DNA and Chromosome Damage: A Crucial Non-Thermal Biological Effect of Microwave Radiation

An Overview of Studies and Models on the Effect Mechanism

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This article will discuss that (i) low-level (SAR < 2 W/kg) radiofrequency electromagnetic fields can also trigger biological effects (so-called non-thermal effects) whereby different variables (e.g. frequency, exposure level, exposure dose, modulation, type of polarization) determine the type and intensity of a given effect; that (ii) a large number of existing studies were able to demonstrate DNA and chromosome damage from RF-EMF exposure, and that (iii) the biological effect mechanism of these genotoxic effects is largely based on the formation of oxidative/nitrosative stress. At the end, the implications of this knowledge are discussed regarding the use of mobile phones.

Which studies show that the exposure of a living organism to radiofrequency electromagnetic fields leads to DNA and chromosome damage? And what is the latest state of research that explains such genotoxic effects of RF radiation? This article is dedicated to answering these questions. It offers an overview of the current state of research in a field that is of utmost importance to public health.

1 Introduction

While exposure to high (SAR > 2 W/kg) radiofrequency electromagnetic fields (RF-EMF) leads to thermal effects in biological systems, a large number of studies show that the exposure to *low-level* (SAR < 2 W/kg) RF-EMFs also triggers biological effects (so-called *non-thermal effects*). An effect is always referred to as non-thermal when it cannot be explained by a rise in temperature (Fröhlich, 1982). The type and intensity of such non-thermal effects depend on different variables (Belyaev, 2005), including *radiation* (e. g. frequency, exposure level, exposure dose, continuous or intermittent exposure, modulation, type of polarization), *exposed organism* (e. g. cell type, cell density, phase of cell cycle, antioxidant status, latency period), and *exposure environment* (e. g. presence of an additional static magnetic field).

The controversy over non-thermal effects of RF-EMFs continues further for two main reasons. On the one hand, it is difficult to replicate a successfully demonstrated effect since many more variables impact the outcome than previously assumed. On the other hand, the effect mechanism of non-thermal effects is not yet very well understood, which has everything to do with its complexity—but nothing with its alleged non-existence. Latest research studies, however, continue to greatly improve our understanding.

Below follows an overview of different variables and their importance regarding the initiation of non-thermal effects (also compare *figure 1*).

i) Frequency

In *E. coli.*, the strongest inhibition of DNA repair mechanisms can be demonstrated for RF-EMF exposures in the frequency intervals 51.62 to 51.84 GHz and 41.25 to 41.50 GHz as well as at intensity levels of 3×10^{-3} W/cm^2 down to 10^{-19} W/cm^2 (Belyaev et al., 1992a, 1992b, 1996; Belyaev and Harms-Ringdahl, 1996). Other studies, for example, showed that a 2-hour exposure of *Lemna minor L.* (duckweed) to 900 MHz signals at 23 V/m decreased its growth whereas the exposure to 400 MHz signals did not cause any such effect (Tkalec et al., 2005).

ii) Exposure Level

Non-thermal RF-EMF effects only occur within certain ranges of low exposure levels. It could be demonstrated, for example, that the DNA repair mechanism of *E. coli.* is inhibited at the resonance frequency 51.675 GHz and only at the exposure range from 10^{-18} to 10^{-8} W/cm^2 (Shcheglov et al., 1997).

iii) Exposure Dose

For e. g. SAR values at 0.021 and 2.1 mW/kg, studies of human epithelial cells showed a linear relationship between SAR value, exposure duration, and changes of cell proliferation: The longer the exposure duration was, the greater the changes in cell proliferation would be (Kwee and Raskmark, 1998). Changes in the chromatin con-

formation of E. coli. and rat thymocytes also showed a dose-dependent relationship. An exposure of 10^{-5} to 10^{-3} W/cm² for 5 to 10 min resulted in changes of chromatin conformation similar to those found at an exposure of 10^{-14} to 10^{-17} W/cm² for 20 to 40 min (Belyaev et al., 1994). For the initiation of biological effects, the exposure dose not only plays a major role in ionizing radiation but in *non-ionizing* EMFs as well.

iv) Continuous or Intermittent Exposure

Studies on human fibroblasts and rat granulosa cells showed that it is important whether a continuous or intermittent exposure pattern is applied. An intermittent (5 min on, 10 min off) microwave exposure at 1.8 GHz (SAR 1.2 or 2 W/kg) resulted in greater single- and double-strand DNA breaks than a continuous exposure of the same intensity level (Diem et al., 2005).

v) Polarization

It could be shown that the exposure of *E. coli.* to the resonance frequency of 51.76 GHz resulted in an inhibition of its DNA repair activity only if linear or right-hand circularly polarized microwaves were used; left-hand circularly polarized microwaves caused no effects. An exposure with the resonance frequency 41.32 GHz reversed the relationship: In this case, only linear or left-hand circularly polarized RF radiation caused a change in the DNA repair activity (Belyaev et al., 1992b, 1992c, 1992d). In both experiments, the right-hand as well as the left-hand circularly polarized RF radiation triggered a greater effect level than the linear polarized alone. If the DNA structure was altered (intercalation by ethidium bromide), a change in the polarization-dependent effect level could be demonstrated (Ushakov et al., 1999), which is regarded as an indication of the role the DNA plays in the relationship between the effect level and the polarization of an exposure.

vi) Modulation

Human lymphocytes showed chromosome damage when they were exposed to phase-modulated (GMSK) GSM-1800 signals whereas a non-modulated microwave signal with the same frequency and at the same exposure level caused *no* effect (D'Ambrosio et al., 2002). Experiments with neutrophil granulocytes of mice showed that the release of an oxidative burst (release of reactive oxygen species) only occurs at a microwave radiation exposure at 41.95 GHz and 50 µW/cm² when its amplitude is modulated at 1 Hz; the modulation 0.1, 16, or 50 Hz did *not* trigger any effect (Gapeev et al., 1997). Studies on mutant Saccharomyces cerevisiae cells (brewer's yeast) demonstrated an increased rate of UV-induced apoptosis when the amplitude of the microwave radiation (900 MHz or 875 MHz, SAR 0.4 W/kg) they were exposed to was modulated at 217 Hz (Markkanen et al., 2004).

vii) Presence of a Static Magnetic Field

In various studies, it was found that the presences of a static magnetic field could either increase or decrease the biological effect of RF-EMFs (Blackman et al., 1985; Belyaev, 1993; Blanchard and Blackman, 1994; Lednev, 1996; Litovitz et al., 1997; Di Carlo et al., 2002). In this context, the impact on the half-life of free radicals appears to be a crucial effect mechanism (Harkins and Grissom, 1994; Scaiano et al., 1994, 1995a, 1995b; Eichwald and Walleczek, 1996).

