December 15, 2023

Static and ELF-EMF-oxidative effects *(E= 286(91%); NE= 30 (9%)) (E= paper reported effect; NE= paper reported no significant effect).*

(VT = in vitro; VO= in vivo; HU= human study; CE = long-term/repeated exposure; AE= acute exposure; LI = low intensity; IFR= increase free radical; DFR= decrease free radical; IOD = increase oxidative damages; DOD = decrease oxidative damages; IAO =increase antioxidant activity; DAO= decrease antioxidant activity; AO= effect of antioxidant/free radical scavenger; IX= interaction with other factor; MC= mechanism)

(E) (VO, CE, IFR) Agrawal N, Verma K, Baghel D, Chauhan A, Prasad DN, Sharma SK, Kohli E. Effects of Extremely Low Frequency Electro Magnetic Field on different developmental stages of *Drosophila melanogaster.* Int J Radiat Biol 97(1):1606-1616, 2021.

Purpose: The model biological organism *Drosophila melanogaster* has been utilized to assess effect of extremely low-frequency electromagnetic field (ELF-EMF) on locomotion, longevity, developmental dynamics, cell viability and oxidative stress. **Materials and method:** Developmental stages of *Drosophila melanogaster* (Oregon R strain) individually exposed to ELF-EMF (75 Hz, 550 μT) for 6 h once for acute exposure. For chronic exposure, complete life cycle of fly, that is, egg to adult fly was exposed to ELF-EMF for 6 h daily. The effect of exposure on their crawling and climbing ability, longevity, development dynamics, cellular damage and oxidative stress (generation of Reactive Oxygen Species (ROS)) was evaluated. **Results:** The crawling ability of larvae was significantly ($p< 0.05$) reduced on acute (third stage instar larvae) as well as chronic exposure (F0 and F1 larvae). When locomotion of flies were tested using climbing assay, no alteration was observed in their climbing ability under both acute and chronic exposure, however, when their speed of climbing was compared, a significant decrease in speed of F1 flies was observed (p value 0.0027) on chronic exposure. The survivability of flies was significantly affected under chronic and acute exposure (at third stage instar larvae). In case of acute exposure of the third stage instar larvae, though all the flies were eclosed by the 17^{th} day, but there was a significant decline in the number of flies (p value 0.007) in comparison to control. While, in case of chronic exposure apart from low number of flies eclosed in comparison to control, there was delay in eclosion by one day (p value 0.0004). Using trypan blue assay the internal gut damage of third stage instar larvae was observed. Under acute exposure condition at third stage instar larvae, 30% larvae has taken up trypan blue, while only 10% larvae from acute exposure at adult stage. On chronic exposure, 50% larvae of the F1 generation have taken up trypan blue. On evaluation of oxidative stress, there is significant rise in ROS in case of acute exposure at third stage instar larvae (p value 0.0004), adult fly stage (p value 0.0004) and chronic exposure (p value 0.0001). **Conclusion:** ELF-EMF has maximum effects on acute exposure of third stage instar larvae and chronic exposure (egg to adult fly stage). These results suggest that electromagnetic radiations, though have become indispensible part of our lives but they plausibly effect our health.

(E) (HU, CE, IFR, IAO) Ahmad IM, Bartenhagen L, Michael K, Abdalla MY. Redox Dysregulation in Imaging Professionals Occupationally Exposed to Ionizing and Non-Ionizing Radiation. Int J Radiat Biol 2023 Sep 13;1-18. doi: 10.1080/09553002.2023.2258194. Online ahead of print.

Purpose: Imaging professionals are occupationally exposed to chronic ionizing radiation (IR) and non-ionizing radiation (NIR). This study aimed to investigate the influence of occupational radiation exposure on oxidative stress and antioxidant levels based on blood biomarkers in different hospital imaging professional groups. **Materials and methods:** The study groups included 66 imaging professionals occupationally exposed to IR (n = 58, 43 Diagnostic Radiography (G1), 7 Nuclear Medicine (G2), 8 Radiation Therapy (G3)), and NIR (n = 8, Ultrasound Imaging (G4)) and 60 non-exposed controls. Blood levels of superoxide (O2•-) as an index of oxidative stress, and the antioxidant activities of superoxide dismutase (SOD), glutathione ratio (GSH/GSSG), and catalase (CAT) were measured. **Results:** The blood values of O2•-, SOD, and CAT were significantly higher in imaging professionals occupationally exposed to radiation than in the control group ($p < 0.05$), while a significant decrease in the ratio of GSH/GSSG was observed ($p < 0.05$). The results from the NIR group were significantly higher compared to IR group. **Conclusion:** Based on these results, chronic exposure to radiation (IR & NIR) is associated with redox dysregulation that may result in damages to cellular biomolecules including lipids, proteins and DNA. Further studies are needed to determine the impact of redox dysregulation and the need for periodic examination among imaging professionals occupationally exposed to IR and NIR.

(E) (VT, AE, IOD, IAO) Ahmadi-Zeidabadi, M., Z. Akbarnejad, M. Esmaeeli, Y, Masoumi-Ardakani, L. Mohammadipoor-Ghasemabad, and H. Eskandary. 2019. Impact of extremely low-frequency electromagnetic field (100 Hz, 100 G) exposure on human glioblastoma U87 cells during Temozolomide administration. *Electromagn. Biol. Med* 38:198-209.

Glioblastoma multiforme (GBM) is a highly malignant brain tumor with an extremely dismal prognosis, a median survival is12 months. Temozolomide (TMZ) is an alkylating agent widely used to treat cancer, resistance to this drug is often found. One unexplored possibility for overcoming this resistance is a treatment based on concomitant exposure to electromagnetic fields (EMF) and TMZ. Indeed, many evidences show that EMF affects cancer cells and drug performance. Therefore, the present study was carried out to evaluate the potential synergistic effect of 100 μM TMZ and EMF (100 Hz, 100 G) on human glioma cell line U87 U87 cells with four experimental groups (I-IV) were exposed to ELF-EMF and TMZ for 120 and 144 h, as follows: (I) control; (II) ELF-EMF; (III) TMZ; (IV) ELF-PEMFs / TMZ. mRNA expression of genes such as (Nestin,CD133, Notch4 and GFAP) were investigated by Real-time PCR and western blot. We also evaluated, SOD activity, MDA and calcium concentration by ELISA assay. Co-treatment synergistically decreased the expression of Nestin,CD133, and Notch4 and increased the GFAP genes. We also observed an increase in Superoxide dismutase (SOD) activity, Malondialdehyde (MDA) and Ca2+concentration in comparison to controls.TMZ prevents cancer progression not only through the induction of cell death, but also by inducing differentiation in cancer cells. In addition, our

data demonstrate ELF-EMF (100 Hz, 100 G) can significantly enhance the effects of TMZ on human glioblastoma U87 cell. These findings may open new window for future studies.

(E) (VT, AE, IFR; IAO) Akan Z, Aksu B, Tulunay A, Bilsel S, Inhan-Garip A. Extremely low-frequency electromagnetic fields affect the immune response of monocyte-derived macrophages to pathogens. Bioelectromagnetics. 31(8):603-612, 2010.

This study aimed to determine the effect of extremely low-frequency electromagnetic fields (ELF-EMF) on the physiological response of phagocytes to an infectious agent. THP-1 cells (human monocytic leukemia cell line) were cultured and 50 Hz, 1 mT EMF was applied for 4-6 h to cells induced with Staphylococcus aureus or interferon gamma/lipopolysaccharide (IFγ/LPS). Alterations in nitric oxide (NO), inducible nitric oxide synthase (iNOS) levels, heat shock protein 70 levels (hsp70), cGMP levels, caspase-9 activation, and the growth rate of S. aureus were determined. The growth curve of exposed bacteria was lower than the control. Field application increased NO levels. The increase was more prominent for S. aureus-induced cells and appeared earlier than the increase in cells without field application. However, a slight decrease was observed in iNOS levels. Increased cGMP levels in response to field application were closely correlated with increased NO levels. ELF-EMF alone caused increased hsp70 levels in a time-dependent manner. When cells were induced with S. aureus or IFγ/LPS, field application produced higher levels of hsp70. ELF-EMF suppressed caspase-9 activation by a small extent. These data confirm that ELF-EMF affects bacterial growth and the response of the immune system to bacterial challenges, suggesting that ELF-EMF could be exploited for beneficial uses.

(E)(VT,AE,IFR, IX) Akbarnejad Z, Eskandary H, Dini L, Vergallo C, SN, Farsinejad A, MFS, Ahmadi M. Cytotoxicity of temozolomide on human glioblastoma cells is enhanced by the concomitant exposure to an extremely low-frequency electromagnetic field (100Hz, 100G). Biomed Pharmacother 92:254-264, 2017.

Glioblastoma multiforme (GBM) is the most malignant brain cancer that causes high mortality in humans. It responds poorly to the most common cancer treatments, such as surgery, chemo- and radiation therapy. Temozolomide (TMZ) is an alkylating agent that has been widely used to treat GBM; resistance to this drug is often found. One unexplored possibility for overcoming this resistance is a treatment based on concomitant exposure to electromagnetic fields (EMF) and TMZ. Indeed, many evidences show that EMF affects cancer cells and drug performance. In this study, we evaluated the potential synergistic effect of 100μM TMZ and EMF (100Hz, 100G) on two human glioma cells line, i.e., U87 and T98G above single treatments, TMZ or EMF. Co-treatment synergistically enhanced apoptosis in U87 and T98G cells, by increasing the expression of P53, Bax, and Caspase-3 and decreasing that of Bcl-2 and Cyclin-D1. We also observed an increase in reactive oxygen species (ROS) production and the overexpression of the heme oxygenase-1 (HO-1) gene in comparison to controls. In conclusion, since EMF enhanced the apoptotic effect of TMZ, possibly

through a redox regulation mechanism, the TMZ/EMF combination may be effective for glioma cancer treating. Further studies are needed to reveal the action mechanism of this possible novel therapeutic approach.

(E) (VO, CE, DFR) Akdag MZ, Bilgin MH, Dasdag S, Tumer C. Alteration of nitric oxide production in rats exposed to a prolonged, extremely low-frequency magnetic field. Electromagn Biol Med. 26(2):99-106, 2007.

The purpose of this study is to investigate the possible effect of an extremely low-frequency magnetic field (ELF-MF) on nitric oxide (NO) level. In this study, 27 male Sprague-Dawley rats were used. The rats were divided into three groups: two experimental and one control (sham-exposed). The first and second experimental group (n = 10) were exposed to 100 microT and 500 microT ELF-MF during 10 months, 2 h a day, respectively, and the third (n = 7) group was treated like an experimental group except for ELF-MF exposure in methacrylate boxes. After ELF-MF and sham exposure, serum nitrite levels were measured by Griess reaction. A significant reduction was observed in nitrite levels among the first and second experimental groups of rats and sham-exposed rats after exposure for 10 months, 2 h a day, to ELF-MF of 100 and 500 microT ($p < 0.01$). These results suggest that prolonged ELF-MF exposure at intensities of exposure limits, determined by ICNIRP for public and occupational, may reduce NO production probably affected by NO generation pathways.

