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Genotoxic effects of radiofrequency electromagnetic fields

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Abstract

101 publications are exploited which have studied genotoxicity of radiofrequency electromagnetic fields (RF-EMF) *in vivo* and *in vitro*. Of these 49 report a genotoxic effect and 42 do not. In addition, 8 studies failed to detect an influence on the genetic material, but showed that RF-EMF enhanced the genotoxic action of other chemical or physical agents. The controversial results may in part be explained by the different cellular systems. Moreover, inconsistencies may depend from the variety of analytical methods being used, which differ considerably with respect to sensitivity and specificity. Taking altogether there is ample evidence that RF-EMF can alter the genetic material of exposed cells i*n vivo* and *in vitro* and in more than one way. This genotoxic action may be mediated by microthermal effects in cellular structures, formation of free radicals, or an interaction with DNA-repair mechanisms.

Keywords: Gene mutations; Cytogenetic effects; DNA fragmentation; Mechanisms of genotoxicity

1. Introduction

Alterations of genetic information in somatic cells are the key event in the process of carcinogenesis [1,2]. Consequently any agent, which has a genotoxic attribute is suspected also to be cancerogenic. This is the driving force behind the multitude of studies on genotoxicity of radiofrequency electromagnetic fields (RF-EMF), conducted so far. A total of 101 publications on genotoxicity studies of RF-EMF are exploited here, of which 49 report genotoxic effects, subsequently marked as GT(+) (Table 1), 43 do not (Table 2), and 9 find, that RF-EMF do not induce genotoxic events by itself but enhance the genotoxic action of other physical or chemical agents (Table 3). Thus, in contrast to several reviews in the past [3–6], it now became evident that non-thermal genotoxic effects of RF-EMF is convincingly demonstrated by a substantial number of published studies. The studies have been performed with a variety of different test systems – some studies used more than one test system – which will be assigned here to the three principle endpoints of a genotoxic action: (1) effect on chromosomes, (2) DNA fragmentation, and (3) gene mutations.

2. Effect on chromosomes

This group comprises the analysis of numerical or structural anomalies of metaphase chromosomes (CA), sister-chromatid-exchanges (SCEs), and formation of micronuclei (MN). Of the 21 studies using CA, 9 are CA-positive, 11 CA-negative, and 1 reports an RF-induced enhancement of genotoxicity by X-rays. In general proliferating cells are required for the study of chromosomal effects, however, micronuclei have also been analysed in polychromatic erythrocytes and in exfoliated cells, for instance from buccal smears [7,8]. Moreover, aneuploidy rates of distinct chromosomes as well as chromosomal translocations can also be studied in interphase nuclei using fluorescence in situ hybridization (FISH). While structural aberrations detected by conventional CA are mainly lethal to the cell, translocations are persistent and may be passed to the cellular progeny. Using FISH increased levels of aneuploidy of chromosome 1, 10, 11, and 17 have been reported in human blood lymphocytes after RF-EMF exposure [9]. In metaphase chromosomes FISH may increase the sensitivity of chromosomal analysis [10] but this has only once been used for RF-EMF studies [11].

CA brings about to detect a variety of chromosomal aberrations. In contrast, micronuclei originate only from acentric

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Table 1
Publications which report RF-EMF related genotoxic effects.