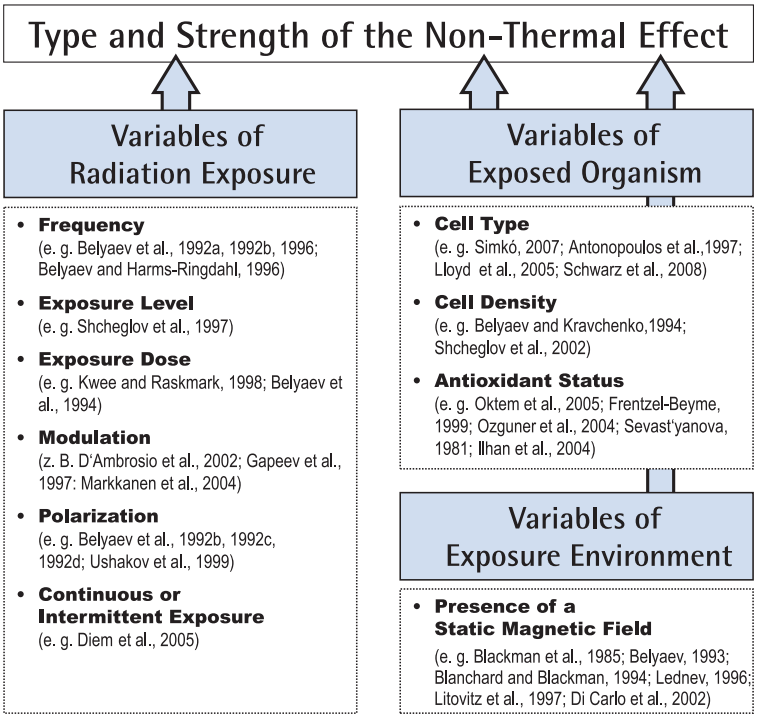

Fig. 1: Dependence of Type and Strength of an RF-EMF Induced Non-Thermal Effect on Different Variables

viii) Cell Type

That not every tissue or cell type responds in the same way to RF-EMF exposures is a fact that has been demonstrated in many studies. Primarily, this is the responsibility of the *redox homeostasis* (Simkó, 2007), which—depending on the cell type—is developed to different degrees. Redox homeostasis can be understood as the cell's

desire to keep its redox status, which can be referred to as the ratio of glutathione (GSH) to glutathione disulfide (GSSG) (Rahman et al., 2005), within a range where oxidative processes do not get out of control. A very strong desire to maintain the physiological redox status can be demonstrated in e. g. *lymphocytes*, which indeed in many studies were found to show no response to RF-EMF exposures (Antonopoulos et al., 1997; Lloyd et al., 2005; Schwarz et al., 2008). Other types of cells, however, are much more susceptible to an external modulation of the redox homeostasis, which explains their greater susceptibility to EMF exposures (Simkó, 2007).

ix) Cell Density

If the cell density of a solution with *E. coli.* cells is changed and exposed to microwave radiation at 51.755 GHz, an increased change in the chromatin conformation of the cells can be observed as a function of their cell density (Belyaev und Kravchenko, 1994). If the cell density is increased from 4 x 107 to 4 x 108 cells/ml, the effect is amplified by a factor of 4.7 (± 0.5). This dependence of the effect level on cell density was also found for the resonance frequencies at 51.672 GHz and 51.688 GHz (Shcheglov et al., 2002). Above a cell density of 5 x 10^8 cells/ml, no further increase of the effect level could be observed, which may be explained by the fact that at this density the distance between the cells is equivalent to the wavelength of microwave radiation at 10^{12} – 10^{13} Hz and that at these measurements a type of "saturation effect" occurs. Interestingly enough, H. Fröhlich postulated the existence of coherent oscillations in biological systems in the frequency range from 10^{11} to 10^{12} Hz (Fröhlich, 1968).

x) Antioxidant Status

The microwave radiation exposure from a GSM900 mobile phone causes an increased MDA (malondialdehyde) value (biomarker for lipid peroxidation) in rats and, at the same time, reduces antioxidant biomarkers such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). When melatonin is administered, these effects can be prevented (Oktem et al., 2005). Melatonin is an antioxidant that neutralizes free radicals by changing electric charges via "internal conversion", which, in turn, results in the formation of radical pairs that neutralize each other. If this process is disturbed, many more free radicals will impact the organism because fewer of them will be neutralized and thus their life span will be extended (Frentzel-Beyme, 1999). When Wister albino rats are exposed to GSM900 signals, this type of radiation causes pathological changes in the skin (e.g. epidermal atrophy), which can be prevented by administering melatonin (Ozguner et al., 2004). In another study, it was found that the antioxidant levels of CAT, SOD, and GSH-Px decreased in the skin of rats after the exposure to the microwave radiation of a GSM1900 mobile phone. Again, it could be demonstrated that the administration of melatonin prevents this effect (Sevast'yanova, 1981). That the administration of the antioxidant Ginkgo biloba (Gb) can prevent damage induced by the microwave exposure to a GSM900 signal could be shown in rat brain tissue: While the exposure without Gb results in an increase in MDA and nitric oxide (NO) and a decrease in SOD and GSH-Px in the rat brain tissue, the administration of Gb prevents these effects (Ilhan et al., 2004).

xi) Latency Period

If and which non-thermal effect is demonstrated when an organism is exposed to RF-EMFs also depends to a large extent on the point in time at which the analysis is performed after the exposure. For example, chromosome damage of RF-EMF exposure could be demonstrated in rat thymocytes after a latency period of only 30 to 60 min, but after 80 min chromosome damage could no longer be detected (Belyaev and Kravchenko, 1994).