(E) (VO, CE, DAO) Akdag MZ, Dasdag S, Ulukaya E, Uzunlar AK, Kurt MA, Taşkın A. Effects of extremely low-frequency magnetic field on caspase activities and oxidative stress values in rat brain. Biol Trace Elem Res. 138(1):238-249, 2010.

This study was aimed to investigate the effect of extremely low-frequency magnetic field (ELF-MF) on apoptosis and oxidative stress values in the brain of rat. Rats were exposed to 100 and 500 microT ELF-MF, which are the safety standards of public and occupational exposure for 2 h/day for 10 months. Brain tissues were immunohistochemically stained for the active (cleaved) caspase-3 in order to measure the apoptotic index by a semi-quantitative scoring system. In addition, the levels of catalase (CAT), malondialdehyde (MDA), myeloperoxidase (MPO), total antioxidative capacity (TAC), total oxidant status (TOS), and oxidative stress index (OSI) were measured in rat brain. Final score of apoptosis and MPO activity were not significantly different between the groups. CAT activity decreased in both exposure groups ($p < 0.05$), while TAC was found to be lower in ELF 500 group than those in ELF-100 and sham groups ($p < 0.05$). MDA, TOS, and OSI values were found to be higher in ELF-500 group than those in ELF-100 and sham groups ($p < 0.05$). In conclusion, apoptosis was not changed by long-term ELF-MF exposure, while both 100 and 500 microT ELF-MF exposure induced toxic effect in the rat brain by increasing oxidative stress and diminishing antioxidant defense system.

(E) (VO, CE, IOD) Akdag MZ, Dasdag S, Cakir DU, Yokus B, Kizil G, Kizil M. Do 100- and 500-μT ELF magnetic fields alter beta-amyloid protein, protein carbonyl and malondialdehyde in rat brains? Electromagn Biol Med. 32(3):363-372, 2013a.

Several studies still state that presently accepted safety standards for extremely low-frequency magnetic fields (ELF-MFs) do not provide adequate protection, and therefore the standards are still open to question. To help resolve this question, the aim of this study was to illuminate the interaction between biomolecules and ELF-MFs by investigating the effect of ELF-MFs on beta-amyloid protein (BAP), protein carbonyl (PC) and malondialdehyde (MDA) in rat brain. For this study, 30 adult male Sprague-Dawley rats were used, which were divided into two experimental groups and a sham exposed group. Rats in two experimental groups were exposed to 100- and 500-μT ELF-MFs (50 Hz) for 2 h/day for 10 months, which are the generally accepted safety standards for public and occupational exposures. The same procedures were applied to the rats in the sham group, but with the generator turned off. The results of this study showed that neither ELF-MFs used in this study altered BAP level significantly ($p>0.05$). However, PC and MDA levels were increased by the exposure to 100- and 500-μT ELF-MFs ($p < 0.0001$). In conclusion, both PC and MDA levels were altered by long-term exposure to either 100 or 500 μT ELF-MF. However, many further and more comprehensive studies will be required to elucidate the interaction mechanisms between ELF-MFs exposure and living organisms.

(NE) (VO, CE) Akdag MZ, Dasdag S, Uzunlar AK, Ulukaya E, Oral AY, Celik N, Akşen F. Can safe and long-term exposure to extremely low frequency (50 Hz) magnetic fields affect apoptosis, reproduction, and oxidative stress? Int J Radiat Biol. 89(12):1053-1060, 2013b.

Abstract Purpose: The purpose of this study was to determine whether 50 Hz Extremely Low Frequency-Magnetic Fields (ELF-MFs) affects apoptotic processes, oxidative damage, and reproductive characteristics such as sperm count and morphology in rat testes. Materials and Methods: 30 male Sprague-Dawley rats were used in the present study, which were divided into three groups (sham group, n: 10, and two experimental groups, n: 10 for each group).Rats in the experimental group were exposed to 100 and 500 μT ELF-MF (2h/day, 7 days/week, for 10 months) corresponding to exposure levels that are considered safe for humans.. Same experimental procedures were applied to the sham group, but the ELF generator was turned off. Tissues from the testes were immunohistochemically stained for active (cleaved) caspase-3 in order to measure the apoptotic index by a semi-quantitative scoring system. The levels of catalase (CAT), malondialdehyde (MDA), myeloperoxidase (MPO), total antioxidative capacity (TAC), total oxidant status (TOS), and oxidative stress index (OSI) were also measured. Additionally, epididymal sperm count and sperm morphology was evaluated. Results: There were no significant differences in the reproductive and oxidative stress parameters between the sham group and the exposed groups ($p>0.05$). While no difference was observed between the final apoptosis score of the sham and the100 μT ELF-MF group ($p>0.05$), the final apoptosis score was higher in the 500 μT ELF-MF exposure group than in the sham group ($p<0.05$). Conclusion: Long-term exposure to 100 μT and 500 μT ELF-MF did not affect oxidative or antioxidative processes, lipid peroxidation, or reproductive components such as sperm count and morphology in testes tissue of rats. However, long-term exposure to 500 μT ELF-MF did affect active-caspase-3 activity, which is a well-known apoptotic indicator.

(E) (VO, CE, IOD) Akpinar D, Ozturk N, Ozen S, Agar A, Yargicoglu P. The effect of different strengths of extremely low-frequency electric fields on antioxidant status, lipid peroxidation, and visual evoked potentials. Electromagn Biol Med. 31(4):436-448, 2012.

The aim of the study was to investigate the effects of extremely low-frequency electric field (ELF EF) on visual evoked potential (VEP), thiobarbituric acid reactive substances (TBARS), total antioxidant status (TAS), total oxidant status (TOS), and oxidant stress index (OSI). Thirty female Wistar rats, aged 3 months, were divided into three equal groups: Control (C), the group exposed to EF at 12 kV/m strength (E12), and the group exposed to EF at 18 kV/m strength (E18). Electric field was applied to the E12 and E18 groups for 14 days (1 h/day). Brain and retina TBARS, TOS, and OSI were significantly increased in the E12 and E18 groups with respect to the control group. Also, TBARS levels were significantly increased in the E18 group compared with the E12 group. Electric fields significantly decreased TAS levels in both brain and retina in E12 and E18 groups with respect to the control group. All VEP components were significantly prolonged in rats exposed to electric fields compared to control group. In addition, all latencies of VEP components were increased in the E18 group with respect to the E12 group. It is conceivable to suggest that EF-induced lipid peroxidation may play an important role in changes of VEP parameters.

(E) (VO, CE, DOD, IOD) Akpınar D, Gok DK, Hidisoglu E, Aslan M, Ozen S, Agar A, Yargicoglu P. Effects of pre- and postnatal exposure to extremely low-frequency electric fields on mismatch negativity component of the auditory event-related potentials: Relation to oxidative stress. Electromagn Biol Med. 35(3):245-259, 2016.

In our previous study, the developmental effects of extremely low-frequency electric fields (ELF-EF) on visual and somatosensory evoked potentials in adult rats were studied. There is no study so far examining the effects of 50 Hz electric field (EF) on mismatch negativity (MMN) recordings after exposure of rats during development. Therefore, our present study aimed to investigate MMN and oxidative brain damage in rats exposed to EF (12 kV/m, 1 h/day). Rats were divided into four groups, namely control (C), prenatal (Pr), postnatal (Po), and prenatal+postnatal (PP). Pregnant rats of Pr and PP groups were exposed to EF during pregnancy. Following birth, rats of PP and Po groups were exposed to EF for three months. After exposure to EF, MMN was recorded by electrodes positioned stereotaxically to the surface of the dura, and then brain tissues were removed for histological and biochemical analyses. The MMN amplitude was higher to deviant tones than to standard tones. It was decreased in all experimental groups compared with the C group. 4-Hydroxy-2-nonenal (4-HNE) levels were significantly increased in the Po group with respect to the C group, whereas they were significantly decreased in the PP group compared with Pr and Po groups. Protein carbonyl levels were significantly decreased in the PP group compared with C, Pr, and Po groups. EF decreased MMN amplitudes were possibly induced by lipid peroxidation.

(E)(VO, CE, IOD) Aksen F, Akdag MZ, Ketani A, Yokus B, Kaya A, Dasdag S. Effect of 50-Hz 1-mT magnetic field on the uterus and ovaries of rats (electron microscopy evaluation). Med Sci Monit. 12(6):BR215-220, 2006.

BACKGROUND: The aim of this study was to investigate the effect of extremely low frequency magnetic fields (ELFMF) on the uterus and ovary of rats. MATERIAL/METHODS: Forty-eight female Wistar albino rats were divided into two groups, one for 50 and the other for 100 days of exposure. Each group was further divided into two groups, one sham exposed (n=12) and the other the experimental group (n=12). The experimental rats were exposed to 50-Hz 1-mT ELFMF for three hours/day for 50 or 100 days. The sham groups of rats were kept under the same circumstances without applying ELFMF. Electron microscopic examination was performed to evaluate the ovaries and uterus. RESULTS: Ultrastructural dissolution, decrease in cell organelles, cavities in cells, heterochromative appearance, and typical structural loss of the nucleus were observed in germinal epithelial cells of the rat ovaries in the 50-days ELFMF exposure group. Ultrastructural alterations in germinal epithelium and tunica albuginea of ovaries, irregularity in nucleus and nucleolus, increase in lipid vacuoles of cell cytoplasm and reduction in organelles were observed in rat ovaries in the 100-days ELFMF exposure group. Similar alterations were observed in uterus. Malondialdehyde concentration (MDA) of the ovaries and uterus increased in rats of the two exposure groups ($p<0.001$). CONCLUSIONS: The results of the study showed that 50 and 100 days of exposure to a 1-mT ELFMF can cause alterations at the cellular level and in MDA concentration.

(NE) (VO, CE, AO) Alcaraz M, Olmos E, Alcaraz-Saura M, Achel DG, Castillo J. Effect of long-term 50 Hz magnetic field exposure on the micronucleated polychromatic erythrocytes of mice. Electromagn Biol Med. 33(1):51-57, 2014.

In recent years extremely low-frequency magnetic fields (ELF-EMF) have become widely used in human activities, leading to an increased chance of exposure to ELF-EMF. There are few reports on in vivo mammalian genotoxic effects using micronucleus (MN) assays, which generally have been used as a short-term screening system. We analyzed the possible genotoxic effect induced by long-term exposure (7, 14, 21, 28 d) of a 50 Hz ELM-MF to mice by measuring the increase in frequency of micronucleated polychromatic erythrocyte in their bone marrow (MNPCEs) and we compared it with that induced by 50 cGy of X-rays. Subsequently, we tried to reduce this chromosomal damage by administering four antioxidants substances with radioprotective capacities: dimethyl sulfoxide (DMSO), 6-n-propyl-2-thiouracil (PTU), grape-procyanidins (P) and citrus flavonoids extract (CE). The increase in micronucleated cells was higher in both physical treatments (Control < ELF-EMF ($p < 0.01$) <X-rays ($p > 0.001$)); however, the antioxidant substances only showed a genoprotective capacity against the damage induced by ionizing radiation (Ci > PTU = DMSO ($p < 0.001$) >P = CE ($p < 0.001$). The 50 Hz ELM-MF increased MNPCEs in mouse bone marrow, expressing a genotoxic capacity. Administration of antioxidant substances with radioprotective capacities known to act through the elimination of free radicals did not diminish the genotoxic effect induced by ELM-MF.

