tissues of infant New Zealand white rabbits.	1800 MHz (GSM), SAR 1.8 W/kg for 7 d (females) or 14 d (males) (15 min/d).	None.	Increased levels of 8-OHdG in females.	↑	Güler et al. 2012
MN in immature erythrocytes in peripheral blood and bone marrow of male ICR mice.	900 MHz (CW), 0.548 W/kg for 7 d (4 h/d).	Ionizing radiation 3 Gy after RF exposure.	Pre-exposure to RF blocked ionizing radiation-induced increase of MN in both tissues.	↓	Jiang et al. 2013
DNA damage in *Eisenia fetida* earthworms.	900 MHz (CW), SAR 0.00013, 0.00035, 0.0011 or 0.00933 W/kg for 2 h. 900 MHz (modulated 80% AM 1kHz sinusoidal), SAR 0.00035 W/kg for 2 or 4 h.	None.	Increased DNA damage in all exposure groups. RF signal modulation increased DNA damage compared to CW.	↑	Tkalec et al. 2013
Oxidative DNA damage in brain tissues and blood samples of Wistar rats.	2450 MHz (217 Hz modulation), SAR 0.02 W/kg for 30 d (1 h/d).	Garlic 500 mg/kg/d.	Increased levels of 8-OHdG in brain and blood samples. Garlic prevented this RF effect.	↑	Gürler et al. 2014

Table 5. Continued

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
DNA damage in cerebral cortex tissue of neonate rats.	950 MHz, SAR1.14-1.32 W/kg for 27 d (21 d gestation and 6 d postnatal) (0.5 h/d).	None.	No effects.		Furtado-Filho et al. 2015
DNA damage in brains of male Fischer 344 rats.	900 MHz, SAR 0.00059 W/kg, 1800 MHz, SAR 0.00058 W/kg, 2450 MHz, SAR 0.00066 W/kg for 60 d (2 h/d, 5 d/week).	None.	Increased DNA damage in all exposure groups.	↑	Megha et al. 2015
DNA damage and repair in blood leukocytes of adult male ICR mice.	900 MHz (CW), SAR 0.05 W/kg for 7 d (4 h/d).	Bleomycin 37.5 mg/kg after RF exposure.	Pre-exposure to RF decreased bleomycin-induced DNA damage.	↓	Zong et al. 2015
DNA damage in different tissues of adult male Wistar albino rats.	2400 MHz, SAR 0.00014 W/kg (whole body average) and maximum 0.007 W/kg for 12 months.	None.	RF exposure increased DNA damage in testes.	↑	Akdag et al. 2016
Oxidative DNA damage in brains of female Wistar albino rats.	2100 MHz (3G), SAR 0.4 W/kg for 10 or 40 d (6 h/d, 5 d/week)	None.	Increased oxidative DNA damage to brain after 10 d and decreased oxidative DNA damage after 40 d exposures.	↑↓	Sahin et al. 2016

Table 5. Continued

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
MN in ovarian tissues of female Sprague-Dawley rats.	1800 MHz (GSM), SAR 0.974 W/kg for 15, 30 or 60 d (2 h/d).	None.	Increased MN after 60 d exposure.	↑	Alchalabi et al. 2017
DNA damage in testicular germ cells of Swiss albino mice.	900 MHz (GSM), SAR 0.0054-0.0516 W/kg for 35 d (4 or 8 h/d).	None.	Increased DNA damage.	↑	Pandey et al. 2017
Carcinogenicity					
Tumour incidence in female B6C3F1 mice.	1966 MHz (UMTS), 4.8 or 48 W/m^2 (SAR 0.62- 5.76 W/kg), from prenatal exposure to 24 months (20 h/d).	Prenatal ENU exposure 40 mg/kg for 4.8 W/m^2 group.	Co-exposure to 4.8 W/m^2 RF radiation increased lung tumours compared to mere ENU-treatment.	↑	Tillman et al. 2010
Tumour incidence in male Swiss albino mice.	112 MHz (AM) at 16 Hz, SAR 0.75 W/kg or 2450 MHz, SAR 0.1 W/kg for 16 weeks (2 h/day, 3 days a week) or 14 d.	DMBA 100 µg/animal before RF exposure or transplanted ascites carcinoma cells.	No effects.		Paulraj and Behari 2011
Tumour incidence in female B6C3F1 mice.	1966 MHz (UMTS), SAR 0.04, 0.4 or 2 W/kg), from prenatal exposure to 72 weeks.	Prenatal ENU exposure 40 mg/kg.	RF radiation exposure increased tumours compared to mere ENU-treatment.	↑	Lerchl et al. 2015