2 DNA and Chromosome Damage Caused by RF-EMF Exposure: On the State of the Research

The favorite answer of mobile phone providers to the question of whether RF-EMF exposures can result in DNA and chromosome damage often reads as follows, e.g. in information brochures by the Information Center of Mobile Telephony (IZMF):

> *"Mobile phone frequencies belong to the non-ionizing portion of the electromagnetic spectrum. The energy of this type of radiation is one million times lower than the energy level required for breaking chemical bonds (e. g. nucleic acid). Unlike UV radiation or x-rays, mobile phone radiation is therefore not energetic enough to damage genes directly and thus to initiate a tumor." (Otto and von Mühlendahl, 2005, p. 11).*

This statement is correct insofar as the energy of mobile phone radiation, indeed, is not sufficient to cause direct damage to the DNA (e. g. single- and double-strand breaks). The reasons for this lie in the fact that the energy of electromagnetic waves in the microwave range

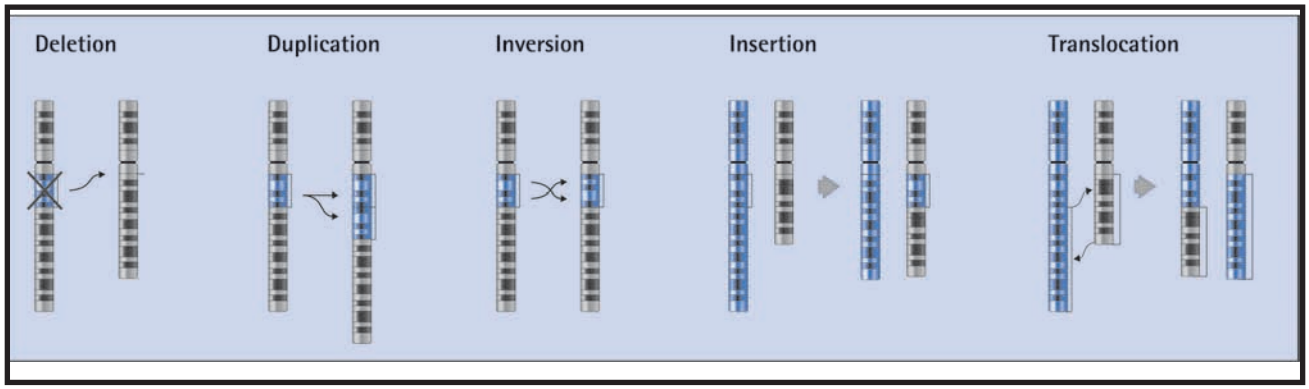

Fig. 2: Selected Types of Chromosome Mutations (Image: based on Wikipedia)

is too small: In order to dissociate molecules of the DNA, the radiation energy absorbed would have to be greater than the intramolecular bonding forces.

While phosphate and deoxyribose within a single DNA strand are bonded through a covalent bond (bonding energy: ca. 1^{-10} eV), in-between single strands or the nucleic bases, respectively, hydrogen bonds are formed (bonding energy: ca. 0.2-0.5 eV). The quantum energy of a microwave at 1 GHz is calculated as follows:

$$E = hf = 6.626 \times 10^{-34}\ Js^{-1} \cdot 1 \times 10^{9}\ Hz \approx 6.6 \times 10^{-25}\ J;$$

Or the relationship:

$$1\ eV = 1.9 \times 10^{-19}\ J \text{ to } E = 3.4 \times 10^{-6}\ eV = 3.4\ \mu eV.$$

The energy is by a factor of 10^6 (=1,000,000) too low to be able to break a covalent bond directly, and about 10^5 (=100,000) times too low to destroy a hydrogen bond. Yet, this does not mean—and this is crucial—that low-level microwave exposure in principle could not have any impact on the DNA. On the contrary, a large number of studies demonstrate that RF-EMF exposures can result in genotoxic effects (single- and double-strand breaks, chromosome aberrations, etc.). These studies use established methods of analysis such as the comet assay (test of DNA primary damage) or the micronuclei test (test of chromosome aberration) (Heddle et al., 1991; Klaude et al, 1996).

2.1 Overview of Studies

Examples of studies, in which increased single- and double-strand DNA breaks were demonstrated after RF-EMF exposure:

- Aitken et al. (2005) (900 MHz, SAR: 90 mW/kg, exposure duration: 12 h/day for 7 days, exposed system: male germ cells of mice)
- Diem et al. (2005) (1.8 GHz, SAR: 1.2 or 2 W/kg, exposure duration: 16 h, exposed system: human fibroblasts and rat granulosa cells)
- Lai and Singh (1995, 1996, 1997a, 1997b, 2004, 2005), Lai and Carino (1997) (2.45 GHz), SAR: 0.6-1.2 W/kg, exposure duration: 2 h, exposed system: rat brain cells)
- Lixia et al. (2006) (1.8 GHz, SAR: 3 W/kg, exposure duration: 2 h, exposed system: human lens epithelial cells)
- Markova et al. (2005) (GSM, 905-915 MHz, SAR: 37 mW/kg, exposure duration: 1 h, exposed system: human lymphocytes)
- Narasimhan and Huh (1991) (2.45 GHz, exposure duration: 2, 4, 8, 12, 16, and 20 s, exposed system: λ-phage DNA)
- Nikolova et al. (2005) (1.71 GHz, SAR: 1.5 W/kg, exposure duration: intermittent, 5 min on/30 min off, for 6 h or 48 h, exposed system: mouse stem cells)
- Paulraj and Behari (2006) (2.45 GHz or 16.5 GHz, SAR: 1 or 2.01 W/kg, exposed system: rat brain cells)
- Phillips et al. (1998) (813.5625 MHz, SAR: 24 µW/g, exposure duration: 2 or 24 h, exposed system: lymphoblastoid cells)
- Sagripanti et al. (1987) (8.75 GHz, SAR: 10 mW/g, exposure duration: 20 min, exposed system: plasmid DNA)
- Schwarz et al. (2008) (1.95 GHz UMTS signal, SAR: 0.05 W/kg, exposure duration: 24 h, exposed system: human fibroblasts)
- Sun et al. (2006) (1.8 GHz, SAR: 3 or 4 W/kg, exposure duration: 2 h, exposed system: human lens epithelial cells)
- Zhang et al. (2006) (1.8 GHz, SAR: 3 W/kg, exposure duration: 24 h, exposed system: hamster lung cells)