(E) (VT, AE, IFR, IAO) Alipour M, Hajipour-Verdom B, Javan M, Abdolmaleki P. Static and Electromagnetic Fields Differently Affect Proliferation and Cell Death Through Acid Enhancement of ROS Generation in Mesenchymal Stem Cells. Radiat Res 198(4):384-395, 2022.

Magnetic fields remotely influence cellular homeostasis as a physical agent through the changes in cell physicochemical reactions. Magnetic fields affect cell fate, which may provide an important and interesting challenge in stem cell behaviors. Here, we investigated the effects of the static magnetic field (SMF, 20 mT) and electromagnetic field (EMF, 20 mT-50 Hz) on reactive oxygen species (ROS) production and the acidic pH conditions as stimuli to change cell cycle progression and cell death in mesenchymal stem cells. Results show that SMF, EMF, and their simultaneous (SMF+EMF) administration increase ROS and expression of nuclear factor erythroid 2-related factor 2 (Nrf2), superoxide dismutase 2 (SOD2), and glutathione-S-transferase (GST) as an antioxidant defense system. Besides, intracellular pH (pHi) decreases in presence of either EMF or SMF+EMF, but not SMF. Decreased ROS content using ascorbic acid in these treatments leads to increased pH compared to the magnetic field treatments alone. Furthermore, each magnetic field has different effects on the cellular process of stem cells, including cell cycle, apoptosis and necrosis. Moreover, treatment by SMF enhances the cell viability after 24 h, while EMF or SMF+EMF decreases it. These observations indicate that fluctuations of ROS generation and acid enhancement during SMF and EMF treatments may reveal their beneficial and adverse effects on the molecular and cellular mechanisms involved in the growth, death, and differentiation of stem cells.

(E) (VO, CE, DAO, IOD) Amara S, Douki T, Garel C, Favier A, Sakly M, Rhouma KB, Abdelmelek H. Effects of static magnetic field exposure on antioxidative enzymes activity and DNA in rat brain. Gen Physiol Biophys. 28(3):260-265, 2009.

The present study was undertaken in order to investigate the effects of static magnetic field (SMF) exposure on the antioxidative enzymes activity, malondialdehyde (MDA) concentration and DNA oxidation in male rat brain. The exposure of rats to SMF (128 mT, 1 h/day during 30 consecutive days) decreased the glutathione peroxidase (GPx; -39%, $p < 0.05$), CuZn superoxide dismutase (CuZn-SOD; -35%, $p < 0.05$) and catalase (-59%, $p < 0.05$) activities in frontal cortex. The same treatment decreased the CuZn-SOD (-51%, $p < 0.05$) and Mn-SOD (-13%, $p < 0.05$) activities in hippocampus. However, the glutathione levels remained unchanged in the both brain structures. In the hippocampus, SMF exposure increased MDA concentration (+32%, $p < 0.05$). Interestingly, exposed-rats to SMF displayed a significant increase of metallothioneins level in frontal cortex (+100%, $p < 0.05$), while the 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodGuo) concentration remained unaffected, indicating the absence of DNA oxidation. Our results indicated that sub-chronic exposure to SMF induced oxidative stress in rat hippocampus and frontal cortex. Metallothionein induction protected probably DNA against oxidative damage.

(E) (VO, CE, DAO, IOD, IX) Amara S, Douki T, Garrel C, Favier A, Ben Rhouma K, Sakly M, Abdelmelek H. Effects of static magnetic field and cadmium on oxidative stress and DNA damage in rat cortex brain and hippocampus. Toxicol Ind Health. 27(2):99-106, 2011.

The present study was undertaken to determine the effect of co-exposure to static magnetic field (SMF) and cadmium (Cd) on the antioxidant enzymes activity and DNA integrity in rat brain. Sub-chronic exposure to CdCl (CdCl(2), 40 mg/L, per os) for 30 days resulted in a significant reduction in antioxidant enzyme activity such as the glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) in frontal cortex and hippocampus. Total GSH were decreased in the frontal cortex of the Cd-exposed group. Cd exposure induced an increase in malondialdehyde (MDA) concentration in the frontal cortex and hippocampus. Moreover, the same exposure increased 8-oxo-7,8-dihydro-2-desoxyguanosine (8-oxodGuo) level in rat brain. Interestingly, the combined effect of SMF (128 mT, 1 hour/day for 30 consecutive days) and CdCl (40 mg/L, per os) decreased the SOD activity and glutathione level in frontal cortex as compared with the Cd group. Moreover, the association between SMF and Cd increased MDA concentration in frontal cortex as compared with Cd-exposed rats. DNA analysis revealed that SMF exposure failed to alter 8-oxodGuo concentration in Cd-exposed rats. Our data showed that Cd exposure altered the antioxidant enzymes activity and induced oxidative DNA lesions in rat brain. The combined effect of SMF and Cd increased oxidative damage in rat brain as compared with Cd-exposed rats.

(E) (VO, AE, CE, IAO) Ansari AM, Farzampour S, Sadr A, Shekarchi B, Majidzadeh-A K. Effects of short term and long term extremely low frequency magnetic field on depressive disorder in mice: Involvement of nitric oxide pathway. Life Sci. 146:52-57, 2016.

AIMS: Previous reports on the possible effects of Extremely Low Frequency Magnetic Fields (ELF MF) on mood have been paradoxical in different settings while no study has yet been conducted on animal behavior. In addition, it was shown that ELF MF exposure makes an increase in brain nitric oxide level. Therefore, in the current study, we aimed to assess the possible effect(s) of ELF MF exposure on mice Forced Swimming Test (FST) and evaluate the probable role of the increased level of nitric oxide in the observed behavior. MAIN METHODS: Male adult mice NMRI were recruited to investigate the short term and long term ELF MF exposure (0.5 mT and 50Hz, single 2h and 2weeks 2h a day). Loco motor behavior was assessed by using Open-Field Test (OFT) followed by FST to evaluate the immobility time. Accordingly, NΩ-nitro-L-arginine methyl ester 30mg/kg was used to exert anti-depressant like effect. KEY FINDINGS: According to the results, short term exposure did not alter the immobility time, whereas long term exposure significantly reduces immobility time ($p<0.01$). However, it was revealed that the locomotion did not differ among all experimental groups. Short term exposure reversed the anti-depressant like effect resulting from 30 mg/kg of NΩ-nitro-L-arginine methyl ester ($p<0.01$). SIGNIFICANCE: It has been concluded that long term exposure could alter the depressive disorder in mice,

whereas short term exposure has no significant effect. Also, reversing the anti-depressant activity of L-NAME indicates a probable increase in the brain nitric oxide.

(E) (VO, AE, IAO) Asghar T, Jamil Y, Iqbal M, Zia-Ul-Haq, Abbas M. Laser light and magnetic field stimulation effect on biochemical, enzymes activities and chlorophyll contents in soybean seeds and seedlings during early growth stages. J Photochem Photobiol B. 165:283-290, 2016.

Laser and magnetic field bio-stimulation attracted the keen interest of scientific community in view of their potential to enhance seed germination, seedling growth, physiological, biochemical and yield attributes of plants, cereal crops and vegetables. Present study was conducted to appraise the laser and magnetic field pre-sowing seed treatment effects on soybean sugar, protein, nitrogen, hydrogen peroxide (H_2O_2) ascorbic acid (AsA), proline, phenolic and malondialdehyde (MDA) along with chlorophyll contents (Chl "a" "b" and total chlorophyll contents). Specific activities of enzymes such as protease (PRT), amylase (AMY), catalyst (CAT), superoxide dismutase (SOD) and peroxides (POD) were also assayed. The specific activity of enzymes (during germination and early growth), biochemical and chlorophyll contents were enhanced significantly under the effect of both laser and magnetic pre-sowing treatments. Magnetic field treatment effect was slightly higher than laser treatment except PRT, AMY and ascorbic acid contents. However, both treatments (laser and magnetic field) effects were significantly higher versus control (un-treated seeds). Results revealed that laser and magnetic field pre-sowing seed treatments have potential to enhance soybean biological moieties, chlorophyll contents and metabolically important enzymes (degrade stored food and scavenge reactive oxygen species). Future study should be focused on growth characteristics at later stages and yield attributes.

(E) (VT, AE, IFR, IX) Ashta A , Motalleb G , Ahmadi-Zeidabadi M. Evaluation of frequency magnetic field, static field, and Temozolomide on viability, free radical production and gene expression (p53) in the human glioblastoma cell line (A172) Electromagn Biol Med 39(4):298-309, 2020.

Thirteen million cancer deaths and 21.7 million new cancer cases are expected in the world by 2030. Glioblastoma is the most common primary malignant tumor of the central nervous system which is the most lethal type of primary brain tumor in adults with the survival time of 12-15 months after the initial diagnosis. Glioblastoma is the most common and most malignant type of brain tumor, and despite surgery, chemotherapy and radiation treatment, the average survival of patients is about 14 months. The current research showed that the frequency magnetic field (FMF) and static magnetic field (SMF) can influence cancer cell proliferation and coupled with anticancer drugs may provide a new strategy for cancer therapy. At the present study, we investigated the effects of FMF (10 Hz, 50 G), SMF (50 G) and Temozolomide (200 μm) on viability, free radical production, and *p53* followed by p53 protein expression in the human glioblastoma cell line (A172) by MTT, NBT, RT-PCR and Western blot. Results showed that the effect of

Temozolomide (TMZ) with SMF and FMF together increased the cytotoxicity, free radical production, and *p53* followed by p53 protein expression in the human glioblastoma cell line (A172).

(E) (VT, CE, IFR) Ayşe IG, Zafer A, Sule O, Işil IT, Kalkan T. Differentiation of K562 cells under ELF-EMF applied at different time courses. Electromagn Biol Med. 29(3):122-130, 2010.

The time-course of ELF-EMF application to biological systems is thought to be an important parameter determining the physiological outcome. This study investigated the effect of ELF-EMF on the differentiation of K562 cells at different time courses. ELF-EMF (50 Hz, 5 mT, 1 h) was applied at two different time-courses; first at the onset of hemin induction for 1 h, and second, daily 1 h for four days. While single exposure to ELF-EMF resulted in a decrease in differentiation, ELF-EMF applied everyday for 1 h caused an increase in differentiation. The effect of co-stressors, magnesium, and heat-shock was also determined and similar results were obtained. ELF-EMF increased ROS levels in K562 cells not treated with hemin, however did not change ROS levels of hemin treated cells indicating that ROS was not the cause. Overall, these results imply that the time-course of application is an important parameter determining the physiological response of cells to ELF-EMF.

(E) (VT, LE, IFR
)Barati M, Javidi MA, Darvishi B, Shariatpanahi SP, Moosavi ZSM, Ghadirian R, Khani T, Sanati H, Simaee H, Barough MS, Farahmand L, Ansari AM. Necroptosis triggered by ROS accumulation and Ca $^{2+}$ overload, partly explains the inflammatory responses and anti-cancer effects associated with 1Hz, 100 mT ELF-MF in vivo. Free Radic Biol Med 169:84-98, 2021.