Table 5. Continued

Assay	RF Exposure	Co-exposure	Response	Response direction	Reference
Tumour incidence in Sprague-Dawley rats.	1800 MHz (GSM), SAR 0.001, 0.003 or 0.1 W/Kg, from prenatal life until natural death (19 h/d).	None.	Increase of heart Schwannomas in male rats at a SAR of 0.1 W/kg.	↑	Falcioni et al. 2018

7,12-dimethylbenz(a)anthracene (DMBA), 8-hydroxy-2 '-deoxyguanosine (8-OHdG), continuous wave (CW), deoxyribonucleic acid (DNA), ethyl-nitrosourea (ENU), Global System for Mobile Communications (GSM), micronuclei (MN) radiofrequency (RF), specific absorption rate (SAR), third generation (3G), universal mobile telecommunications system (UMTS)

1.8 ELECTROMAGNETIC FIELDS AND GENOMIC INSTABILITY

The relationship between IGI and EMFs has been investigated in only four studies. All of them were performed with ELF MFs and reported positive findings (Table 6). There are currently no studies addressing IGI and exposure to IF MFs or RF EMFs.

Cho et al. (2007) examined the effects of 60 Hz, 800 μT MFs on delayed chromosomal instability induced by bleomycin (BLM) in human fibroblast cells. The frequencies of micronuclei and aneuploidy were analysed 28, 88, and 240 h after a 3-h treatment with BLM. Magnetic field exposure was applied continuously throughout the culture period after BLM treatment. Co-exposure to BLM and MF resulted in a significant increase in the frequencies of micronuclei and aneuploidy compared to the cells treated with BLM alone. No difference was observed between MF-exposed cells and sham-exposed control cells without BLM treatment.

Mairs et al. (2007) studied mutagenicity by analysing microsatellite sequences in human glioma cells exposed to 50 Hz MFs at a magnetic flux density of 1 mT for 12 h, either alone or combined with exposure to ionizing radiation before MF treatment. The frequency of microsatellite mutations measured 38 days after the treatments was increased by the MF treatment alone in comparison to the unexposed controls. Magnetic field treatment also increased mutations in cells irradiated at 0.3 and 3 Gy. One of the three mutation types that were evaluated was allelic imbalance. This type of genetic change is caused by allelic loss occurring in the progeny of the exposed cells during the post-exposure incubation, and therefore indicates IGI. The MF-induced increase of mutations was particularly pronounced for allelic imbalance.

Luukkonen et al. (2014) exposed human neuroblastoma cells to 50 Hz, 100 μT MF for 24 h, followed by 3-h treatment with menadione. Micronuclei in the progeny of exposed cells were measured at 8 and 15 d after the exposures. The frequency of micronuclei was increased in MF-exposed cells, both at 8 and 15 days. The MF-induced increase was observed independent of whether the cells had also been exposed to menadione. Other delayed effects in MF-exposed cells included increased mitochondrial activity at 8 d, and increased ROS production and lipid peroxidation at 15 d after the exposures. In a later study, the follow-up time was increased to 45 days after exposure to 50 Hz, 100 μT MF with or without co-exposure to menadione (Kesari et al., 2016). As in the previous study, the level of micronuclei was elevated 15 d after exposure in MF-exposed cells, and the MF effect did not depend on co-exposure to menadione. A similar effect was observed at 30 d, but not at 45 d after exposure. To study the possible causal role of ROS in the delayed effects of MFs, the antioxidant *N*-acetylcysteine was administered before MF exposure. However, it did not block the MF effect, indicating that an increase in ROS is not needed as a causal link between MF exposure and the induction of delayed effects.

Table 6. Studies on genomic instability and ELF MFs.