Radical Reactive Oxygen Species (ROS)

Name	*Alternate Name*	*Formula*
Hyperoxide anion radical	Superoxide	$O_2^{\cdot -}$
Hydroxyl radical	-	$HO^{\cdot}$
Perhydroxyl radical	Perhydroxyl	$HOO^{\cdot}$
Peroxyl radical	Alkyldioxal, Hyperoxyl	$ROO^{\cdot}$
Alkyl radical	-	$RO^{\cdot}$

DNA segment, which was released from the chromosome by a double strand break, is reversed and re-inserted), and *translocation* (broken chromosome segments translocate to the chromatid of another chromosome). We speak of genome mutations when the number of chromosomes change, which is a result of errors that occur during the process of cell division.

Chromosome aberrations caused by RF-EMF exposures could be demonstrated in e. g. the following studies (the variables, at which an effect showed, are given in brackets):

- Busljeta et al. (2004) (2.45 GHz, 5-10 mW/cm², exposure duration: 2, 8, 15, and 30 days for 2 h, exposed system: rats)
- D'Ambrosio et al. (2002) (1.748 GHz, phase modulated (GMSK), 5 W/kg, exposure duration: 15 min, exposed system: human peripheral blood)
- Fucic et al. (1992) (1.25-1.35 GHz, 0.1-200 W/m², occupational exposure, exposed system: lymphocytes in vivo)
- Garaj-Vrhovac et al. (1990) (7.7 GHz, 30 mW/cm², exposure duration: 15, 30, or 60 min, cell type: hamster fibroblasts)
- Mashevich et al. (2003) (830 MHz, SAR: 1.6-8.8 W/kg, exposure duration: 72 h, exposed system: human lymphocytes in vitro)
- Sarimov et al. (2004) (895-915 MHz, SAR: 5.4 mW/kg, exposure duration: 30 min – 1 h, exposed system: human lymphocytes in vitro)
- Sarkar et al. (1994) (2.45 GHz, 1 mW/cm², exposure duration: 2h/day for 120, 150, or 200 days, exposed system: rats)
- Tice et al. (2002) (837 MHz, 1.9098 GHz, SAR: 5-10 W/Kg, exposure duration: 24 h, exposed system: human lymphocytes in vitro)
- Trosic et al. (2002) (2.45 GHz, 5-10 mW/cm², exposure duration: 2, 8, 15 days for 2 h, exposed system: rats)
- Zotti-Martelli et al. (2000) (2.45 GHz, 7.7 GHz, 30 mW/cm², exposure duration: 30-60 min, exposed system: human lymphocytes in vitro)

2.2 Effect Mechanism

The above-listed studies show that RF-EMF exposures can cause genotoxic effects. This is astounding insofar as it must be *non-thermal effects* since the quantum energy of this radiation—as explained earlier—is not sufficient to cause direct damage to the DNA or chromosomes, respectively. How then do these genotoxic effects come about?

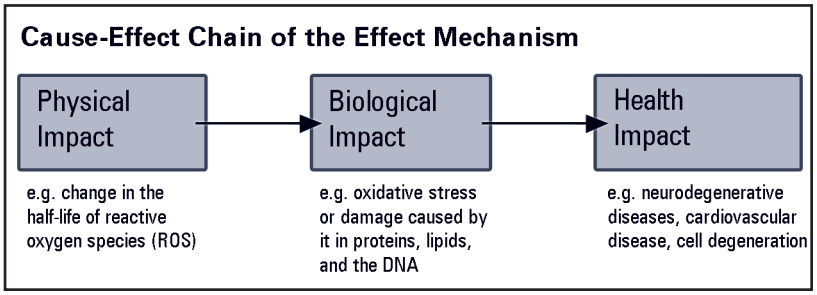

Fig. 3: Cause-Effect Chain of the Effect Mechanism

The answer to this question is still the object of research. As of today, there is no unifying model of explanation yet. However, there are models for individual steps or aspects of the effect mechanism, which explain the impact of RF-EMFs on biological systems in great detail and depth. The term "effect mechanism" refers to the cause-and-effect chain of events, starting from the (i) *physical impacts* of RF-EMF exposure through to the (ii) *biological impacts* up to the (iii) *health impacts* (Glaser, 2008) (compare *figure 3*).