Whereas the anti-neoplastic activity of extremely low frequency magnetic fields (ELF-EMF) is well-documented in literature, little is known about its underlying anti-cancer mechanisms and induced types of cell death. Here, for the first time, we reported induction of necroptosis, a specific type of programed necrotic cell death, in MC4-L2 breast cancer cell lines following a 2 h/day exposure to a 100 Hz, 1 mT ELF-EMF for five days. For in vivo assessment, inbred BALB/c mice bearing established MC-4L2 tumors were exposed to 100 mT, 1 Hz ELF-EMF 2 h daily for a period of 28-day, following which tumors were dissected and fixed for evaluation of tumor biomarkers expression and types of cell death induced using TUNEL assay, Immunohistochemistry and H&E staining. Peripheral blood samples were also collected for assessing pro-inflammatory cytokine profile following exposure. An exaggerated proinflammatory response evident form enhancement of IFN-γ (4.8 ± 0.24 folds) and TNF-α (3.1 ± 0.19 folds) and number of tumors infiltrating lymphocytes (TILs), specially $CD8^+$ T_h cells (~20 folds), proposed occurrence of necroptosis in vivo. Meanwhile, exposure could effectively suppress tumor growth and expression of Ki-67, CD31, VEGFR2 and MMP-9. In vitro studies on ELF-EMF exposed MC-4L2 cells demonstrated a meaningful increase in phosphorylation of RIPK1/RIPK3/MLKL proteins and cleavage of caspase-9/caspase-3, confirming occurrence of both necroptosis and apoptosis. Complementary in vitro studies by treating ELF-EMF

exposed MC-4L2 cells with verapamil (a calcium channel inhibitor), N-acetyl cysteine (a ROS scavenger) or calcium chloride confirmed the role of elevated intracellular calcium and ROS levels in ELF-EMF induced necroptosis.

Barnes F, Greenebaum B. Role of radical pairs and feedback in weak radio frequency field effects on biological systems. Environ Res. 163:165-170, 2018. (Review)

Radio frequency electromagnetic fields (RF) have been shown to modify the concentrations of the radical O_2^-, H_2O_2 and cancer cell growth rates at exposure levels below those that cause significant heating. Reactive oxygen species (ROS) are both signaling molecules and species that can do damage, depending on timing, location and concentrations. We briefly look at some mechanisms by which electromagnetic fields can modify the concentrations of ROS and some of the feedback and repair processes that lead to variable biological effects. Of particular interest are the role of radical pairs and their spins, which have received considerable attention recently, and the role of feedback in biological systems, to which less attention has been paid.

(E) (VT, AC, IX) Bawin SM, Satmary WM, Jones RA, Adey WR, Zimmerman G. Extremely-low-frequency magnetic fields disrupt rhythmic slow activity in rat hippocampal slices. Bioelectromagnetics. 17(5):388-395, 1996.

Several studies have indicated that weak, extremely-low-frequency (ELF; 1-100 Hz) magnetic fields affect brain electrical activity and memory processes in man and laboratory animals. Our studies sought to determine whether ELF magnetic fields could couple directly with brain tissue and affect neuronal activity in vitro. We used rat hippocampal slices to study field effects on a specific brain activity known as rhythmic slow activity (RSA), or theta rhythm, which occurs in 7-15 s bursts in the hippocampus during memory functions. RSA, which, in vivo, is a cholinergic activity, is induced in hippocampal slices by perfusion of the tissue with carbachol, a stable analog of acetylcholine. We previously demonstrated that the free radical nitric oxide (NO), synthesized in carbachol-treated hippocampal slices, lengthened and destabilized the intervals between successive RSA episodes. Here, we investigate the possibility that sinusoidal ELF magnetic fields could trigger the NO-dependent perturbation of the rate of occurrence of the RSA episodes. Carbachol-treated slices were exposed for 10 min epochs to 1 or 60 Hz magnetic fields with field intensities of 5.6, 56, or 560 microT (rms), or they were sham exposed. All exposures took place in the presence of an ambient DC field of 45 microT, with an angle of -66 degrees from the horizontal plane. Sinusoidal 1 Hz fields at 56 and 560 microT, but not at 5.6 microT, triggered the irreversible destabilization of RSA intervals. Fields at 60 Hz resulted in similar, but not statistically significant, trends. Fields had no effects on RSA when NO synthesis was pharmacologically inhibited. However, field effects could take place when extracellular NO, diffusing from its cell of origin to the extracellular space,was chelated by hemoglobin. <u>These results suggest that ELF magnetic fields exert a strong influence on NO systems in the brain;</u> therefore, they could modulate the functional state of a variety of neuronal ensembles.

(E) (VO, CE, IOD) Bediz CS, Baltaci AK, Mogulkoc R, Oztekin E. Zinc supplementation ameliorates electromagnetic field-induced lipid peroxidation in the rat brain. Tohoku J Exp Med. 208(2):133-140, 2006.

Extremely low-frequency (0-300 Hz) electromagnetic fields (EMFs) generated by power lines, wiring and home appliances are ubiquitous in our environment. All populations are now exposed to EMF, and exposure to EMF may pose health risks. Some of the adverse health effects of EMF exposure are lipid peroxidation and cell damage in various tissues. This study has investigated the effects of EMF exposure and zinc administration on lipid peroxidation in the rat brain. Twenty-four male Sprague-Dawley rats were randomly allocated to three groups; they were maintained untreated for 6 months (control, n = 8), exposed to low-frequency (50 Hz) EMF for 5 minutes every other day for 6 months (n = 8), or exposed to EMF and received zinc sulfate daily (3 mg/kg/day) intraperitoneally (n = 8). We measured plasma levels of zinc and thiobarbituric acid reactive substances (TBARS), and levels of reduced glutathione (GSH) in erythrocytes. TBARS and GSH levels were also determined in the brain tissues. TBARS levels in the plasma and brain tissues were higher in EMF-exposed rats with or without zinc supplementation, than those in controls ($p < 0.001$). In addition, TBARS levels were significantly lower in the zinc-supplemented rats than those in the EMF-exposed rats ($p < 0.001$). GSH levels were significantly decreased in the brain and erythrocytes of the EMF-exposed rats ($p < 0.01$), and were highest in the zinc-supplemented rats ($p < 0.001$). Plasma zinc was significantly lower in the EMF-exposed rats than those in controls ($p < 0.001$), while it was highest in the zinc-supplemented rats ($p < 0.001$). The present study suggests that long-term exposure to low-frequency EMF increases lipid peroxidation in the brain, which may be ameliorated by zinc supplementation.

(E) (VT, AE, IFR, DFR, MC) Belova NA, Potselueva MM, Skrebnitskaia LK, Znobishcheva AV, Lednev VV. The influence of weak magnetic fields on the production of the reactive oxygen species in peritoneal neutrophils in mice. Biophysics (Biofizika). 55(4):586-591, 2010.

The influence of weak magnetic fields of different types on the rate of the formation of reactive oxygen species in mouse peritoneal neutrophils has been studied. It was found that the exposure of neutrophils activated by phorbol 12-myristate 13-acetate to the magnetic field tuned to the parametric resonance for Ca2+ ions leads to a decrease in the rate of the reactive oxygen species (ROS) generation by 23%. Conversely, the generation of ROS in neutrophils exposed to the same field but stimulated by the bacterial peptide FMLP (N-formyl-L-methionyl-L-leucyl-L-phenylalanine) increased by about 21%. Pulsed magnetic fields also changed the rate of ROS generation in phorbol-stimulated neutrophils by about 20%, but the sign of the effects observed in this case was opposite to those induced by the magnetic field tuned to the parametric resonance for Ca2+ ions.

(E) (VT, AE, IOD, IX) Benassi B, Filomeni G, Montagna C, Merla C, Lopresto V, Pinto R, Marino C, Consales C. Extremely low frequency magnetic field (ELF-MF) exposure sensitizes SH-SY5Y cells to the pro-Parkinson's Disease toxin MPP. Mol Neurobiol. 53(6):4247-4260, 2016.

Parkinson's disease (PD) is a neurodegenerative disorder characterized by dopaminergic neuron loss, with an etiopathogenesis involving both genetic and environmental factors. The occupational/residential exposure to the electromagnetic fields has been recently associated with an increased risk of neurodegenerative diseases; it has been thus proposed that the extremely low frequency magnetic field (ELF-MF) may contribute to neurodegenerative etiopathogenesis, as its interaction with biological systems directly impairs redox homeostasis in specific areas of the brain. The molecular mechanisms elicited by ELF-MF, and their potential involvement in PD onset, still remain unclear. To this end, we set up a generator of ELF-MF able to stably and homogeneously reproduce environmental prolonged exposure to ELF-MF (50 Hz, 1 mT). Results obtained indicate that ELF-MF exposure alters cell response of SH-SY5Y cells to MPP^+. We demonstrate that ELF-MF does not affect per se survival, shape, and morphology of both proliferating and differentiated SH-SY5Y cells but significantly impairs redox homeostasis and thiol content, triggering an increase in protein carbonylation. As a result, toxicity of MPP^+, even at low doses, is highly enhanced in ELF-MF-exposed cells due to a significant increase in ROS levels, potentiation of oxidative damage, and induction of a caspase-dependent apoptosis. Pre-incubation with the thiol antioxidants N-acetyl-L-cysteine and GSH ethyl-ester significantly reduces the extent of oxidative damage and protects cells from death induced by the combined treatment ELF-MF/MPP^+. Taken overall, our results demonstrate the redox-based molecular interaction between ELF-MF and PD neurotoxins in vitro, and open a new scenario for defining the synergy of environmental factors in PD onset.

(E) (VO, CE, DAO) Bertea CM, Narayana R, Agliassa C, Rodgers CT, Maffei ME. Geomagnetic Field (Gmf) and Plant Evolution: Investigating the Effects of Gmf Reversal on Arabidopsis thaliana Development and Gene Expression. J Vis Exp. (105):53286, 2015.

One of the most stimulating observations in plant evolution is a correlation between the occurrence of geomagnetic field (GMF) reversals (or excursions) and the moment of the radiation of Angiosperms. This led to the hypothesis that alterations in GMF polarity may play a role in plant evolution. Here, we describe a method to test this hypothesis by exposing Arabidopsis thaliana to artificially reversed GMF conditions. We used a three-axis magnetometer and the collected data were used to calculate the magnitude of the GMF. Three DC power supplies were connected to three Helmholtz coil pairs and were controlled by a computer to alter the GMF conditions. Plants grown in Petri plates were exposed to both normal and reversed GMF conditions. Sham exposure experiments were also performed. Exposed plants were photographed during the experiment and images were analyzed to calculate root length and leaf areas. Arabidopsis total RNA was extracted and Quantitative Real Time-PCR (qPCR) analyses were performed on gene expression of CRUCIFERIN 3 (CRU3), copper transport protein1 (COTP1), Redox Responsive Transcription Factor1 (RRTF1), Fe Superoxide Dismutase 1, (FSD1), Catalase3 (CAT3), Thylakoidal Ascorbate Peroxidase (TAPX), a cytosolic Ascorbate Peroxidase1 (APX1), and NADPH/respiratory burst oxidase protein D (RbohD). Four different reference genes were analysed to normalize the results of the qPCR. The best of the four genes was selected and the most stable gene for normalization was used. Our data show for the first time that reversing the GMF polarity using triaxial coils has significant effects on plant growth and gene expression. This supports the

hypothesis that GMF reversal contributes to inducing changes in plant development that might justify a higher selective pressure, eventually leading to plant evolution.