Reference	Biological system	Genotoxic endpoint	Results and comments
Aitken et al. [45]	Mouse sperm	QPCR and comet assay	Gel electrophoresis revealed no gross evidence of increased single- or double-DNA strand breakage in spermatozoa. However, a detailed analysis of DNA integrity using QPCR revealed damage to both the mitochondrial genome ($p < 0.05$) and the nuclear-globin locus ($p < 0.01$).
Balode [46]	Cow erythrocytes	Micronuclei (MN)	The counting of micronuclei in peripheral erythrocytes gave low average incidences, 0.6 per 1000 in the exposed group and 0.1 per 1000 in the control, but statistically significant ($p < 0.01$) differences were found in the frequency distribution between the control and exposed groups.
Belyaev et al. [47]	Human blood lymphocytes	Chromatin condensation and 53BP1 foci	Decrease in background levels of 53BP1 foci and may indicate decrease in accessibility of 53BP1 to antibodies because of stress-induced chromatin condensation.
Busljeta et al. [48]	Rat hematopoietic tissues	MN	Erythrocyte count, haemoglobin and haematocrit were increased in peripheral blood (days 8 and 15). Concurrently, anuclear cells and erythropoietic precursor cells were decreased ($p < 0.05$) in the bone marrow on day 15, but micronucleated cells' (MNCs) frequency was increased.
d'Ambrosio et al. [49]	Human blood lymphocytes	MN	The micronucleus frequency was not affected by CW exposure; however, a statistically significant micronucleus effect was found following exposure to phase modulated field.
Diem et al. [23]	Human cultured fibroblasts and rat granulosa cells	Alkaline and neutral comet assay	The intermittent exposure showed a stronger effect in the comet assay than continuous exposure.
Ferreira et al. [50]	Rat hematopoietic tissues exposed during embryogenesis	MN	The irradiated group showed a significant increase in MN occurrence.
Fucic et al. [15]	Human blood lymphocytes	MN	X-rays and microwaves were preferentially clastogens while vinyl chloride monomer showed aneugenic activity as well. Microwaves possess some mutagenic characteristics typical of chemical mutagens.
Gadhia et al. [51]	Human blood lymphocytes	Chromosomal aberrations and SCE	There was a significant increase ($p < 0.05$) in dicentric chromosomes among mobile users who were smoker–alcoholic as compared to nonsmoker–nonalcoholic. Synergistic action with MMC, SCEs showed a significant increase among mobile users.
Gandhi and Singh [7]	Human blood lymphocytes and buccal mucosa cells	Chromosomal aberrations and MN	Increased number of micronucleated buccal cells and cytological abnormalities in cultured lymphocytes.
Gandhi, 2005 [52]	Human blood lymphocytes	Comet assay, *in vivo* capillary MN	Mean comet tail length (26.76 ± 0.054 mm; 39.75% of cells damaged) in mobile phone users was highly significant from that in the control group. The *in vivo* capillary blood MNT also revealed highly significant (0.25) frequency of micronucleated cells.
Garaj-Vrhovac et al [53]	Human blood lymphocytes	Chromosomal aberrations and MN	In all experimental conditions, the frequency of all types of chromosomal aberrations was significantly higher than in the control samples. In the irradiated samples the presence of dicentric and ring chromosomes was established. The incidence of micronuclei was also higher in the exposed samples.
Garaj-Vrhovac et al. [54]	Chinese hamster cells V79	DNA synthesis by [3H]thymidine uptake, and chromosomal aberrations	In comparison with the control samples there was a higher frequency of specific chromosome lesions in cells that had been irradiated.
Garaj-Vrhovac et al. [55]	Chinese hamster cells V79	Chromosomal aberrations and MN	Significantly higher frequency of specific chromosome aberrations such as dicentric and ring chromosomes in irradiated cells. The presence of micronuclei in irradiated cells confirmed the changes that had occurred in chromosome structure.
Garaj-Vrhovac et al. [56]	Human blood lymphocytes	MN	Increase in frequency of micronuclei as well as disturbances in the distribution of cells over the first, second and third mitotic division in exposed subjects compared to controls.
Haider et al. [57]	*Tradescantia* flower buds	MN	The results at all exposure sites except one were statistically significant.
Koyama et al. [12]	CHO-K1 cells	MN + kinetochore determination	RF at SAR of 78 W/kg and higher form MN with a particular increase of kinetochore-positive MN and potentiate MN formation induced by bleomycine treatment.
Lai et al. [58]	Rat brain cells	Comet assay	RFR exposure significantly increased DNA double strand breaks in brain cells of the rat, and the effect was partially blocked by treatment with naltrexone.
Lai and Singh [59]	Rat brain cells	Alkaline comet assay	No effects immediately after 2 h of exposure to pulsed microwaves, whereas a dose rate-dependent increase in DNA single strand breaks was found in brain cells of rats at 4 h post-exposure with CW and pulsed waves.