A particularly successful model of explaining genotoxic effects of low-level RF-EMFs is based on the insight that EMF exposures impact the formation and stability of certain reduced forms of oxygen in a given organism (Lai and Singh, 1997a, 1997b, 2004; Oral et al., 2006; Simkó, 2007). These are referred to as *reactive oxygen species* or ROS (Jamieson et al., 1986), and we distinguish between radical and non-radical ROS (compare *table 1*). While oxygen radicals (radical ROS) such as $O2^{\cdot -}$, $HO^{\cdot}$, or $HOO^{\cdot}$ contain one electron or several unpaired electrons that react among each other or with non-radical molecules, non-radical ROS such as H_2O_2, O_3, or $^1O_2$, cannot

Non-Radical Reactive Oxygen Species (ROS)		Reactive Nitrogen Species (RNS)	
Name	*Formula*	*Name*	*Formula*
Ozone	O_3	Peroxynitrite	$ONOO^-$
Singlet oxygen	$^1O_2$	Nitric oxide	$NO^{\cdot}$
Hydrogen peroxide	H_2O_2	Nitric dioxide	N_2O_2
Hydroperoxide	ROOH	Nitric trioxide	N_2O_3

Table 1: Classification of ROS and RNS

easily be converted into radicals. In a living organism, ROS are generated through both endogenous and exogenous factors. In aerobic organisms, the endogenous formation of ROS occurs during mitochondrial respiration when electrons and protons are transferred to oxygen molecules (Joenje et al., 1989). Ca. 2 % of the total oxygen inhaled by a human is converted into ROS (especially superoxide anion radicals) (Halliwell, 1994). The immune response of phagocytic cells is another source of the endogenous formation of ROS (Curnutte, 2004). Exogenous factors include e.g. tobacco smoke (Frei et al., 1991), UV radiation (Epe, 1991), or certain environmental toxins, which contain ROS or from which ROS are generated during metabolism (Nuhn, 2001, Simkhovich et al., 2008).

Superoxide anion radicals ($O_2^{\cdot -}$) can react with the nitric oxide (NO) present in an organism, thereby forming highly reactive peroxide nitrite ($ONOO^-$). NO occurs naturally in living organisms and plays a crucial role in regulating important physiological functions (e. g. respiration, circulation, metabolism, immune response) (Stuehr and Marletta, 1985; Wu and Morris, 1998; Pfeiffer et al., 1999; Ralt, 2008). In the process of synthesizing NO, NADPH is used up through NO synthases—of which there are four: iNOS, eNOS, nNOS, mtNOS (Ghafourifar and Richter, 1997; Alderton et al., 2001; Li et al., 2002; Lowenstein and Padalko, 2004)—from oxygen and the amino acid L-arginine. In analogy to the term ROS, both NO and $ONOO^-$ are combined under the term *reactive nitrogen species* (RNS).

ROS and RNS (referred to as ROS/RNS below) have the potential of being hazardous to the organism since they are highly reactive molecules, which react with proteins, lipids, and the DNA and can actually damage any of these. Since the formation of ROS/RNS in the cell is inevitable, throughout evolution an efficient protective system has been established that is based on (i) the provision of specific molecules (antioxidants), which are capable of neutralizing ROS/RNS. It also provides (ii) mechanisms for repairing the cell structures (e. g. DNA) that become damaged by ROS/RNS (Dröge, 2002; Kuklinski and van Lunteren, 2005). Antioxidants are subdivided into enzymatic (e. g. glutathione peroxidase, superoxide dismutase, hydroxyperoxidase) and non-enzymatic (e. g. vitamin E, vitamin C, flavonoids, polyphenols) antioxidants (Nuhn, 2001).

Under physiological conditions, there is a balance in the organism between the presence of ROS/RNS and their removal through antioxidants. This balance, however, can be disturbed by an excessive production of ROS/RNS or a lack of antioxidants, respectively. An excess of *ROS* results in a condition referred to as *oxidative stress* (Halliwell, 1994; Dröge, 2002; Kuklinski and van Lunteren, 2005; Döll, 2008). In the event of excessive RNS, we speak of *nitrosative stress* (Hausladen et al., 1996, 1998). Since both oxidative stress and nitrosative stress are closely linked, and oxidative stress usually leads to nitrosative stress, the term *oxidative/nitrosative stress* was coined (Kremer, 2002; Warnke, 2005; Kuklinski and van Lunteren, 2005; Yücel, 2006).

During oxidative/nitrosative stress, specific transcription factors such as NF-kappa B are activated (Kratsovnik et al., 2005, Bar-Shai and Reznick, 2006; Vile et al., 2008), resulting in reactions between ROS/RNS and proteins, lipids, and the DNA.

i) Impact of ROS/RNS on Proteins

When ROS/RNS come into contact with proteins, the latter will become oxidized, resulting in the modification and degeneration of amino acids (e.g. formation of new functional groups such as hydroxyl and carbonyl groups), which in the end cause the protein to loose its function (Dean et al., 1997; Kirsch et al., 2002, 2003). The brain tissue of Alzheimer's patients, for example, shows high levels of protein oxidation (Aksenov et al., 2001; Butterfield and Lauderback, 2002). Frequently, oxidized proteins accumulate in the cell as "waste," of which, however, only a part can be metabolized by proteases. The remaining fragments form complexes that, for instance, show as age spots on the skin (Kuklinski and van Lunteren, 2005).

ii) Impact of ROS/RNS on Lipids

The process by which ROS/RNS cause oxidation in lipids is referred to as lipid peroxidation. Polyunsaturated fatty acids in the cell membrane (due to the highly reactive methyl groups present) are particularly susceptible to it, resulting in structural and functional changes to its membrane (Esterbauer et al., 1992). During lipid peroxidation, waste products such as hydroxyl radicals are generated, which can cause damage to the DNA (Joenje, 1989; Hruszkewycz, 1992). Lipid peroxidation plays a crucial role in degenerative diseases (Dix and Aitkens, 1993) and in the aging process in general (Ames et al., 1993; Halliwell, 1994; Praticò, 2002). DNA damages (as a result of the concomitant ROS/RNS), therefore, can already be caused by lipid peroxidation alone. This process is started when the mitochondrial transmembrane potential is lost through severe lipid peroxidation (Quillet et al., 1997). In addition, apoptogenic factors (factors that induce apoptosis) such as cytochrome c and AIF (apoptosis-inducing factor) are released (Liu et al., 1996). A chain reaction is triggered that leads to the opening of permeability transition pores (PTP) of other mitochondria so that, in turn, even more ROS and apoptogenic factors are re-

leased. AIFs induce DNA fragmentation in the cell nucleus (Susin et al., 1999). This shows how lipid peroxidation and the resulting release of ROS/RNS as well as AIFs can cause DNA damage.