(F) (VO, AE, IFR, IAO) Bhardwaj, J., Anand, A., Nagarajan, S. Biochemical and biophysical changes associated with magnetopriming in germinating cucumber seeds. Plant Physiology and Biochemistry 57: 67-73, 2012.

Seeds of cucumber were exposed to static magnetic field strength from 100 to 250 mT for 1, 2 or 3 h. Germination-percentage, rate of germination, length of seedling and dry weight increased by 18.5, 49, 34 and 33% respectively in magnetoprimed seeds compared to unexposed seeds. Among different magnetic field doses, 200 mT for 1 h showed significant effect on germination parameters and hence selected for studying changes in water uptake, ^{1}H transverse relaxation time (T_2), hydrolytic enzymes, reactive oxygen species and antioxidant enzyme system in germinating seeds. Water uptake and T_2 values were significantly higher in treated seeds during imbibition. The activities of hydrolytic enzymes, amylase and protease were greater than the untreated controls by 51% and 13% respectively. Superoxide radicals also enhanced by 40% and hydrogen peroxide by 8% in magnetically exposed seeds. In magetoprimed seeds, increased activities of antioxidant enzymes, superoxide dismutase (8%), catalase (83%) and glutathione reductase (77%) over control was recorded. We report that magnetopriming of dry seeds can be effectively used as a pre-sowing treatment for seed invigoration in cucumber. Unlike other priming treatments seed is not required to be dehydrated after priming, allowing easy storage.

(E) (VO, AE, IFR. IAO) Bhardwaj J, Anand A, Pandita VK, Nagarajan S. Pulsed magnetic field improves seed quality of aged green pea seeds by homeostasis of free radical content. J Food Sci Technol. 53(11):3969-3977, 2016.

To elucidate the mechanism responsible for magnetic field induced seed invigoration in aged seeds an experiment was conducted on six year old Pulsed MF, 6 minON/6 min OFF, 100 stored under controlled (20 °C and 40% RH) condition. Aged seeds were magnetoprimed by exposing to pulsed magnetic field (PMF) of 100 mT for 1 h in three pulsed modes. The 6 min on and off PMF showed significant improvement in germination (7.6%) and vigor (84.8%) over aged seeds. Superoxide and hydrogen peroxide production increased in germinating primed seeds by 27 and 52%, respectively, over aged seeds. Nicotinamide adenine dinucleotide (reduced) (NADH) peroxidase and superoxide dismutase involved in generation of hydrogen peroxide showed increased activity in PMF primed seeds. Increase in catalase, ascorbate peroxidase and glutathione reductase activity after 36 h of imbibition in primed seeds demonstrated its involvement in seed recovery during magnetopriming. An increase in total antioxidants also helped in maintaining the level of free radicals for promoting germination of magnetoprimed seeds. A 44% increase in level of protein carbonyls after 36 h indicated involvement of protein oxidation for counteracting and/or utilizing the production of ROS and faster mobilization of reserve proteins. Higher production of free radicals in primed seeds did not cause lipid peroxidation as malondialdehyde content was low. Lipoxygenase was involved in the germination associated events as the magnitude of activity was higher in primed aged

seeds compared to aged seeds. Our study elucidated that PMF mediated improvement in seed quality of aged pea seeds was facilitated by fine tuning of free radicals by the antioxidant defense system and protein oxidation.

Brocklehurst B, McLauchlan KA. Free radical mechanism for the effects of environmental electromagnetic fields on biological systems. Int J Radiat Biol. 69(1):3-24, 1996. (Review)

The radical pair mechanism is discussed as a possible route whereby a magnetic field of environmental strength might affect a biological system. It is well established as the origin of reproducible field effects in chemistry, and these can be observed even at very low magnetic field strengths, including that of the geomagnetic field. Here it is attempted to give a description which might assist experimentalists working in biological laboratories to device tests of its relevance to their work. The mechanism is well understood and a specific theoretical approach is taken to explore and emphasize the importance of the lifetime of the radical pair and the precise chemical natures of the radicals which comprise it in affecting the size of the low-field effects. Further subsequent processes are likely necessary to cause this primary effect to attain biological significance. Arguments are provided to suggest that the encounters of freely diffusing pairs (F-pairs) of radicals are unlikely to produce significant effects in biology.

(E) (VT, AE, IOD) Buczyński A, Pacholski K, Dziedziczak-Buczyńska M, Henrykowska G, Jerominko A. The assessment of oxygen metabolism selected parameters of blood platelets exposed to low frequency magnetic radiation in cars--in vitro studies. Rocz Akad Med Bialymst. 50 Suppl 1:23-25, 2005.

PURPOSE: The aim of the study was to determine how free radicals generation in blood platelets exposed to electromagnetic field (EMF) occurring in cars affects the process of these morphotic elements cell membranes phospholipid peroxidation. MATERIAL AND METHODS: The suspension of human blood platelets was exposed to EMF of proper characteristics in a specially arranged research stand. After 30, 60 and 90 min exposure of the platelet specimen to EMF, free radicals generation was measured with chemiluminescence and malondialdehyde concentration according to Placer et al. method. The obtained results were compared with the control values. RESULTS: The increase of free radicals generation was observed after 30 and 90 min exposure of platelets to magnetic field. Malondialdehyde reached the highest values also after 30 and 90 min exposure of the platelets to EMF as compared to the control. CONCLUSIONS: The increase in oxygen reactive species generation under the effect of exogenic magnetic radiation as well as proportional intensification of the peroxidation process determined on the basis of malondialdehyde concentration (the marker of this phenomenon) point to the platelet sensitivity to the investigated environmental factor.

(E) (VO, CE, LI, DAO, IAO) Budziosz J, Stanek A, Sieroń A, Witkoś J, Cholewka A, Sieroń K. Effects of Low-Frequency Electromagnetic Field on Oxidative Stress in Selected Structures of the Central Nervous System. Oxid Med Cell Longev. 2018:1427412, 2018.

OBJECTIVE: The aim of the study was to evaluate the effects of a 28-day exposure to a 50 Hz electromagnetic field of 10 kV/m on the oxidative stress in selected rat central nervous system (CNS) structures. MATERIAL AND METHODS: Twenty male Wistar rats served as experimental subjects. Ten rats were exposed to an electromagnetic field with a frequency of 50 Hz, intensity of 10 kV/m, and magnetic induction of 4.3 pT for 22 hours a day. The control group of ten rats was subject to sham exposure. Homogenates of the frontal cortex, hippocampus, brainstem, hypothalamus, striatum, and cerebellum were evaluated for selected parameters of oxidative stress. RESULTS: Following the four-week exposure to a low-frequency electromagnetic field, the mean malondialdehyde levels and total oxidant status of CNS structures did not differ significantly between the experimental and control groups. However, the activities of antioxidant enzymes in brain structure homogenates were decreased except for frontal cortex catalase, glutathione peroxidase, and hippocampal glutathione reductase. The low-frequency electromagnetic field had no effect on the nonenzymatic antioxidant system of the examined brain structures except for the frontal cortex. CONCLUSION: The four-week exposure of male rats to a low-frequency electromagnetic field did not affect oxidative stress in the investigated brain structures.

(E) (VT, AE, DOD, IAO, IX) Bułdak RJ, Polaniak R, Bułdak L, Zwirska-Korczala K, Skonieczna M, Monsiol A, Kukla M, Duława-Bułdak A, Birkner E. Short-term exposure to 50 Hz ELF-EMF alters the cisplatin-induced oxidative response in AT478 murine squamous cell carcinoma cells. Bioelectromagnetics. 33(8):641-651, 2012.

The aim of this study was to assess the influence of cisplatin and an extremely low frequency electromagnetic field (ELF-EMF) on antioxidant enzyme activity and the lipid peroxidation ratio, as well as the level of DNA damage and reactive oxygen species (ROS) production in AT478 carcinoma cells. Cells were cultured for 24 and 72 h in culture medium with cisplatin. Additionally, the cells were irradiated with 50 Hz/1 mT ELF-EMF for 16 min using a solenoid as a source of the ELF-EMF. The amount of ROS, superoxide dismutase (SOD) isoenzyme activity, glutathione peroxidase (GSH-Px) activity, DNA damage, and malondialdehyde (MDA) levels were assessed. Cells that were exposed to cisplatin exhibited a significant increase in ROS and antioxidant enzyme activity. The addition of ELF-EMF exposure to cisplatin treatment resulted in decreased ROS levels and antioxidant enzyme activity. A significant reduction in MDA concentrations was observed in all of the study groups, with the greatest decrease associated with treatment by both cisplatin and ELF-EMF. Cisplatin induced the most severe DNA damage; however, when cells were also irradiated with ELF-EMF, less DNA damage occurred. Exposure to ELF-EMF alone resulted in an increase in DNA damage compared to control cells. ELF-EMF lessened the effects of oxidative stress and DNA damage that were induced by cisplatin; however, ELF-EMF alone was a mild

oxidative stressor and DNA damage inducer. We speculate that ELF-EMF exerts differential effects depending on the exogenous conditions. This information may be of value for appraising the pathophysiologic consequences of exposure to ELF-EMF.

(E)(VO, CE, IFR) Burcu A, Nevin E, Ilkay A, Amac K, Alper BH, Muge K. The effects of prenatal and postnatal exposure to electromagnetic field on rat ovarian tissue. Toxicol Ind Health 36(12):1010-1018, 2020.

Exposure to an electromagnetic field (EMF) can have adverse effects on many organs and tissues, including the reproductive system. This study aimed to investigate the effects of EMF exposure during prenatal and postnatal periods on ovarian development in rat offspring. In this study, rat pups born from eight pregnant rats were used. EMF exposure was initiated on the first day of pregnancy and continued until the 42nd postnatal day. The blood and ovarian tissue samples of female offspring in sham and EMF groups were collected when they reached the age of 42 days. Follicle-stimulating hormone levels were significantly higher in the EMF group than in the sham group. Estradiol levels were significantly lower in the EMF group than in the sham group. Tissue-inducible nitric oxide synthase (iNOS) levels and expression were significantly greater in the EMF group than in the sham group. In the EMF group, congestion, bleeding areas, and degeneration of follicle structures were observed in ovarian tissue. The findings suggest that exposure to 50-Hz, 3-mT EMF used in this study during prenatal and postnatal periods may lead to impaired ovarian structure and function in female offspring. EMF may affect ovarian physiology by increasing iNOS levels and may lead to fertility disorders.

(E)(VT, AE, IFR) Calabrò E, Condello S, Currò M, Ferlazzo N, Caccamo D, Magazù S, Ientile R. Effects of low intensity static magnetic field on FTIR spectra and ROS production in SH-SY5Y neuronal-like cells. Bioelectromagnetics. 34(8):618-629, 2013.