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Lai and Singh [60]	Rat brain cells	Comet assay	Significantly higher levels of DNA single and double strand breaks. Exposure to 'noise' alone did not significantly affect the levels, however, simultaneous 'noise' exposure blocked microwave-induced increases in DNA strand breaks.
Lai and Singh [61]	Rat brain cells	Comet assay	An increase in DNA strand breaks was observed after exposure to either the pulsed or continuous-wave radiation, no significant difference was observed between the effects of the two forms of radiation.
Lai and Singh [35]	Rat brain cells	Comet assay	Treatment immediately before and after RFR exposure with either melatonin or *N*-tert-butyl-alpha-phenylnitrone (PBN) blocks induction of DSB by RFR. It is hypothesized that free radicals are involved in RFR-induced DNA damage in the brain cells of rats.
Lixia et al. [62]	Human lens epithelial cells	Comet assay and BudR incorporation	No DNA breaks at 1 and 2 W/kg but increase 0 and 30 min after exposure to 3 W/kg. Exposure at 2 and 3 W/kg for 2 h significantly increased HsP 70 protein but not mRNA expression.
Maes et al. [63]	Human blood lymphocytes	Chromosome aberrations	Some cytogenetic damage was obtained *in vitro* when blood samples were very close to the antenna. The questionable *in vivo* results (six maintenance workers) are not considered here.
Maes et al. [64]	Human blood lymphocytes	Chromosomal aberrations, SCE, and MN	Marked increase in the frequency of chromosome aberrations (including dicentric chromosomes and acentric fragments) and 19 micronuclei. On the other hand, the microwave exposure did not influence the cell kinetics nor the sister-chromatid-exchange (SCE) frequency.
Markova et al. [65]	Human blood lymphocytes	p53 binding protein and γH2AX foci	MWs from GSM mobile telephones affect chromatin conformation and 53BP1/gamma-H2AX foci similar to heat shock.
Mashevich et al. [66]	Human blood lymphocytes	Chromosomal aberrations	A linear increase in chromosome 17 aneuploidy was observed as a function of the SAR value.
Mazor et al. [9]	Human blood lymphocytes	Aneuploidy rate of Chr. # 1, 10, 11, 17 determined by interphase FISH	Increased levels of aneuploidy in chromosomes 1 and 10 at higher SAR, while for chromosomes 11 and 17 the increases were observed only for the lower SAR.
Nikolova et al. [67]	Mouse nestin-positive neural progenitor cells	Transcript of specific genes and proteins, proliferation, apoptosis, DNA DSB	Down-regulation of neural-specific Nurr1and up-regulation of bax and GADD45 mRNA levels. Short-term RF-EMF exposure for 6 h, but not for 48 h, resulted in a low and transient increase of DNA double strand breaks.
Paulraj and Behari [68]	Rat brain cells	Comet assay	Statistically significant ($p < 0.001$) increase in DNA single strand breaks in brain cells of rat.
Pavicic and Trosic [13]	V79 cells	Alteration of microtubule proteins	The microtubule structure altered after 3 h of irritation.
Phillips et al. [69]	Molt-4 T-lymphoblastoid cells	Comet assay	DNA damage decreased by (1) exposure to the iDEN signal (2.4 μW/g for 2 h or 21 h), (2) exposure to the TDMA signal (2.6 μW/g for 2 h and 21 h), (3) exposure to the TDMA signal (26 μW/g for 2 h), exposure to the iDEN signal (24 μW/g for 2 h) and 21 h significantly increased DNA damage.
Sarimov et al. [70]	Human blood lymphocytes	Chromatin condensation by anomalous viscosity	Analysis of pooled data from all donors showed statistically significant effect of 1-h exposure to MW. Effects differ at various GSM frequencies and vary between donors.
Sarkar et al. [71]	Mouse testis and brain cells	Restriction pattern after HinfI treatment	As compared to control animals, band patterns in exposed animals were found to be distinctly altered in the range of 7–8 kb which was also substantiated by densitometric analysis.
Schwarz et al. [33]	Human cultured fibroblasts and lymphocytes	Alkaline comet assay and MN	UMTS exposure increased the CTF and induced centromere-negative micronuclei in human cultured fibroblasts in a dose- and time-dependent way. No UMTS effect was obtained with lymphocytes, either unstimulated or stimulated with phytohemagglutinin.
Sykes et al. [22]	pKZ1 mice	lacZ transgene inversion	No difference between the control and treated groups in the 1- and 5-day exposure groups, but a reduction in inversions below the spontaneous frequency in the 25-day exposure group. This suggests that RF radiation can lead to a perturbation in recombination frequency.
Tice et al. [72]	Human blood lymphocytes	Alkaline comet assay and MN	Exposure for either 3 or 24 h with the unmodulated signal did not induce a significant increase in DNA DSB or MN in lymphocytes. However, with the modulated signal there was a significant and reproducible increase in the frequency of micronucleated lymphocytes.
Tkalec et al. [14]	*Allium cepa* seeds	Germination, mitotic index, mitotic abnormalities	Increased mitotic aberrations in root meristematic cells of *A. cepa*. Effects were markedly dependent on the field frequencies applied as well as on field strength and modulation. Findings also indicate that mitotic effects of RF-EMF could be due to impairment of the mitotic spindle.
Trosic et al. [73]	Rat hematopoietic tissues	MN and polychromatic erythrocytes (PCEs)	The incidence of micronuclei/1000 PCEs in peripheral blood was significantly increased ($p < 0.05$) in the subgroup exposed to fro/MW radiation after eight irradiation treatments of 2 h each in comparison with the sham-exposed control group.

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Table 1 (*Continued*)