iii) Impact of ROS/RNS on the DNA

Hyperoxide anion radicals ($O_2^{\cdot -}$) that are generated during respiration and formed by phagocytic cells are relatively weak radicals whose potential for causing direct damage to the DNA is rather limited (Brawn and Fridovich, 1981; Imlay and Linn, 1988; Keyer, 1995). After all, $O_2^{\cdot -}$ immediately reacts with protons and is dismutated into hydrogen peroxide (H_2O_2) and molecular oxygen (O_2), which, on the one hand, proceeds slowly and spontaneously and, on the other hand, more quickly by the catalytic effect of superoxide dismutase (SOD) (Fridovich, 1975, 1995): $2\ O_2^{\cdot -} + 2\ H+ \rightarrow H_2O_2 + O_2$. The resulting hydrogen peroxide is then reduced (Fenton reaction) by metal ions (Fe_2+ or Cu+) so that hydroxyl ions (HO^-) and hydroxyl radicals ($HO^{\cdot}$) are formed: $Fe_2+/Cu+ + H_2O_2 \rightarrow Fe_3+/Cu_2+ + OH- + OH^{\cdot}$. Hydroxyl radicals are highly reactive and long-lasting (ca. 10-9 s), which is why they react with almost all organic compounds and cause severe damage (Pryor, 1986). Hydrogen peroxide is capable of passing through cell membranes (Halliwell and Gutteridge, 1985) so that it can cause direct damage to the DNA. The metal ion complexes present in the DNA (or released by oxidative stress from transport proteins) react with the hydrogen peroxide, resulting in the formation of highly reactive hydroxyl radicals directly at the DNA and in the damage of the sugar-phosphate skeleton (Aruoma and Halliwell, 1998), which in the end causes the sugar-phosphate skeleton to fragment, single and double DNA strands to break, and bases to be modified (Halliwell and Aruoma, 1991). This type of DNA damage can also be caused by hydrogen peroxide (Demple et al., 1986) and singlet oxygen (Epe, 1991). The most frequent damage is the modification of DNA bases (Sies, 1991), whereby more than 100 different oxidative DNA modifications are known (Epe, 1995). Since the base pyridine has the lowest oxidation potential of all bases of the DNA (Hüttermann, 1982), changes occur most frequently in guanine (Nackerdien et al., 1992). In this process, a hydroxyl radical bonds to the C8 atom of guanine and forms 8-oxo-Gua (specifically: 7,8-dihydro-8-oxoguanine) (Halliwell and Aruoma, 1991). ROS also cause changes in the methylation patterns of the DNA, which can lead to changes in gene expression (epigenetic effects) (Cerda and Weitzman, 1997). Cells react to oxidative damage of their DNA with an increased activation of their antioxidant protective mechanisms and DNA repair mechanisms. Single-strand DNA breaks are removed by nucleotide excision repair (NER), DNA base damage

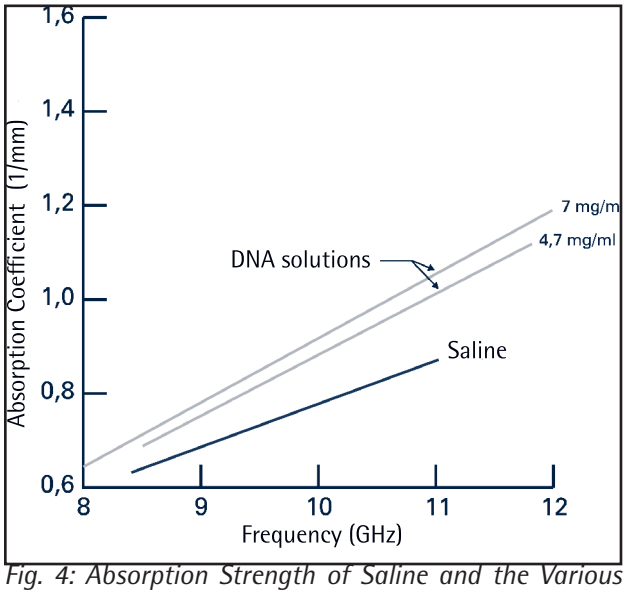

Fig. 4: Absorption Strength of Saline and the Various Concentrations of DNA Dissolved in It (7 mg/ml, 4.7 mg/ml). It is obvious that the DNA solution shows a stronger absorption than the solution alone. (Image: Edwards et al., 1985, graph from original paper).

by base excision repair (BER) (Speit and Dennog, 2000). The process of reverse transcription also plays an important role in DNA repair (Temin and Baltimore, 1972; Temin, 1985; Varmus, 1987; Shin et al., 2004; Scholkmann, 2007).

If there are not enough antioxidants available or if the rate of DNA damage exceeds the rate of repair, genetic regulation processes or protein expression become impaired, leading to diverse pathogenic ramifications. Thus, the likelihood of cancer formation increases (Trush and Kensler, 1991; Wiseman and Halliwell, 1996) because the processes of initiation and promotion of carcinogenesis are promoted by DNA damage mediated by ROS/RNS (Totter, 1980; Goldstein et al., 1981; Guerrero et al., 1984; Ames, 1989; Janssen et al., 1993; Takabe et al., 2001). Oncogenes are also activated in this process (Shibutani et al., 1991; Cheng et al., 1992). Damage to the DNA in mitochondria is particularly fatal (mtDNA, mitochondrial DNA) because mtDNA is ten times more susceptible to oxidative stress than DNA in the cell nucleus (nDNA). This has to do with the fact that mtDNA is not protected by histone proteins and does not possess any effective repair mechanism (Hruszkewycz and Bergtold, 1988; Druzhyna et al., 2008). Mitochondria can be damaged so severely by damage to their mtDNA that (i) the various steps of respiration can no longer proceed as usual, but even more ROS are generated and (ii) the energy production will fall below a critical threshold, as a result of which the cell will die (apoptosis) (Kremer, 2002; Kuklinski and van Lunteren, 2005). In case the mechanisms of