Assay and cells	MF Exposure	Co-exposure	Response	Response direction	Reference
MN and aneuploidy in human CCD-986sk fibroblasts 28, 88 and 240 h after exposure to BLM.	60 Hz, 0.8 mT for up to 240 h.	BLM 0, 0.2, or 1 µg/ml for 3 h before MF exposure.	Enhancement of BLM-induced MN and aneuploidy.	↑	Cho et al. 2007
Microsatellite mutations in human UVW glioma cells 38 d after the exposures.	50 Hz, 1 mT, 12 h.	γ radiation 0, 0.3 or 3 Gy prior to MF exposure.	Increased microsatellite mutations with and without γ radiation.	↑	Mairs et al. 2007
MN in human neuroblastoma SH-SY5Y cells 8 and 15 d after the exposures.	50 Hz, 0.1 mT, 24 h.	Menadione 1 or 20 µM for 3 h after MF exposure.	Increased MN with and without menadione.	↑	Luukkonen et al. 2014
MN in human neuroblastoma SH-SY5Y cells 15, 30 and 45 d after the exposures.	50 Hz, 0.1 mT, 24 h.	NAC for 1 h before, and menadione 20 µM for 3 h after MF exposure.	Increased level of MN at 15 and 30 d with and without menadione. The antioxidant NAC did not block the MF effect.	↑	Kesari et al. 2015

bleomycin (BLM), extremely low frequency (ELF), magnetic field (MF), micronuclei (MN), N-acetyl cysteine (NAC),

2 AIMS OF THE STUDY

The general aim of this study is to investigate possible genome-damaging effects of electromagnetic fields and to increase understanding of the mechanisms of such effects. To this end, several studies assessing genotoxicity and induced genomic instability were performed with ELF, IF and RF fields. The specific aims of the study are:

1. To investigate the genotoxicity of ELF MFs;
2. To test the radical pair mechanism by studying interactions between ELF MFs and blue light;
3. To evaluate IF MF effects on DNA damage, DNA repair and IGI;
4. To investigate whether RF fields can cause DNA damage or IGI; and
5. To study the effects of combined exposure to EMFs and genotoxic chemicals.

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Chapter 6.

General discussion

1 METHODOLOGICAL CONSIDERATIONS

The results of EMF studies are often inconsistent and difficult to interpret. There are many possible reasons for these inconsistencies. First, there might be real differences between various frequencies, exposure times, exposure levels or the cells and animal strains used. However, it is also possible that most of the differences can be explained by the quality of the studies, as the most of the detected effects are small and, for example, *in vitro* studies are very sensitive to small changes in temperature. Especially in the case of RF fields, controlling the temperature is essential for the reliability of the studies. In the present study, well-controlled exposure systems and protocols were used in high-quality facilities, which increases the reliability of the results. The *in vitro* experiments of the present study always involved a 24-h exposure, because previous data indicated that EMF exposure needs to be long enough to produce measurable effects. However, it would have been interesting to test even longer exposure times to gain further insights into the influence of exposure duration.

One challenge in the present study was the use of primary cells, even though it was at the same time a main strength of this study. The majority of the experiments of this study were performed with rat primary astrocytes, while most of the earlier studies assessing the effects of EMFs have been performed with secondary cell lines. Primary cells were chosen because they more closely represent the state of cells *in vivo*. A disadvantage of primary cells is that they divide slowly and are more challenging to culture than secondary cell lines. For example, in the IF MF experiments, statistically significant differences in the Comet assay results were seen between the MF-exposed and sham-exposed cells in those groups that did not include chemical treatments, but the direction of the MF effect was inconsistent. As the experiments without chemical treatment were identical, these findings must have arisen by chance in spite of the statistical significances. This indicates that the Comet assay results may be generally unstable in primary astrocytes, at least at the low DNA damage levels that are present in cells not exposed to chemicals.

Moreover, primary cells caused problems especially in the studies assessing genomic instability when a long incubation time was needed. Because these cells divide slowly, a long-duration study is needed to assess genomic instability in the distant progeny. During the long incubation (36 d after exposure), the primary cell

cultures apparently became unstable, as the genotoxicity measures indicated large differences between replicate experiments, even in the unexposed control cultures. Instability of the experimental system itself may have affected its ability to detect IGI. It would have been good to repeat experiments with secondary cell lines to confirm the results, as the earlier results performed with secondary cells indicated ELF MF effects.

In addition, it was not a huge surprise that genomic instability was not detected with the Comet assay. The Comet assay is a good and widely used method to detect immediate DNA damage and to study DNA repair, but it might not be the most sensitive method to detect delayed effects a long time after the DNA repair processes. However, if the genome is unstable, the frequency of DNA strand breaks could also be higher than in stable cells, as suggested by a study on transgenerational genomic instability induced by ionizing radiation in mice (Barber et al., 2006).

The study on ELF MFs was the first study on the combined effects of MFs and blue light on ROS levels and genotoxicity. The study was limited by a relatively simple design involving only one light intensity. In the future, it would be good to use a more sophisticated exposure system where the intensity of light can be modified.