Reference	Biological system	Genotoxic endpoint	Results and comments
Trosic et al. [74]	Rat hematopoietic tissues	MN and polychromatic erythrocytes	In polychromatic erythrocytes significant differences ($p < 0.05$) for experimental days 8 and 15. The frequency of micronucleated PCEs was also significantly increased on experimental day 15 ($p < 0.05$).
Trosic and Busljeta [75]	Rat hematopoietic tissues and peripheral blood	MN and polychromatic erythrocytes	BMPCEs were increased on days 8 and 15, and PBPCEs were elevated on days 2 and 8 ($p < 0.05$).
Vijayalaxmi et al. [76]	C3H/HeJ cancer prone mice, peripheral blood and bone marrow	MN	No observed RF effects. A correction was published, stating that there was actually a significant MN increase in peripheral blood and bone marrow cells after chronic exposure to RF [Vijayalaxmi, M.R. Frei, S.J. Dusch, V. Guel, M.L. Meltz, J.R. Jauchem, Radiat. Res. 149 (3) (1998) 308].
Wu et al. [39]	Human epithelial lens cells	Comet assay and intracellular ROS	RF at 4 W/kg for 24 h significantly increased intracellular ROS and DNA damage. Both can be blocked completely by electromagnetic noise.
Yadav and Sharma [8]	Exfoliated buccal cells	MN in buccal cells	In exposed subjects 9.84 ± 0.745 micronucleated cells and 10.72 ± 0.889 total micronuclei (TMN) as compared to zero duration of exposure along with average 3.75 ± 0.774 MNC and 4.00 ± 0.808 TMN in controls. Correlation between 0–1, 1–2, 2–3 and 3–4 years of exposure and the frequency of MNC and TMN.
Yao et al. [40]	Human lens epithelial cells	Alkaline comet assay, gamma-H2AX foci, ROS level	SAR of 3 and 4 W/kg induced significant DNA damage in the comet assay, while no statistical difference in double strand breaks was found by γH2AX foci. Electromagnetic noise could block RF-induced ROS formation and DNA damage.
Yao et al. [41]	Human lens epithelial cells	Alkaline comet assay, γH2AX foci, ROS level	DNA damage was significantly increased by comet assay at 3 and 4 W/kg, whereas double strand breaks by γH2AX foci were significantly increased only at 4 W/kg. Significantly increased ROS levels were detected in the 3 and 4 W/kg groups.
Zhang et al. [77]	Chinese hamster lung cells (CHL)	γH2AX foci	Increased percentage of γH2AX foci positive cell of 1800 MHz RF EMF exposure for 24 h ($37.9 \pm 8.6\%$) or 2-acetylaminofluorene exposure ($50.9 \pm 9.4\%$). However, there was no significant difference between the sham-exposure and RF EMF exposure for 1 h ($31.8 \pm 8.7\%$).
Zotti-Martelli et al. [78]	Human blood lymphocytes	MN	Both spontaneous and induced MN frequencies varied in a highly significant way among donors ($p < 0.009$) and between experiments ($p < 0.002$), and a statistically significant increase of MN, although rather low, was observed dependent on exposure time ($p = 0.0004$) and applied power density ($p = 0.0166$).
Zotti-Martelli et al. [79]	Human blood lymphocytes	MN	The results showed for both radiation frequencies an induction of micronuclei as compared to the control cultures at a power density of 30 mW/cm^2 and after an exposure of 30 and 60 min.

Abbreviations: Mitomycin C (MMC), bleomycin (BLM), methylmethansulfonate (MMS), 4-nitroquinoline-1-oxide (4-NQ1O), ethylmethansulfonate (EMS), chromosomal aberration analysis (CA), micronucleus assay (MN), reactive oxygen species (ROS), and fluorescence *in vitro* hybridization (FISH).

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Table 2
Publications which do not report RF-EMF related genotoxic effects.