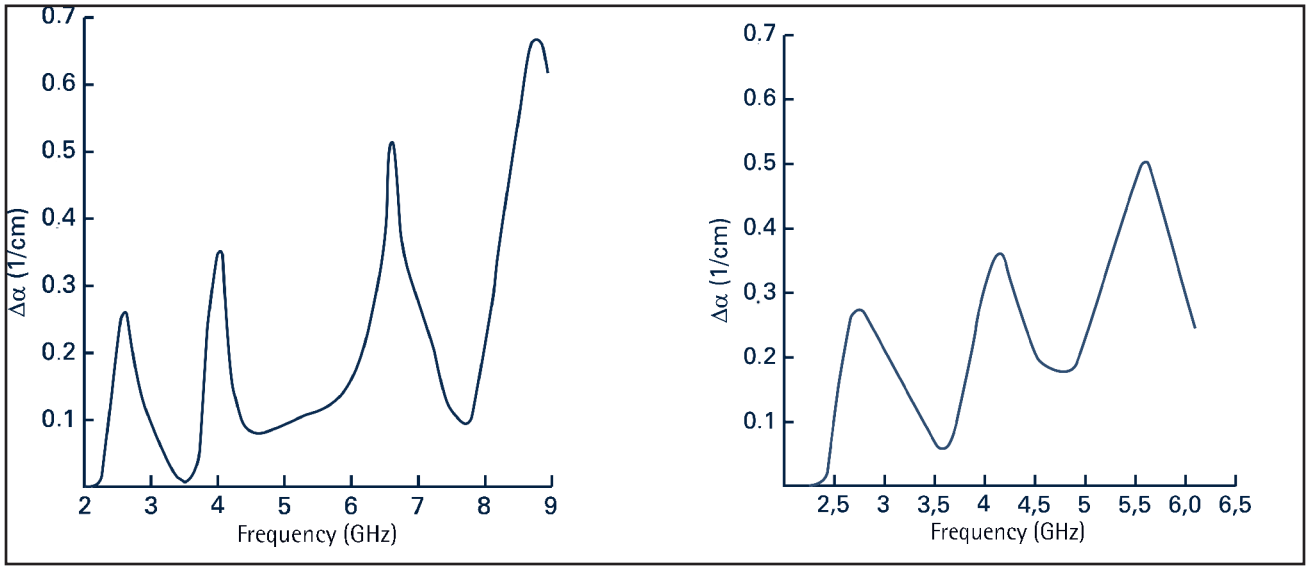

Fig. 5: Dependence of Absorption Strength of Circular DNA (left graph) and Linear DNA (right graph) on the Frequency of Microwave Radiation (Image: Edwards et al., 1985, graph from original paper).

apoptosis are blocked, the cell will become transformed into a cancer cell (Kremer, 2002) and, at the same time, its energy production process will be converted as well: from an oxygen dependent ATP production in the mitochondria to a non-oxygen enzymatic ATP production in the cell plasma (Warburg et al., 1924; Warburg, 1956; Gatenby and Gillies, 2004). This physiological switch of energy production is a counterregulation by the cell because during anaerobic glycolysis far fewer ROS/RNS are generated and, thus, the oxidative stress situation is defused (Brand and Hermfiess, 1997; Kremer, 2002). In healthy cells, energy production is also switched periodically (during late-stage cell division) in order to protect exposed chromosomes from ROS/RNS. This reaction is regulated by the mitochondrial permeability transition pore whose activity, in turn, is controlled by NO and $O2^{\cdot-}$ (Kremer, 2002). mtDNA damage mediated by ROS/RNS plays a significant role in the formation of cancer (Carew and Huang, 2002; Copeland et al., 2002). The decisive factor of whether a cell is transformed into a cancer cell depends on the redox status of the mitochondria or the mitochondrial membrane potential, respectively (Chen, 1988; Kremer, 2002). This fact explains the observation that cells may also be transformed into cancer cells when the DNA of the nucleus (nDNA) is not damaged (Lijinsky, 1973, 1992; Weaver and Gilbert, 2004; Maffini et al., 2004). Why an increased ROS/RNS production has an adverse health impact can then be easily understood: The resulting damage to proteins, lipids, and the DNA lead to adverse health effects, which may cause cancer and degenerative diseases.

While the association between ROS/RNS and their effects on health are thus resolved, the crucial question *how* RF-EMFs impact ROS/RNS processes still remains. There is much to be said for finding relevant explanations in the realm of physical effect mechanisms based on quantum mechanical/physicochemical models and the physics of non-linear as well as non-equilibrium systems (Fröhlich, 1968, 1982; Popp and Strauß, 1979; Popp, 1984, 200 6; Edwards et al., 1985; Adey, 1993; Scaiano et al., 1994; Kaiser, 1995; Ho, 1995; Brocklehurst and McLauchlan, 1996; Galvanovskis and Sandblom, 1997; Scott, 1999; Adair, 1999, 2002; Hyland, 2000, 2008; Panagopoulos et al., 2000, 2002; Binhi and Savin, 2002; Pokorny, 2004; Warnke, 2004a, 2004b, 2005; Binhi and Rubin, 2007; Warnke, 2008). The research by Edwards et al. shall serve as an example. Based on the fact that water strongly absorbs RF-EMFs in the microwave range, this research team investigated how the absorption capacity of water is changed when small amounts of isolated DNA of E. coli are added. Surprisingly, it was observed that the absorption increases depended on the RF-EMF frequency (Swicord and Davis, 1982; Swicord and Davis, 1983) (compare *figure 4*). Further studies directly investigating the DNA showed that the absorption strength depends on the length of the DNA fragments and the DNA conformation (linear, circular). For example, circular DNA with a length of 2740 base pairs (bp) caused absorption maxima at 2.55, 4.00, 6.00, and 8.75 GHz. A solution of linear DNA with a length of 948-1792 bp showed absorption maxima at around 2.65, 4.10, and 5.6 GHz (compare figure 5). These frequency-dependent absorption maxima of the DNA, the research team explains with resonance coupling between the microwave field and the oscillation modes of the DNA (Edwards et al., 1985). Experiments with static magnetic fields of varying

field strength showed that magnetic fields increase the half-life of free radicals or ROS/RNS (Batchelor et al., 1992; Harkins and Grissom, 1994; Roy et al., 1995; Scaiano et al., 1995a, 1995b; Santana et al., 1996; Suri et al., 1996; Zmyslony and Jajte, 1998; Warnke, 2008), which is associated with an increased probability of pathogenic oxidative processes. Unfortunately, there are only a very few studies available today that investigate the impact of RF-EMFs on free radicals or ROS/RNS in biological systems. The studies available to date, however, demonstrate already that:

1. Human exposure to 900 MHz for 4 h leads to an increase in lipid peroxidation in the plasma and a decrease in antioxidants (SOD, GSH-Px, catalase) in erythrocytes (Moustafa et al., 2001); 2. Rats exposed to 900 MHz RF-EMFs (SAR: 0.52 W/kg, 20 min/day, 7 days/week, 1 month) showed increased malondialdehyde (MDA) values (MDA: marker for lipid peroxidation) in their brains (Dasdag, 2004), which has been confirmed by another study (Ilhan, 2004); 3. An increased level of ROS in rat lymphocytes can be shown when the rats are exposed with 930 MHz RF-EMFs (SAR: 1.5 W/kg) for 5 or 15 min (Zmyslony, 2004); 4. The kidney tissue of exposed rats (900 MHz, 30 min/day, 1 month, SAR: 4 W/kg) shows an increased level of ROS and a decreased level of antioxidant enzymes (Ozguner, 2005); 5. Brain tissue of pigs exposed to GSM mobile phone signals (890-915 MHz, 12 h/day, 30 days) shows an increased level of MDA and a decreased level of GSH (glutathione) (Meral, 2007); 6. Exposed human monocytes and lymphocytes (GSM signal, 1.8 GHz, 2 W/kg, 30 or 45 min) show higher levels of ROS than non-exposed ones (Lantow et al., 2006).

It is also highly significant that researchers discovered that an exposure of HeLa and Rat2 cells with RF-EMFs (800, 865, and 950 MHz, 0.005-0.3 mW/cm²) leads to an immediate activation of the cell membrane component NADH oxidase, which causes an increased production of ROS (Friedman et al., 2007). As a result, the MPA kinase signaling cascade is activated, which among other things is involved in the regulation of cell differentiation, apoptosis, and cell growth (Pearson and Robinson, 2001; Seger and Krebs, 1995). That an EMF exposure also results in increased NO synthesis could be demonstrated in several studies (Miura et al., 1993; Seaman et al., 1999; Diniz et al., 2002; Hirohisa et al., 2006; Schnoke and Midura, 2007; Fitzsimmons et al., 2008). These results are exceptional in that a disturbance of the NO system in a given organism may not only lead to nitrosative stress—followed by DNA damage (Burney et al, 1999)—, but may also have impacts on major regulation processes. An increased synthesis of NO, for example, increases the permeability of the blood-brain barrier (Mayhan, 1996, 2000; Mayhan and Didion, 1999; Yamauchi et al., 2007), which encourages the formation of neurodegenerative diseases (James, 1992; Khan, 2006; Kuklinski, 2006).

3 Summary and Outlook

As is shown above, there are many studies that prove that the exposure of living organisms to low-level RF-EMFs may lead to DNA and chromosome damage. The genotoxic effect depends on many variables (e.g. frequency, dose, modulation, cell type, cell density, polarization, latency period), which require highly sophisticated research methods to investigate. Seemingly conflicting study results are traced back to the fact that even the smallest variation in one of these variables can lead to a completely different behavior of the system under study.

As to the effect mechanism of RF-EMF induced genotoxic effects, two of the three aspects of the cause-effect chain of events (physical impact → biological impact → health impact) are resolved. Thus, oxidative/nitrosative stress is the biological consequence of an increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) while at the same time antioxidant protective mechanisms are reduced all of which, in turn, may trigger pathogenic processes such as neurodegenerative diseases (health impact). Regarding the physical effects caused by RF-EMF exposure, there are currently various models of explanation that explain the observed effects by direct impacts on (i) the DNA or on (II) the half-life of radicals, respectively. It is very important that further research looks into this aspect of the cause-effect chain so that a uniform model of the effect mechanism can be found.

In view of the well-documented effects of DNA and chromosome damage caused by low-level RF-EMFs, it is imperative that RF electromagnetic fields utilized in wireless communication technologies are optimized in such a way that those frequencies, modulations, and intensity levels are selected which minimize potential pathogenic effects. This approach is of utmost importance because the parameters selected for RF electromagnetic fields currently in use do not take those considerations into account and are not optimized to trigger as few biological effects as possible. As was shown by the most recent research (Yao et al., 2008), the risk could probably already be minimized by, for example, the superposition

of additional electromagnetic noise in the form of a fluctuating magnetic field (2 µT, 30-90 Hz, white noise) because, in this experiment, it was demonstrated that the latter prevented the formation of DNA and chromosome damage. Although the impact of an RF-EMF exposure on the DNA/chromosomes plays a crucial role in the health impact of this type of radiation, it is important to realize that the described genotoxic effects represent only a single aspect of the effects caused by RF-EMFs in living systems. A multitude of other effects is also documented, among others, impacts on ATP synthesis (Blank and Soo, 1993, 1996, 2001, Blank 2005; Kuzmanova et al., 1994) and gene expression (Lupke et al., 2006; Nylund and Leszczynski, 2006; Zhao et al., 2007; Leszczynski, 2007; Karinen et al., 2008).

As long as wireless communication technologies are not switched to non-pathogenic field parameters, everybody is urgently advised to avoid using mobile phones, Wi-Fi networks for prolonged periods, and to avoid spending time in the vicinity of mobile phone base stations.

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