Biological effects of man-made electromagnetic fields (EMFs) have been studied so far by experimental approaches exposing animals and cell cultures to EMFs. However, the evidence for cell toxicity induced by static magnetic field (SMF) is still uncertain. We investigated the effects produced by the exposure of human SH-SY5Y neuronal-like cells to a uniform magnetic field at intensities of 2.2 mT, which is less than the recommended public exposure limits set by the International Commission on Non-Ionizing Radiation Protection (ICNIRP). A decrease of membrane mitochondrial potential up to 30% was measured after 24 h of exposure to SMF in SH-SY5Y cells, and this effect was associated with reactive oxygen species production increase. Fourier transform infrared spectroscopy (FTIR) analysis showed that exposure to a static magnetic intensity around 2.2 mT changed the secondary structure of cellular proteins and lipid components. The vibration bands relative to the methylene group increased significantly after 4 h of exposure, whereas further exposure up to 24 h produced evident shifts of amide I and II modes and a relative increase in β-sheet contents with respect to

α-helix components. Our study demonstrated that a moderate SMF causes alteration in cell homeostasis, as indicated by FTIR spectroscopy observations of changes in protein structures that are part of cell response to magnetic field exposure.

(VT, AE, IFR, IOD, DAO) Calcabrini C, Mancini U, De Bellis R, Diaz AR, Martinelli M, Cucchiarini L, Sestili P, Stocchi V, Potenza L. Effect of extremely low-frequency electromagnetic fields on antioxidant activity in the human keratinocyte cell line NCTC 2544. Biotechnol Appl Biochem. 64(3):415-422, 2017.

Some epidemiological studies have suggested possible associations between exposure to extremely low-frequency electromagnetic fields (ELF-EMFs) and various diseases. Recently, ELF-EMF has been considered as a therapeutic agent. To support ELF-EMF use in regenerative medicine, in particular in the treatment of skin injuries, we investigated whether significant cell damage occurs after ELF-EMF exposure. Reactive oxygen species (ROS) production was evaluated in the human keratinocyte exposed for 1 H to 50 Hz ELF-EMF in a range of field strengths from 0.25 to 2 G. Significant ROS increases resulted at 0.5 and 1 G and under these flux densities ROS production, glutathione content, antioxidant defense activity, and lipid peroxidation markers were assessed for different lengths of time. Analyzed parameters of antioxidant defense and membrane integrity showed a different trend at two selected magnetic fluxes, with a greater sensitivity of the cells exposed to 0.5 G, especially after 1 H. All significant alterations observed in the first 4 H of exposure reverted to controls 24 H after suggesting that under these conditions, ELF-EMF induces a slight oxidative stress that does not overwhelm the metabolic capacity of the cells or have a cytotoxic effect.

(E) (VT, AE, DFR) Calota V, Dragoiu S, Meghea A, Giurginca M. Decrease of luminol chemiluminescence upon exposure of human blood serum to 50 Hz electric fields. Bioelectrochemistry. 69(1):126-127, 2006.

The chemiluminescence of luminol, after 1 and 2 h in vitro exposure of human serum to 50 Hz electric fields of different intensities, decreases as compared to the controls. This indicates a field-induced decrease in the concentration of the free radicals. The report is limited to the key kinetic and field data, inviting independent kinetic analysis of the data in terms of reaction moments or reaction susceptibilities for the various normal modes indicated by the data.

(E)(VT, AE, IFR) Calota V, Dragoiu S, Meghea A, Giurginca M. Effects of prooxidants on human serum exposed to 50 Hz magnetic fields. Electromagn Biol Med.26(2):135-140, 2007.

The purpose of this article is to evaluate magnetic field effects (50 Hz, different magnetic intensities) on the chemiluminescence intensity of human serum. We find that 1 and 2 h of exposure increased the chemiluminescence emission. The addition to the serum of prooxidants FeCl(2) and H(2)O(2) in different concentrations increased the chemiluminescence intensity even more.

(E)(VO, CE, DOD, IOD, DFR, IFR) Canseven AG, Coskun S, Seyhan N. Effects of various extremely low frequency magnetic fields on the free radical processes, natural antioxidant system and respiratory burst system activities in the heart and liver tissues. Indian J Biochem Biophys. 45(5):326-331, 2008.

Magnetic fields (MFs) can affect biological systems by increasing the release of free radicals that are able to alter cell defense systems and breakdown tissue homeostasis. In the present study, the effects of extremely low frequency (ELF) electromagnetic fields (EMF) were investigated on free radical levels, natural antioxidant systems and respiratory burst system activities in heart and liver tissues of guinea pigs exposed to 50 Hz MFs of 1, 2 and 3 mT for 4 h/day and 8 h/day for 5 days by measuring malondialdehyde (MDA), nitric oxide (NO), glutathione (GSH) levels and myeloperoxidase (MPO) activity. A total of sixty-two male guinea pigs, 10-12 weeks old were studied in seven groups as control and exposure groups: Group I (control), II (1 mT, 4 h/day), III (1 mT, 8 h/day), IV (2 mT, 4 h/day), V (2 mT, 8 h/day), VI (3 mT, 4 h/day), and VII (3 mT, 8 h/day). Controls were kept under the same conditions without any exposure to MF. MDA levels increased in liver in groups II and IV, but decreased in group VII for both liver and heart tissues. NOx levels declined in heart in groups II and III and in liver in groups III, V, and VI, but increased in liver in group VII. GSH levels increased in heart in groups II, IV, V, and in liver in groups V and VI and VI, but decreased in groups II and IV in liver. MPO activity decreased in liver in groups III, IV, VI and VII with respect to controls and in heart tissues in groups II, III and IV; however, there was a significant increase MPO activity in heart in group VII. From the results, it can be concluded that the intensity and exposure duration of MFs are among the effective conditions on the formation of free radicals and behaviour of antioxidant enzymes.

(E) (VT, AE, IFR) Chen Y, Hong L, Zeng Y, Shen Y, Zeng Q. Power frequency magnetic fields induced reactive oxygen species-related autophagy in mouse embryonic fibroblasts. Int J Biochem Cell Biol. 57:108-114, 2014.

Power frequency magnetic fields (PFMF) have been reported to affect several cellular functions, such as cell proliferation and apoptosis. In this study, we investigated the effects of PFMF on mouse embryonic fibroblasts (MEF) autophagy. After cells were exposed to 50 Hz PFMF at 2 mT for 0.5 h, 2 h, 6 h, 12 h, and 24 h, we observed a significant increase in autophagic markers at 6 h, including (i) higher microtubule-associated protein 1 light chain 3-II (LC3-II), (ii) the increased formation of GFP-LC3 puncta, and (iii) increased numbers of autophagic vacuoles under transmission electron microscope. Moreover, we provide convincing evidence using chloroquine (CQ) that the increase of autophagic markers was the result of enhanced autophagic flux and not the suppression of lysosomal function. In a search for molecular mechanisms underlying PFMF-mediated autophagy, we observe that the autophagic process involved reactive oxygen species (ROS) and was independent of the mammalian target of rapamycin (mTOR) signaling pathway.

(E) (VT, CE, IFR) Chen Y, M
Menger MM, Braun BJ, Schweizer S, Linnemann C, Falldorf K, Ronniger M, Wang H, Histing T, Nussler AK, Ehnert S.

Modulation of Macrophage Activity by Pulsed Electromagnetic Fields in the Context of Fracture Healing. Bioengineering (Basel) 8(11):167, 2021.

Delayed fracture healing and fracture non-unions impose an enormous burden on individuals and society. Successful healing requires tight communication between immune cells and bone cells. Macrophages can be found in all healing phases. Due to their high plasticity and long life span, they represent good target cells for modulation. In the past, extremely low frequency pulsed electromagnet fields (ELF-PEMFs) have been shown to exert cell-specific effects depending on the field conditions. Thus, the aim was to identify the specific ELF-PEMFs able to modulate macrophage activity to indirectly promote mesenchymal stem/stromal cell (SCP-1 cells) function. After a blinded screening of 22 different ELF-PEMF, two fields (termed A and B) were further characterized as they diversely affected macrophage function. These two fields have similar fundamental frequencies (51.8 Hz and 52.3 Hz) but are emitted in different groups of pulses or rather send-pause intervals. Macrophages exposed to field A showed a pro-inflammatory function, represented by increased levels of phospho-Stat1 and CD86, the accumulation of ROS, and increased secretion of pro-inflammatory cytokines. In contrast, macrophages exposed to field B showed anti-inflammatory and pro-healing functions, represented by increased levels of Arginase I, increased secretion of anti-inflammatory cytokines, and growth factors are known to induce healing processes. The conditioned medium from macrophages exposed to both ELF-PEMFs favored the migration of SCP-1 cells, but the effect was stronger for field B. Furthermore, the conditioned medium from macrophages exposed to field B, but not to field A, stimulated the expression of extracellular matrix genes in SCP-1 cells, i.e., *COL1A1*, *FN1*, and *BGN*. In summary, our data show that specific ELF-PEMFs may affect immune cell function. Thus, knowing the specific ELF-PEMFs conditions and the underlying mechanisms bears great potential as an adjuvant treatment to modulate immune responses during pathologies, e.g., fracture healing.

(E) (VO, AE, IOD, DAO) Chen YB, Li J, Liu JY, Zeng LH, Wan Y, Li YR, Ren D, Guo GZ. Effect of Electromagnetic Pulses (EMP) on associative learning in mice and a preliminary study of mechanism. Int J Radiat Biol. 87(12):1147-1154, 2011.

PURPOSE: To investigate the effects of electromagnetic pulses (EMP) on associative learning in mice and test a preliminary mechanism for these effects. MATERIALS AND METHODS: A tapered parallel plate gigahertz transverse electromagnetic (GTEM) cell with a flared rectangular coaxial transmission line was used to expose male BALB/c mice to EMP (peak-intensity 400 kV/m, rise-time 10 ns, pulse-width 350 ns, 0.5 Hz and total 200 pulses). Concurrent sham-exposed mice were used as a control. Associative learning, oxidative stress in the brain, serum chemistry and the protective action of tocopherol monoglucoside (TMG) in mice were measured, respectively. RESULTS: (1) Twelve hour and 1 day post EMP exposure associative learning was reduced significantly compared with sham control ($p<0.05$) but recovered at 2 d post EMP exposure. (2) Compared with the sham control, lipid peroxidation of brain tissue and chemiluminescence (CL) intensity increased

significantly ($p<0.05$), while the activity of the antioxidant enzymes Superoxide Dismutase [SOD], Glutathione [GSH], Glutathione Peroxidase [GSH-Px], Catalase [CAT]) decreased significantly ($p<0.05$) at 3 h, 6 h, 12 h and 1 d post EMP exposure. All these parameters recovered at 2 d post EMP exposure. (3) No significant differences between the sham control group and EMP exposed group were observed in serum cholesterol and triglycerides. (4) Pretreatment of mice with TMG showed protective effects to EMP exposure. CONCLUSIONS: EMP exposure significantly decreased associative learning in mice and TMG acted as an effective protective agent from EMP exposure. This mechanism could involve an increase of oxidative stress in brain by EMP exposure

(E) (VT, AE, IX) Cheun BS, Yi SH, Baik KY, Lim JK, Yoo JS, Shin HW, Soh KS. Biophoton emission of MDCK cell with hydrogen peroxide and 60 Hz AC magnetic field. J Environ Biol. 28(4):735-740, 2007.