Reference	Biological system	Genotoxic endpoint	Results and comments
Antonopouloset al. [80]	Human blood lymphocytes	SCE	No increase in SCE or cell cycle progression found.
Belyaev et al. [81]	Rat brain, spleen, and thymus	Comet assay	GSM MWs at 915 MHz did not induce PFGE-detectable DNA double stranded breaks or changes in chromatin conformation, but affected expression of genes in rat brain cells.
Bisht et al. [82]	Mouse C3H 10T cells	MN	CDMA (3.2 or 4.8 W/kg) or FDMA (3.2 or 5.1 W/kg) RF-EMF radiation for 3, 8, 16 or 24 h did not result in a significant increase either in the percentage of binucleated cells with micronuclei or in the number of micronuclei per 100 binucleated cells.
Chang et al. [83]	*Escherichia coli* tester strain	Bacterial mutagenicity (Ames test)	No mutagenic or co-mutagenic effect with 4-NQ1O.
Ciaravino et al. [84]	CHO cells	SCE	Radiofrequency electromagnetic radiation (RF-EMF) did not change the number of SCEs that were induced by adriamycin.
Garson et al. [85]	Human blood lymphocytes	CA	No RF-EMF effect observed.
Gorlitz et al. [86]	B6C3F1 mice lymphocytes, erythrocytes, and keratinocytes	MN	No visible effect.
Gos et al. [87]	*Saccharomyces cerevisiae*	Mutation rates	No effects in fluctuation tests on forward mutation rates at CAN1, on the frequency of petite formation, on rates of intra-chromosomal deletion formation, or on rates of intra-genic recombination in the absence or presence of MMS.
Hook et al. [88]	Molt-4 T lymphoblastoid cells	Comet assay	No RF-EMF effects observed.
Juutilainen et al. [89]	Female CBA/S mice and K2 female transgenic mice	MN in erythrocytes	No effect on MN frequency.
Kerbacher et al. [90]	CHO cells	CA	No alteration was observed in the extent of chromosome aberrations induced by either simultaneous fro radiation exposure or convection heating to equivalent temperatures.
Komatsubara et al. [91]	Mouse m5S cells	CA	No effect on CA; temperature increase up to 41 °C at 100 W/kg.
Koyama et al. [92]	CHO cells	MN	No MN increase in cells exposed to HFEMF at a SAR of lower than 50 W/kg, while those at SARs of 100 and 200 W/kg were significantly higher when compared with the sham-exposed controls (temperature effect).
Lagroye et al. [93]	Rat brain cells	Alkaline comet assay	No observed effect.
Lagroye et al. [94]	C3H 10T1/2 cells	Comet assay, DNA–protein crosslinks	No observed effect.
Li et al. [95]	Murine C3H 10T cells	Comet assay	No observed effect.
Maes et al. [96]	Human blood lymphocytes	CA, SCE	Combined exposure of RF-EMF and to MMC and X-rays. Overall, no indication was found of a mutagenic, and/or co-mutagenic/synergistic effect.
Maes et al. [97]	Human blood lymphocytes	CA, SCE	Combined treatments with X-rays or MMC did not provide any indication of a synergistic action between the RF-EMF fields and X-rays or MMC.
Maes et al. [98]	Human blood lymphocytes	CA, SCE, Comet assay	The alkaline comet assay, SCE, and CA tests revealed no evidence of RF-EMF-induced genetic effects. No cooperative action was found between the electromagnetic field exposure and MMC using either the comet assay or SCE test.
Malyapa et al. [99]	Rat brain cells	Comet assay	No significant differences observed.
Malyapa et al. [100]	U87MG and C3H 10T1/2 cells	Comet assay	No significant differences observed.
Malyapa et al. [101]	U87MG and C3H 10T1/2 cells	Comet assay	No significant differences observed.
McNamee et al. [102]	Human blood lymphocytes	Comet assay and MN	No significant differences observed.
McNamee et al. [103]	Human blood lymphocytes	Comet assay and MN	No significant differences observed.
McNamee et al. [104]	Human blood lymphocytes	Comet assay	No significant differences observed.
Meltz et al. [105]	L5178Y mouse leukemic cells	Mutation in TK locus	No effect of RF-EMF alone or in the induced mutant frequency due to the simultaneous exposure to RF-EMF and proclaim, as compared with the proflavin exposures alone.
Ono et al. [106]	lacZ-transgenic mice	Mutations at the lac gene in spleen, liver, brain and testis	Mutation frequencies at the lacZ gene in spleen, liver, brain, and testis were similar to those observed in non-exposed mice.

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Table 2 (*Continued*)

Reference	Biological system	Genotoxic endpoint	Results and comments
Roti Roti et al. [107]	C3H 10T1/2 cells	Transformed foci	No statistically significant differences observed.
Sakuma et al. [108]	Human glioblastoma A172 cells and fetal lung fibroblasts	DNA strand breaks (comet assay?)	No statistically significant differences.
Scarfi et al. [109]	Human blood lymphocytes	MN	No statistically significant differences observed.
Speit et al. [24]	Human cultured fibroblasts	Comet assay and MN	No statistically significant differences observed.
Stronati et al. [110]	Human blood lymphocytes	Comet assay, CA, SCE, MN	By comparison with appropriate sham-exposed and control samples, no effect of RF-EMF alone could be found for any of the assay endpoints. In addition RF-EMF did not modify any measured effects of the X-radiation.
Takahashi et al. [111]	Big Blue mice brain tissues	lacZ transgene inversion	No statistically significant differences observed.
Verschaeve et al. [112]	Rat brain and liver tissues, erythrocytes	MN (erythrocytes) and comet assay	No genotoxic effect of RF-EMF alone. Co-exposures to MX and RF-EMF radiation did not significantly increase the response of blood, liver and brain cells compared to MX exposure only.
Vijayalaxmi et al. [113]	Human blood lymphocytes	CA and MN	No observed RF-EMF effects.
Vijayalaxmi et al. [114]	Human blood lymphocytes	CA and MN	No observed RF-EMF effects.
Vijayalaxmi et al. [115]	Human blood lymphocytes	Comet assay	No observed RF-EMF effects.
Vijayalaxmi et al. [116]	Human blood lymphocytes	CA, MN	No observed RF-EMF effects.
Vijayalaxmi et al. [117]	Rat hematopoietic tissues and erythrocytes	MN	No observed RF-EMF effects.
Vijayalaxmi et al. [118]	Rat whole body and head only exposures. BM erythrocytes	MN	No observed RF-EMF effects.
Vijayalaxmi et al. [119]	CF-1 male mice, peripheral blood and bone marrow	MN	No observed RF-EMF effects.
Zeni et al. [120]	Human blood lymphocytes	Comet assay, CA, SCE	No observed RF-EMF effects.
Zeni et al. [121]	Human blood lymphocytes	MN	No observed RF-EMF effects.