Moreover, in the RF field studies, the well-designed exposure system had a limitation, as it allowed only two petri dishes to be used at a time. It would have been useful to test more chemical doses and also to study DNA repair after RF field exposure.

2 GENOTOXICITY, GENOMIC INSTABILITY AND ELECTROMAGNETIC FIELDS

2.1 SUMMARY OF THE FINDINGS

The present study does not support genotoxicity or co-genotoxicity of IF MFs and RF fields. On the contrary, the results indicate that IF MFs might reduce the level of genetic damage. The present study also revealed a lack of IGI in rat primary astrocytes exposed to IF MFs or RF fields. The results from the ELF MF studies do not support the simple hypothesis that MF effects would be observed only in the presence of blue light, but interactions between blue light and ELF MFs were nevertheless observed. Extremely low frequency magnetic fields were found to cause biological effects in the absence of light, and there was evidence that MFs and blue light may counteract the effects of each other.

2.2 GENOTOXICITY AND OTHER IMMEDIATE EFFECTS

The genotoxicity findings and other endpoints measured immediately after exposure are summarized in Table 1.

2.2.1 ELF and IF MFS

ELF MFs

It was demonstrated that ELF MFs increased cytosolic superoxide production and decreased mitochondrial superoxide production. This finding is in line with earlier studies, as ELF MFs have been reported to affect ROS production (Luukkonen et al., 2014; Mattsson & Simko, 2014; Kesari et al., 2016; Wang & Zhang, 2017). This indicates that changes in mitochondrial and cytosolic superoxide levels serve as indicators of such MF-induced changes that occur early and may affect cellular responses to subsequent environmental stressors. In contrast to superoxide levels, ELF MFs did not affect micronucleus frequency in a way that was statistically significant. This result differs from those of earlier studies (Luukkonen et al., 2011; Kesari et al., 2016) in which pre-exposure to ELF MFs increased menadione-induced micronuclei. This difference may be related to the different timings of menadione exposure in the previous studies and the present study. In the present study, menadione exposure was administered during the last 3 h of the 24-h MF treatment, while in previous studies a separate menadione exposure followed the 24-h MF exposure.

The experiments with ELF MFs sought to test the radical pair mechanism as an explanation for earlier findings indicating that ELF MFs may induce or increase

genotoxicity and induce genomic instability. Interaction of ELF MFs and blue light was observed, although the original simple hypothesis (blue light is needed for MF effects) was not supported. Extremely low frequency magnetic fields were found to cause biological effects in the absence of light, and there was evidence that MFs and blue light may counteract the effects of each other. This indicates that the interactions between the MFs and light could be more complex than was previously expected. The ELF MF effects that occurred without blue light indicate that MFs may also affect light-independent radical reactions.

In the future it would be useful to test more extensively how the timing of MF exposure and co-exposure to chemicals affects genotoxicity, as comparison with earlier studies indicates that timing may be an important parameter.

IF MFs

The present study did not support genotoxicity or co-genotoxicity of 7.5 kHz MFs at magnetic flux densities up to 300 µT *in vitro* or *in vivo*. On the contrary, there was some evidence that exposure to 7.5 kHz MFs might reduce the level of genetic damage. Strongest evidence for biological effects was obtained from measurements of relative cell numbers, which were significantly and consistently increased after MF exposure in all *in vitro* experiments performed with rat primary astrocytes.

These findings, 'protective' effects in animals and increased vitality in cells, are in contrast to the earlier IF MF studies (Chapter 1, section 1.6) that did not find any evidence of biological effects. Possible reasons for this difference include differences in the frequencies, field strengths and cell lines used. Also, the 24-h exposure used in this study was longer than those used in most of the previous *in vitro* studies. As the reason for the increased relative survival is not known, it is not possible to draw conclusions concerning possible relevance to human health effects. In further studies the reasons and possible mechanisms of these observations should be assessed, possibly by measuring proliferation and apoptosis after IF MF exposure.

2.2.2 RF fields

The present study revealed that RF fields alone did not cause genotoxicity. Radio-frequency fields combined with chemical exposure indicated some statistically significant differences, but these are likely to be chance findings, as there was no clear consistent SAR- or modulation-dependent pattern. Overall, co-genotoxicity of RF fields and genotoxic chemicals was not consistently supported by the results. The results are in line with earlier studies, as literature reviews and meta-analyses have generally concluded that there is little evidence that RF radiation is genotoxic (Vijayalaxmi & Prihoda, 2008, 2012; Verschaeve et al., 2010; Luukkonen, 2011).