We studied biophoton characteristics of Madin-Darby canine kidney (MDCK) cells under the influence of H2O2 by employing a photomultiplier tube (PMT) and a fluorescence microscope. H2O2 was used for producing reactive oxygen species (ROS) in the measurement. Images from a fluorescence microscope show an increase of photon intensity emitted from the sample due to H2O2. By using a PMT we measured quantitative change in biophoton emission with application of H2O2 to the MDCK cell culture, found that the increase of the biophoton is dependent upon the amount of H2O2. The agreement between the results of the PMT and the fluorescence microscope suggests the possibility of quantitative measurement of the influence of ROS on living tissue or cell. In addition we applied a 60 Hz AC magnetic field on the cells to investigate the change in reaction between MDCK cell and ROS. It showed that a decay of chemiluminescence intensity has taken a different path following exposure to the magnetic field. As a result, the PMT measurement might be considered as a useful tool for studying biochemical characteristics in relation to ROS.

(E) (VT, AE, IFR, IOD, IAO) Chu LY, Lee JH, Nam YS, Lee YJ, Park WH, Lee BC, Kim D, Chung YH, Jeong JH. Extremely low frequency magnetic field induces oxidative stress in mouse cerebellum. Gen Physiol Biophys. 30(4):415-421, 2011.

We have investigated whether extremely low frequency magnetic field (ELF-MF) induces lipid peroxidation and reactive oxygen species in mouse cerebellum. After exposure to 60 Hz ELF-MF at 2.3 mT intensity for 3 hours, there was a significant increase in malondialdehyde level and hydroxyl radical. ELF-MF significantly induced concomitant increase in superoxide dismutase without alteration in glutathione peroxidase activity. While glutathione contents were not altered, ascorbic acid levels were significantly decreased by ELF-MF exposure. These results indicate that ELF-MF may induce oxidative stress in mouse cerebellum. However, the mechanism remains further to be characterized.

(E) (VO, AE, IFR) Chung YH, Lee YJ, Lee HS, Chung SJ, Lim CH, Oh KW, Sohn UD, Park ES, Jeong JH. Extremely low frequency magnetic field modulates the level of neurotransmitters. Korean J Physiol Pharmacol. 19(1):15-20, 2015.

This study was aimed to observe that extremely low frequency magnetic field (ELF-MF) may be relevant to changes of major neurotransmitters in rat brain. After the exposure to ELF-MF (60 Hz, 2.0 mT) for 2 or 5 days, we measured the levels of biogenic amines and their metabolites, amino acid neurotransmitters and nitric oxide (NO) in the cortex, striatum, thalamus, cerebellum and hippocampus. The exposure of ELF-MF for 2 or 5 days produced significant differences in norepinephrine and vanillyl mandelic acid in the striatum, thalamus, cerebellum and hippocampus. Significant increases in the levels of serotonin and 5-hydroxyindoleacetic acid were also observed in the striatum, thalamus or hippocampus. ELF-MF significantly increased the concentration of dopamine in the thalamus. ELF-MF tended to increase the levels of amino acid neurotransmitters such as glutamine, glycine and γ -aminobutyric acid in the striatum and thalamus, whereas it decreased the levels in the cortex, cerebellum and hippocampus. ELF-MF significantly increased NO concentration in the striatum, thalamus and hippocampus. The present study has demonstrated that exposure to ELF-MFs may evoke the changes in the levels of biogenic amines, amino acid and NO in the brain although the extent and property vary with the brain areas. However, the mechanisms remain further to be characterized.

(E) (VO, HU, CE, IAO) Cichoń N, Bijak M, Miller E, Saluk J. Extremely low frequency electromagnetic field (ELF-EMF) reduces oxidative stress and improves functional and psychological status in ischemic stroke patients. Bioelectromagnetics. 38(5):386-396, 2017a.

As a result of ischaemia/reperfusion, massive generation of reactive oxygen species occurs, followed by decreased activity of antioxidant enzymes. Extremely low frequency electromagnetic fields (ELF-EMF) can modulate oxidative stress, but there are no clinical antioxidant studies in brain stroke patients. The aim of our study was to investigate the effect of ELF-EMF on clinical and antioxidant status in post-stroke patients. Fifty-seven patients were divided into two groups: ELF-EMF and non-ELF-EMF. Both groups underwent the same 4-week rehabilitation program. Additionally, the ELF-EMF group was exposed to an ELF-EMF field of 40 Hz, 7 mT for 15 min/day for 4 weeks (5 days a week). The activity of catalase and superoxide dismutase was measured in hemolysates, and total antioxidant status (TAS) determined in plasma. Functional status was assessed before and after the series of treatments using Activities of Daily Living (ADL), Mini-Mental State Examination (MMSE), and Geriatric Depression Scale (GDS). Applied ELF-EMF significantly increased enzymatic antioxidant activity; however, TAS levels did not change in either group. Results show that ELF-EMF induced a significant improvement in functional (ADL) and mental (MMSE, GDS) status. Clinical parameters had positive correlation with the level of enzymatic antioxidant protection.

(E) (HU, CE, IFR) Cichoń N, Czarny P, Bijak M, Miller E, Śliwiński T, Szemraj J, Saluk-Bijak J. Benign Effect of Extremely Low-Frequency Electromagnetic Field on Brain Plasticity Assessed by Nitric Oxide Metabolism during Poststroke Rehabilitation. Oxid Med Cell Longev. 2017:2181942, 2017b.

Nitric oxide (NO) is one of the most important signal molecules, involved in both physiological and pathological processes. As a neurotransmitter in the central nervous system, NO regulates cerebral blood flow, neurogenesis, and synaptic plasticity. The aim of our study was to investigate the effect of the extremely low-frequency electromagnetic field (ELF-EMF) on generation and metabolism of NO, as a neurotransmitter, in the rehabilitation of poststroke patients. Forty-eight patients were divided into two groups: ELF-EMF and non-ELF-EMF. Both groups underwent the same 4-week rehabilitation program. Additionally, the ELF-EMF group was exposed to an extremely low-frequency electromagnetic field of 40 Hz, 7 mT, for 15 min/day. Levels of 3-nitrotyrosine, nitrate/nitrite, and TNFα in plasma samples were measured, and NOS2 expression was determined in whole blood samples. Functional status was evaluated before and after a series of treatments, using the Activity Daily Living, Geriatric Depression Scale, and Mini-Mental State Examination. We observed that application of ELF-EMF significantly increased 3-nitrotyrosine and nitrate/nitrite levels, while expression of NOS2 was insignificantly decreased in both groups. The results also show that ELF-EMF treatments improved functional and mental status. We conclude that ELF-EMF therapy is capable of promoting recovery in poststroke patients.

(E) (HU, CE, IAO) Cichon N, Bijak M, Synowiec E, Miller E, Sliwinski T, Saluk-Bijak J. Modulation of antioxidant enzyme gene expression by extremely low frequency electromagnetic field in post-stroke patients. Scand J Clin Lab Invest. 78(7-8):626-631, 2018a.

Oxidative stress plays the most important role in the pathogenesis of stroke. Extremely low frequency electromagnetic field (ELF-EMF) therapy may be complementary in post-stroke therapy, as it modulates oxidative stress. The aim of this study was to evaluate the messenger ribonucleic acid (mRNA) levels of certain antioxidant genes in post-stroke patients given ELF-EMF therapy. Forty-eight post-stroke patients were divided into two groups: an ELF-EMF group and a non-ELF-EMF group. All patients underwent the same program of physical therapy, but the ELF-EMF group was additionally given ELF-EMF treatment. In order to determine the level of gene expression, we evaluated the level of mRNA expression of catalase, superoxide dismutase, and glutathione peroxidase. We observed that after ELF-EMF therapy, the mRNA expression of the studied genes (CAT, SOD1, SOD2, GPx1, and GPx4) significantly increased, which enhanced the antioxidant defence of the body. ELF-EMF therapy intensifies the endogenous antioxidant system by increasing the mRNA expression of genes encoding antioxidant enzymes and enhances the effectiveness of post-stroke patient therapy.

(E) (HU, CE, DOD) Cichoń N, Rzeźnicka P, Bijak M, Miller E , Miller S, Saluk J. Extremely low frequency electromagnetic field reduces oxidative stress during the rehabilitation of post-acute stroke patients. Adv Clin Exp Med. 27(9):1285-1293, 2018b.

Background: One of the therapeutic methods used in stroke rehabilitation is magnetotherapy using extremely low frequency and variable pulse shape electromagnetic field (ELF-EMF). **Objectives:** The aim of our study was to investigate the effect of magnetotherapy on the condition of postacute stroke patients, as measured by plasma oxidative stress markers and clinical parameters which show the progress of rehabilitation. **Material and methods:** The selected 57 post-stroke patients were divided into 2 groups, those with ELFEMF therapy and those without. The level of oxidative stress in the plasma was estimated by typical markers: thiobarbituric acid reactive substances (TBARS), thiol groups, and carbonyl groups. The effect of ELF-EMF on the course of the patients' rehabilitation following ischemic stroke was evaluated with the use of scales of physical activity and mental state: Activities of Daily Living (ADL), Mini-Mental State Examination (MMSE) and Geriatric Depression Scale (GDS). **Results:** Our comparative analysis showed that all parameters of oxidative stress are significantly reduced during rehabilitation using ELF-EMF, compared to the control group rehabilitated only by kinesiotherapy. We also recorded much higher therapeutic benefits using magnetotherapy, which revealed a significant improvement of clinimetric parameters. **Conclusions:** The ELF-EMF therapy meaningfully improves the overall condition of patients through a decrease of oxidative stress markers and it significantly affects the psychophysical abilities of patients after stroke. The change in carbonyl group level correlates with the change in the degree of physical and mental disability; therefore, it could be a marker for the effectiveness of rehabilitation.

(E) (VO, CE, IAO, DAO) Ciejka EB, Goraca A. The influence of low-frequency magnetic field on plasma antioxidant capacity and heart rate. Wiad Lek. 62(2):81-86, 2009.

INTRODUCTION: Low-frequency magnetic field is widely applied as magnetotherapy in physiotherapeutic treatment. Recognition of positive and negative effects of the magnetic field has been the subject of numerous studies. Experimental studies concern, among others, the effect of this field on the heart rate and plasma antioxidant capacity. The aim of the study was to check whether a time-variable magnetic field of constant frequency and induction affects the heart rate and plasma antioxidant capacity. MATERIAL AND METHODS: The tests were performed on Spraque-Dawley rats exposed to the magnetic field of the following parameters: frequency - 40 Hz, induction - 7 mT, time of exposure - 30 and 60 minutes. The measurements of ECG and plasma antioxidant capacity expressed in the number of reduced iron ions were performed on experimental animals: before, after a single exposure and after 14 days of exposure. RESULTS: A significant decrease of the heart rate was observed after 14 days of exposure. A variable magnetic field of the parameters: frequency - 40 Hz, induction - 7 mT and exposure time of 14 days caused an increase of the organism antioxidant defence, whereas a variable magnetic field of the frequency of 40 Hz, induction - 7 mT and exposure time 60 minutes for 14 days caused a significant decrease of the organism antioxidant defence. CONCLUSIONS: The exposure time affects heart rate, plasma antioxidant capacity and the organism defense ability against free radicals.