Abbreviations: Chromosomal aberration analysis (CA), methotrexat (MX), mitomycin C (MMC), 4-nitroqinoline-1-oxide (4-NQ1O), methylmethansulfonate (MMS), code division multiple access (CDMA), frequency division multiple access (FDMA), and time division multiple access (TDMA).

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Table 3
Publications which report synergistic RF-EMF effects in combination with other genotoxicants.

Reference	Genotoxic agents	Biological system	Genotoxic endpoint	Results and comments
Baohong et al. [122]	MMC, BLM, MMS, 4-NQ1O	Human blood lymphocytes	Alkaline comet assay	1.8 GHz RFR (SAR, 3 W/kg) for 2 h did not induce DSB, but could enhance the human lymphocyte DNA damage effects induced by MMC and 4-NQ1O. The synergistic DNA damage effects with BLM or MMS were not obvious.
Baohong et al. [123]	254 nm UVC	Human blood lymphocytes	Alkaline comet assay	RF exposure for 1.5 and 4 h did not enhance significantly human lymphocyte DNA damage, but could reduce and increase DNA damage of human lymphocytes induced by UVC at 1.5 and 4 h incubation respectively.
Kim et al. [124]	Cyclophosphamide, 4-NQ1O, EMS	L5178Y mouse lymphoma cells (comet assay) and CHL cells (CA)	Alkaline comet assay and CA	No direct cytogenetic effect of RF alone or in combination with cyclophosphamide or 4-NQ1O was found in the CA test and in the comet assay. However, RF had a potentiating effect in combination with cyclophosphamide or 4-NQ1O.
Maes et al. [125]	MMC	Human blood lymphocytes	SCE	Synergistic effect was observed with MMC.
Maes et al. [126]	MMC	Human blood lymphocytes	CA, SCE, comet assay	The combined exposure of the cells to the radiofrequency fields followed by their cultivation in the presence of mitomycin C revealed a very weak effect when compared to cells exposed to mitomycin C alone.
Manti et al. [11]	Previous 4 Gy X-ray radiation	Human blood lymphocytes	Chromosome aberration by FISH	No significant variations due to the UMTS exposure in the fraction of aberrant cells, but frequency of exchanges per cell in X-ray irradiated cells was significantly increased by UMTS at 2 W/kg.
Wang et al. [127]	254 nm UVC	Human blood lymphocytes	Comet assay	RF did not induce DNA damage but reduced or enhanced DNA damage by UVC at 1.5 or 4.0 h respectively.
Wang et al. [128]	MMC, BLM, MMS, 4-NQ1O	Human blood lymphocytes	Comet assay	RF did not induce DNA damage but enhanced DNA damage induced by MMC and 4-NQ1O.
Zhang et al. [129]	MMC	Human blood lymphocytes	Comet assay, micronucleus assay	No RF-induced DNA and chromosome damage, but increased MMC DNA damage by RF in comet assay.

Abbreviations: Mitomycin C (MMC), bleomycin (BLM), methylmethansulfonate (MMS), 4-nitroquinoline-1-oxide (4-NQ1O), ethylmethansulfonate (EMS), chromosomal aberration analysis (CA), fluorescence *in vitro* hybridization (FISH).

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fragments of chromosomes or from lagged chromosomes secondary to mitotic non-disjunction, the latter being detected by indirect immunofluorescence using kinetochore antibodies. Kinetochore-positive MN arise by epigenetic mechanisms (disturbances of the spindle apparatus). Kinetochore-negative MN arise from acentric chromosomal fragments. This is an important distinction, but has been performed in a few RF-EMF studies only, of which only one [12] reports an increase of kinetochore-positive MN albeit after a high SAR $\geq$ 78 W/kg. Two studies describe RF-EMF-induced disturbances of the spindle apparatus [13,14], and one reports an aneugenic RF-EMF effect on the basis of the size distribution of MN [15]. Of a total of 39 studies using the micronucleus assay 22 are MN-positive, and 17 MN-negative.

SCEs are analysed in metaphase chromosomes after two rounds of replication in the presence of 5-bromodeoxyuridine (BUDR). SCEs, which are induced during the S-phase of the cell cycle, represent an exchange between homologous chromatids, an event which by itself is genetically neutral. Nevertheless it is considered to reflect a recombinational repair of DNA double strand breaks (DSB), and may therefore serve as an indicator of genotoxic stress. Of 10 studies using SCE a GT(+) effect was reported in one only, 8 were negative, and one study reports RF-induced enhancement of genotoxicity by mitomycin C.