Table 1. Findings of experiments conducted to detect immediate effects.

Assay	EMF Exposure	Co-exposure	EMF effect	Chapter
Proliferation in human neuroblastoma SH-SY5Y cells.	50 Hz, 100 µT for 24 h.	BL during MF exposure. Menadione 10 or 20 µM for the last 3 h of exposure.	No effects.	2
Mitochondrial superoxide levels in human neuroblastoma SH-SY5Y cells.	50 Hz, 100 µT for 24 h.	BL during MF exposure. Menadione 10 or 20 µM for the last 3 h of exposure.	MF exposure decreased superoxide levels. The level of superoxide in the BL+MF group was systematically between those observed in the BL and MF groups.	2
Cytosolic superoxide levels in human neuroblastoma SH-SY5Y cells.	50 Hz, 100 µT for 24 h.	BL during MF exposure. Menadione 10 or 20 µM for the last 3 h of exposure.	MF exposure increased superoxide production and co-exposure to BL suppressed this effect.	2
Viability in human SH-SY5Y neuroblastoma cells.	50 Hz, 100 µT for 24 h.	BL during MF exposure. Menadione 10 or 20 µM for the last 3 h of exposure.	No effects.	2
MN in human neuroblastoma SH-SY5Y cells.	50 Hz, 100 µT for 24 h.	BL during MF exposure. Menadione 10 µM for the last 3 h of exposure.	The MF+BL group showed higher MN level than the unexposed controls, but not differ significantly from the BL only group.	2
DNA damage and DNA repair in rat primary astrocytes.	7.5 kHz, 30 or 300 µT for 24 h.	Menadione 15 or 20 µM or MMS 15 or 40 µg/ml for 3 h after MF exposure.	No consistent effect from MF exposure without chemicals. Co-exposure with chemicals showed some statistically significant differences, but the effects were inconsistent.	3
MN and relative cell number in rat primary astrocytes.	7.5 kHz, 30 or 300 µT for 24 h.	Menadione 15 or 20 µM or MMS 15 or 40 µg/ml for 3 h after MF exposure.	MF exposure at 300 µT decreased MMS-induced MN. MF exposure increased the relative cell number in all experiments.	3
DNA damage in blood samples of male C57BL/6J mice.	7.5 kHz, 12 or 120 µT for 5 weeks.	None.	MF exposure at 12 and 120 µT decreased DNA damage.	3

Table 1. Continued

Assay	EMF Exposure	Co-exposure	EMF effect	Chapter
MN in blood samples of male C57BL/6J mice.	7.5 kHz, 12 or 120 µT for 5 weeks.	None.	Some statistically significant differences, but no consistent dose response.	3
DNA damage in rat primary astrocytes.	872 MHz (CW or GSM), SAR 0.6 or 6 W/kg for 24 h.	Menadione 15 µM or MMS 40 µg/ml for 3 h after MF exposure.	Pre-exposure to RF radiation (GSM) at SAR of 6 W/kg increased and at SAR of 0.6 W/kg decreased DNA damage compared to mere MQ-exposure.	5
MN in rat primary astrocytes.	872 MHz (CW or GSM), SAR 0.6 or 6 W/kg for 24 h.	Menadione 15 µM or MMS 40 µg/ml for 3 h after MF exposure.	Pre-exposure to RF radiation (CW) at a SAR of 0.6 W/kg increased MN compared to mere MMS-treatment.	5

blue light (BL), continuous wave (CW), deoxyribonucleic acid (DNA), electromagnetic field (EMF), Global System for Mobile Communications (GSM), magnetic field (MF), methyl methanesulphonate (MMS), micronuclei (MN), RF radiofrequency, specific absorption rate (SAR)

2.3 GENOMIC INSTABILITY

Possible induction of genomic instability by IF MFs or RF fields was investigated for the first time in the present study. The results of the experiments (Table 2) indicated that neither IF MFs nor RF fields induced genomic instability or increased it in combination with chemical treatments in rat primary astrocytes. On the contrary and surprisingly, IF MF exposure seemed to decrease micronuclei, indicating a possible decrease of genomic instability. Earlier studies, although performed on ELF MFs (Cho et al., 2007; Mairs et al., 2007; Luukkonen et al., 2014; Kesari et al., 2016), have reported that MFs can cause IGI.