3. DNA fragmentation

The comet assay, also known as a "Single Cell Gel electrophoresis assay" (SCG), and the detection of gamma-H2AX foci are the most frequently used techniques to study RF-EMF-induced DNA strand breaks. The comet assay uses interphase nuclear DNA, which is unwinded under alkaline conditions and subsequently subjected to an electric field. Here DNA fragments migrate towards the anode, thereby forming a comet-like tail [16,17]. The alkaline comet assay detects DNA single strand as well as double strand breaks, but is not applicable in the presence of DNA crosslinking agents [18]. These breaks may occur not only by toxic influences but also by transcriptional and repair processes and by alkali-sensitive sites. Therefore this frequently used and very sensitive assay has a poor specificity. Of 41 studies using the comet assay 15 report comet-positive and 19 comet-negative results after RF-EMF exposure. RF-EMF enhancement of comet assay effects caused by other genotoxic agents is described in 7 studies.

Out of a multitude of DNA damage checkpoint proteins two have been used to detect DBS: H2AX, a member of the nuclear histone family [19], and P53 binding protein (53BP1). Both are rapidly phosphorylated only minutes after DNA damage and are then gathered in the vicinity of DNA double strand breaks. Here they form foci which can be visualized by indirect immunofluorescence [20,21]. These foci represent an initial and specific step in the repair process of exogenously induced DNA double strand breaks. It is important to realize, however, that repair processes of DSB are quantified, not DSB themselves. The method has been employed in 4 studies, predominantly using the yH2AX foci test. In all instances GT(+) effects have been detected.

DNA alterations have also been analysed by the anomalous viscosity time dependency test (AVTD, 1 GT(+) study), detecting conformational changes, and by quantitative PCR (QPCR, 1 GT(+) study) detecting structural changes in the DNA.

4. Gene mutations

In this category 6 studies have been performed using 4 different endpoints: (1) Altered restriction fragments (1 GT(+) study), (2) lacZ inversion in transgenic mice. This method has been used in 3 studies which all failed to detect an increased rate of inversions, but one found a reduced rate as compared to unexposed controls [22], which is interpreted as a RF-EMF-induced reduction of recombination repair. (3) Mutation at the thymidine kinase (TK) locus (1 negative study). (4) Bacterial his^- revertants (Ames test, 1 negative study).

5. Discussion

The large number of contradictory results among the 101 published studies on a genotoxic action of RF-EMF is tangling. Nevertheless patterns can be perceived. GT(+) as well as GT(−) findings have been reported at a standard absorption ratio (SAR) below 0.05 up to 100 W/kg and an exposure of 15 min and 48 h *in vitro*, and between hours and years *in vivo*. The outcome of studies was nearly independent from RF frequencies between 300 and 7700 MHz and the type of RF signal, either continuous wave (CW) or pulse-modulated (PM). GT(+) was obtained in 15 CW and 26 PM exposures, GT(−) in 14 CW and 27 PM exposures (some studies did not indicate the type of signal used). Contradictory results have been obtained even when two experienced groups performed the same experiments using the same cells and identical exposure conditions [23,24]. This may reflect a general problem of genotoxic studies being dependent on a multitude of factors which are difficult to control [25]. Some of the studies exploited here have shortcomings with respect to incompletely described or unreliable exposure conditions and/or an inadequate experimental design. Even a considerable publication bias in favour of negative results has been suspected (www.microwavenews.com/RR.html, 2006) [26].

The proportion of GT(+) effects is much higher *in vivo* (23/40) than i*n vitro* (29/77). (Since some studies have been performed on more than one biological system, the total number of GT(+) and GT(−) effects exceeds the total number of published studies.) Considering all genotoxic endpoints applied, the frequently used parameters chromosome analysis (9/21 GT(+)), comet assay (15/41 GT(+)), and sister-chromatid-exchange (1/10 GT(+)) showed the highest

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proportion of negative results, while the micronucleus assay yielded more positive than negative results (22/39 GT(+)). Since the SCE test which was negative in nearly all cases is known to be rather insensitive to radiomimetic (clastogenic) agents it can be speculated, that a clastogenic mechanism is involved in RF-EMF genotoxic action.

Epigenetic influences may also contribute to genotoxicity as demonstrated by RF-EMF-induced chromosomal non-disjunction and disturbances of the mitotic spindle. This is in agreement with the higher proportion of 22/39 GT(+) findings among studies using the micronucleus assay as compared to those using CA, because some of the micronuclei may represent lagged chromosomes. Epigenetic mechanisms may also be effective after a combined exposure to RF-EMF and various physical or chemical mutagens (Table 4). RF-EMF preferentially enhanced the genotoxic effect of 4-NQ1O (4/4), MMC (4/8), UVC (2/2), and cyclophosphamide (2/2). No synergistic effect was obtained using MMS and EMS (3/3), BLM (2/2), and adriamycine (2/2). Only one out of 3 studies reported a synergistic effect with X-rays.

Cells and tissues of different origin exhibit a clearly variable sensitivity for genotoxic RF-EMF effects (Table 4). This has also been observed with extremely low frequency (ELF)-EMF [27] and may be dependent on genetic differences [28]. GT(+) effects of RF-EMF were reported predominantly in the following biological systems: human lens epithelial cells (4/4), human buccal mucosa cells (2/2), rodent brain tissues (8/13), and rat hemopoietic tissues (5/7). GT(−) results have been obtained with mouse permanent cell lines (7/7) and permanent lymphoblastoid cells of various origin (7/7). This is in a striking analogy to RF-EMF-induced reduction of ornithine decarboxylase activity being detected in primary but not in secondary neural cells [29].