In the case of RF fields, it may not be a surprise that IGI effects were not seen, as the only established effects of RF fields are the thermal effects. In this study, the temperature during exposure was controlled, as the RF exposure system was equipped with a cooling system, which prevented the heating caused by exposure at an SAR of 6 W/kg.

Instead, in the IF range the effects would have been expected to be similar to those observed in cells exposed to ELF MFs, if the underlying mechanism is assumed to be the RPM. Theoretically, the RPM should be valid up to MHz frequencies (Sheppard et al., 2008; Hore & Mouritsen, 2016). However, it is possible, as suggested by the results of this study, that other mechanisms are involved, and MF-induced genomic instability is a frequency-dependent phenomenon that does not exist in the IF range. Overall, these findings stress the importance of studying the frequency dependence of the biological effects of weak MFs.

A limitation of the present study is the use of primary astrocytes, in contrast to earlier studies on genomic instability induced by ELF MFs, which were performed with secondary cell lines. As the intrinsic instability of primary astrocytes may have affected the results, additional studies with secondary cell lines would be useful to confirm the results, especially in the IF range.

Table 2. Summary of the genomic instability findings.

Assay	EMF Exposure	Co-exposure	EMF effect	Chapter
DNA damage and MN in rat primary astrocytes measured 36 d after the exposure.	7.5 kHz, 300 µT for 24 h.	Menadione 20 µM or MMS 40 µg/ml for 3 h after MF exposure.	MF suggestively decreased MN.	4
DNA damage and MN in rat primary astrocytes measured 36 d after the exposure.	872 MHz (GSM), SAR 0.6 or 6 W/kg for 24 h.	Menadione 15 µM for 3 h after MF exposure.	No effects.	5

deoxyribonucleic acid (DNA), electromagnetic field (EMF), Global System for Mobile Communications (GSM), methyl methanesulphonate (MMS), micronuclei (MN), specific absorption rate (SAR)

3 CONCLUSIONS

Exposure to 50 Hz 100 µT MF for 24 h affected ROS production but did not increase micronuclei alone or in combination with menadione in human neuroblastoma SH-SY5Y cells. Combined exposure to blue light and ELF MFs was studied for the first time and it was found that interactions between blue light and ELF MFs are probably more complex than expected. The finding that MF effects occurred without blue light indicates that MFs may also affect light-independent radical reactions. These observations may be important for understanding the effects of weak MFs and further studies on the interactions of light and MFs are warranted.

Exposure to 7.5 kHz MFs up to 300 µT for 24 h *in vitro* or *in vivo* did not cause genotoxicity alone or in combination with chemicals in rat primary astrocytes. There was some evidence that IF MFs might reduce the level of genetic damage, and rather strong evidence that relative cell number was increased after exposure to IF MFs. Furthermore, exposure to vertical or horizontal 7.5 kHz MFs at 300 µT did not induce genomic instability alone or in combination with chemicals in rat primary astrocytes. On the contrary, the results indicate that exposure to 7.5 kHz MFs at 300 µT may decrease genomic instability. However, this was the first time that induction of genomic instability by IF MFs was studied, and further studies are needed to confirm the results of the present study, preferably with more stable cells than primary astrocytes.

Exposure to 872 MHz EMFs at 0.6 or 6 W/kg for 24 h alone did not cause genotoxicity in rat primary astrocytes and the results of combined exposure with chemicals were inconsistent. Modulation-dependent effects were not seen. Induction of genomic instability by RF fields was evaluated for the first time using 24-h exposure to 872 MHz GSM-modulated RF fields at 0.6 or 6 W/kg alone or in combination with menadione in rat primary astrocytes. No induction or increase of genomic instability was observed.

Based on these results and the studies reviewed in Chapter 1, it seems that EMFs may affect the genome but the effects are subtle and sensitive to experimental conditions. Even genome-stabilizing effects may be possible. More studies are needed to confirm the observed effects and especially to clarify possible mechanisms behind them. This is important, as environmental exposure to different EMFs is still increasing and new applications are actively developed. Furthermore, understanding the possible beneficial effects of EMFs might lead to therapeutic applications.

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Electromagnetic fields are ubiquitous in the environment, but there are still uncertainties concerning the risks to human health, particularly below the current exposure limits. This thesis provides new information about possible genotoxicity, co-genotoxicity and genomic instability induced by extremely low frequency, intermediate frequency and radiofrequency electromagnetic fields. The radical pair mechanism as a basis for magnetic field effects was also investigated.

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