6. Proposed mechanisms of RF-EMF genotoxicity

Cells are unusually sensitive to electromagnetic fields [30]. Weak fields may accelerate electron transfer and thereby destabilize the H-bond of cellular macromolecules. This could explain the stimulation of transcription and protein expression, which has been observed after RF-EMF exposure [31,32]. However, the energy of weak EM fields is not sufficient directly to break a chemical bond in DNA. Therefore it can be concluded, that genotoxic effects are mediated by indirect mechanisms as microthermal processes, generation of oxygen radicals (ROS), or a disturbance of DNA-repair processes.

6.1. Thermal effects

An increase of temperature in the culture medium of RF-EMF exposed cells has been observed at very high SAR levels only [12]. The vast majority of GT(+) studies were conducted at SAR < 2.0 not leading to a detectable increase of temperature in the culture medium. Moreover, similar or larger effects have been observed at a 5′ on/10′ off intermittent exposure [23,33], a result that contradicts a

Table 4
Distribution RF-EMF effects in 101 published studies.

Biological system	RF-EMF effects		Synergistic effects	
	Positive	Negative	Positive	Negative
In vitro (all cells and tissues)	29	39	9	11
Human blood lymphocytes	18	23	8	4
Human lens epithelial cells	4			
Human cultured fibroblasts	2	2		
Human glioblastoma cells		3		
Human lymphoblastoid cells		2		
Mouse permanent cell lines		6		1
Mouse lymphoblastoid cells		1	1	1
Chinese hamster cells (CHO, V79)	4	2		3
E. coli		1		2
Yeast		1		
Rat granulosa cells	1			
In vivo (all species and tissues)	23	17	0	1
Human blood lymphocytes	4	2		
Human buccal mucosa cells	2			
Mouse sperm	1			
Mouse brain tissues	2			
Mouse polychromatic erythrocytes		4		
Rat brain tissues	6	4		1
Rat hemopoietic tissues	5	2		
Rat spleen, liver		2		
lacZ-transgenic mice		3		
Plants	2			
Cattle polychromatic erythrocytes	1			

Since several published studies have used more than 1 biological system the total of negative and positive effects exceeds the number of 101 publications.

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simple temperature-based mechanism of the observed genotoxic action. However, experimental results with microwave absorption at colloidal interfaces have demonstrated that the electric absorption of microwaves between 10 and 4000 MHz goes through a maximum with the size of bride droplets >100 and <10,000 nm, and depends on the type of ions and their concentrations [34]. This local absorption of microwaves may therefore lead to a considerable local heating in living cells during low energy microwave exposure.

6.2. Oxygen radicals

There is evidence that RF-EMF may stimulate the formation of reactive oxygen species in exposed cells *in vivo* [35–37] and *in vitro* [38–41]. Free oxygen radicals may form base adducts in DNA, the most important lesion being 8-OHdG, and oxidize also other cellular components, such as lipids leaving behind reactive species, that in turn can couple to DNA bases [42]. The first step in the generation of ROS by microwaves is mediated in the plasma membrane by NADH oxidase [43]. Subsequently ROS activates matrix metalloproteases (MMP), thereby initiating intracellular signalling cascades. It is interesting to note that these processes start within 5 min of radiation and at a very low field intensity of 0.005 W/cm^2. Moreover, higher effects have been obtained by intermittent radiation, when cells were left unirradiated for 10 min. This is in agreement with *in vitro* genotoxicity studies using the comet assay [23,33].

6.3. Alteration of DNA-repair processes

A considerable proportion of studies have investigated the consequences of a combined exposure to RF-EMF and various chemical or physical mutagens. 8/12 studies using human blood lymphocytes have demonstrated that RF-EMF enhanced the genotoxic action of other agents, preferentially of UV, MMC, or 4-NQ1O (an UV-mimetic agent). Since in all these experiments microwave exposure failed to induce detectable genotoxic effect by itself, an interference with DNA-repair mechanisms has been postulated, however, there is no direct experimental proof yet. An alteration of recombinational repair has also been proposed by Sykes et al. [22] as an explanation of the reduced rate of inversions in lacZ-transgenic mice after RF-EMF treatment.

An influence of microwave exposure on DNA-repair processes has long been proposed for power frequency electromagnetic fields [35]. A recent epidemiological investigation into the frequency of polymorphisms of DNA-repair genes in children with acute leukemia living in the vicinity of power line transformers [44] emphasizes the significance DNA-repair impairment for an EMF related increase of this malignancy. There was a significant gene–environment interaction (COR = 4.31) between the electromagnetic field intensities and a less active genetic variant of XRCC1, a crucial enzyme in base excision repair.

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