(E) (VO, CE, IFR) Ciejka E, Skibska B, Kleniewska P, Goraca A. [Influence of low frequency magnetic field on chosen parameters of oxidative stress in rat's muscles]. Pol Merkur Lekarski. 29(174):361-364, 2010. [Article in Polish]

Free radicals are atoms, molecules or their fragments, which excess leads to the development of the oxidative stress, which is caused of many neoplasmic, neurodegenerative, inflammatory diseases and aging the organism. The main of exogenous sources of free radicals are among others: industrial pollution, tobacco smoke, ionizing radiation, ultrasound and magnetic field. The low magnetic field is applied in the physician therapy. The aim of this study was to evaluate the influence of low magnetic field on the parameters of oxidative stress in rat's muscles. **MATERIALS AND METHODS:** Thirty male rats, weight of 280-300 g were randomly divided into three experimental groups: control I and treatment II and III (ELFMF-exposed), each containing seven animals. Animals in treat group II were exposed to 40 Hz, 7 mT for 0.5 h/day for 14 days (this kind of the ELFMF is mostly use in magnetotherapy) while, group III was exposed to 40 Hz, 7 mT for 1 h/day for 14 days. Control rats were in separate room without exposing to ELFMF. Immediately after the last exposure, the part of muscles was taken under pentobarbital anaesthesia. The effects of exposure to ELFMF on oxidative states were assessed on the measurements of concentration of -SH group, H2O2, and the concentration of proteins in muscles homogenates. **RESULTS:** Exposure to ELFMF: 40 Hz, 7 mT, 30 and 60 min/day used for 2 weeks caused significant increase in -SH group concentration and decrease of the protein concentration in the muscles homogenates. **CONCLUSION:** Low magnetic field used in magnetotherapy causes the significant changes of the generating the reactive forms of oxygen in the muscles which depend on the parameters of low magnetic field.

(E) (VO, CE, IOD) Ciejka E, Kleniewska P, Skibska B, Goraca A. Effects of extremely low frequency magnetic field on oxidative balance in brain of rats. J Physiol Pharmacol. 62(6):657-661, 2011.

Extremely low frequency magnetic field (ELF-MF) may result in oxidative DNA damage and lipid peroxidation with an ultimate effect on a number of systemic disturbances and cell death. The aim of the study is to assess the effect of ELF-MF parameters most frequently used in magnetotherapy on reactive oxygen species generation (ROS) in brain tissue of experimental animals depending on the time of exposure to this field. The research material included adult male Sprague-Dawley rats, aged 3-4 months. The animals were divided into 3 groups: I - control (shame) group; II - exposed to the following parameters of the magnetic field: 7 mT, 40 Hz, 30 min/day, 10 days; III - exposed to the ELF-MF parameters of 7 mT, 40 Hz, 60 min/day, 10 days. The selected parameters of oxidative stress: thiobarbituric acid reactive substances (TBARS), hydrogen peroxide (H(2)O(2)), total free sulphydryl groups (-SH groups) and protein in brain homogenates were measured after the exposure of rats to the magnetic field. ELF-MF parameters of 7 mT, 40 Hz, 30 min/day for 10 days caused a significant increase in lipid peroxidation and insignificant increase in H(2)O(2) and free -SH groups. The same ELF-MF parameters but applied for 60 min/day caused a significant increase in free -SH groups and protein concentration in the brain homogenates indicating the adaptive mechanism. The study has shown that ELF-MF applied for 30 min/day for 10 days

can affect free radical generation in the brain. Prolongation of the exposure to ELF-MF (60/min/day) caused adaptation to this field. The effect of ELF-MF irradiation on oxidative stress parameters depends on the time of animal exposure to magnetic field.

(E) (VO, CE, IAO) Ciejka E, Jakubowska E, Zelechowska P, Huk-Kolega H, Kowalczyk A, Goraca A. [Effect of extremely low frequency magnetic field on glutathione in rat muscles]. Med Pr. 65(3):343-349, 2014. [Article in Polish]

BACKGROUND: Free radicals (FR) are atoms, molecules or their fragments. Their excess leads to the development of oxidizing stress, the cause of many neoplastic, neurodegenerative and inflammatory diseases, and aging of the organism. Industrial pollution, tobacco smoke, ionizing radiation, ultrasound and magnetic field are the major FR exogenous sources. The low frequency magnetic field is still more commonly applied in the physical therapy. The aim of the presented study was to evaluate the effect of extremely low frequency magnetic field used in the magnetotherapy on the level of total glutathione, oxidized and reduced, and the redox state of the skeletal muscle cells, depending on the duration of exposure to magnetic field. MATERIAL AND METHODS: The male rats, weight of 280-300 g, were randomly devided into 3 experimental groups: controls (group I) and treatment groups exposed to extremely low frequency magnetic field (ELF-MF) (group II exposed to 40 Hz, 7 mT for 0.5 h/day for 14 days and group III exposed to 40 Hz, 7 mT for 1 h/day for 14 days). Control rats were kept in a separate room not exposed to extremely low frequency magnetic field. Immediately after the last exposure, part of muscles was taken under pentobarbital anesthesia. Total glutathione, oxidized and reduced, and the redox state in the muscle tissue of animals were determined after exposure to magnetic fields. RESULTS: Exposure to low magnetic field: 40 Hz, 7 mT for 30 min/day and 60 min/day for 2 weeks significantly increased the total glutathione levels in the skeletal muscle compared to the control group ($p < 0.001$). CONCLUSIONS: Exposure to magnetic fields used in the magnetic therapy plays an important role in the development of adaptive mechanisms responsible for maintaining the oxidation-reduction balance in the body and depends on exposure duration.

(E) (VT, CE, IFR) Cios A, Ciepielak M, Stankiewicz W, Szymański L. The Influence of the Extremely Low Frequency Electromagnetic Field on Clear Cell Renal Carcinoma. Int J Mol Sci 2021;22(3):1342.

The development of new technologies and industry is conducive to the increase in the number and variety of electromagnetic field (EMF) sources in our environment. The main sources of EMF are high-voltage lines, household appliances, audio/video devices, mobile phones, radio stations, and radar devices. In the growing use of electronic devices, scientists are increasingly interested in the effects of EMF on human health. Even though many studies on the effects of EMF have already been carried out, none of them has shown a significant effect on mammals, including humans. Moreover, it is not entirely clear how EMF influences cell behavior. The International Agency for Research on Cancer on 31 May 2011, classified PEM as a possible carcinogenic factor. This study aimed to investigate the effect of the electromagnetic field on morphological and functional changes in clear cell renal carcinoma. The research was carried out on in vitro cultures of four cell lines: HEK293, 786-O 769-P, and Caki1. The results of the research showed that the

EMF of low frequency had a slight effect on the viability of cells. EMF, which induced cell arrest in the G1 phase, increased the number of early apoptotic cells and decreased the number of viable cells in the 786-O line. EMF did not affect the proliferation and viability of HEK293 cells. Extreme low-frequency EMF (ELF-EMF) also showed an inhibitory effect on the migration and metastatic properties of clear cell kidney cancer cells. Moreover, shortly after the end of ELF-EMF exposure, significant increases in ROS levels were observed in all tested cell lines. As part of the work, it was shown that low-frequency EMF shows an inhibitory effect on the proliferation of primary cancer cells, diminishing their migratory, invasive, and metastatic abilities. It also increases the apoptosis of cancer cells and the amount of reactive oxygen species. Based on the results of our research, we want to point up that the effect of ELF-EMF depends on a specific metabolic state or at a specific stage in the cell cycle of the cells under study.

(E) (VO, CE, DFR, DOD, IAO, IX) Coballase-Urrutia E, Navarro L, Ortiz JL, Verdugo-Díaz L, Gallardo JM, Hernández ME, Estrada-Rojo F. Static magnetic fields modulate the response of different oxidative stress markers in a restraint stress model animal. Biomed Res Int. 2018:3960408, 2018.

Stress is a state of vulnerable homeostasis that alters the physiological and behavioral responses. Stress induces oxidative damage in several organs including the brain, liver, kidney, stomach, and heart. Preliminary findings suggested that the magnetic stimulation could accelerate the healing processes and has been an effective complementary therapy in different pathologies. However, the mechanism of action of static magnetic fields (SMFs) is not well understood. In this study, we demonstrated the effects of static magnetic fields (0.8 mT) in a restraint stressed animal model, focusing on changes in different markers of oxidative damage. A significant increase in the plasma levels of nitric oxide (NO), malondialdehyde (MDA), and advanced oxidation protein products (AOPP), and a decrease in superoxide dismutase (SOD), glutathione (GSH), and glycation end products (AGEs) were observed in restraint stress model. Exposure to SMFs over 5 days (30, 60, and 240 min/day) caused a decrease in the NO, MDA, AGEs, and AOPP levels; in contrast, the SOD and GSH levels increased. The response to SMFs was time-dependent. Thus, we proposed that exposure to weak-intensity SMFs could offer a complementary therapy by attenuating oxidative stress. Our results provided a new perspective in health studies, particularly in the context of oxidative stress.

Consales C, Merla C, Marino C, Benassi B. Electromagnetic fields, oxidative stress, and neurodegeneration. Int J Cell Biol. 2012:683897, 2012. (Review)

Electromagnetic fields (EMFs) originating both from both natural and manmade sources permeate our environment. As people are continuously exposed to EMFs in everyday life, it is a matter of great debate whether they can be harmful to human health. On the basis of two decades of epidemiological studies, an increased risk for childhood leukemia

associated with Extremely Low Frequency fields has been consistently assessed, inducing the International Agency for Research on Cancer to insert them in the 2B section of carcinogens in 2001. EMFs interaction with biological systems may cause oxidative stress under certain circumstances. Since free radicals are essential for brain physiological processes and pathological degeneration, research focusing on the possible influence of the EMFs-driven oxidative stress is still in progress, especially in the light of recent studies suggesting that EMFs may contribute to the etiology of neurodegenerative disorders. This review synthesizes the emerging evidences about this topic, highlighting the wide data uncertainty that still characterizes the EMFs effect on oxidative stress modulation, as both pro-oxidant and neuroprotective effects have been documented. Care should be taken to avoid methodological limitations and to determine the patho-physiological relevance of any alteration found in EMFs-exposed biological system.

(E) (VT, AE, IFR) Consales C, Cirotti C, Filomeni G, Panatta M, Butera A, Merla C, Lopresto V, Pinto R, Marino C, Benassi B. Fifty-hertz magnetic field affects the epigenetic modulation of the miR-34b/c in neuronal cells. Mol Neurobiol. 55(7):5698-5718, 2018.

The exposure to extremely low-frequency magnetic fields (ELF-MFs) has been associated to increased risk of neurodegenerative diseases, although the underlying molecular mechanisms are still undefined. Since epigenetic modulation has been recently encountered among the key events leading to neuronal degeneration, we here aimed at assessing if the control of gene expression mediated by miRNAs, namely miRs-34, has any roles in driving neuronal cell response to 50-Hz (1 mT) magnetic field in vitro. We demonstrate that ELF-MFs drive an early reduction of the expression level of miR-34b and miR-34c in SH-SY5Y human neuroblastoma cells, as well as in mouse primary cortical neurons, by affecting the transcription of the common pri-miR-34. This modulation is not p53 dependent, but attributable to the hyper-methylation of the CpG island mapping within the miR-34b/c promoter. Incubation with N-acetyl-l-cysteine or glutathione ethyl-ester fails to restore miR-34b/c expression, suggesting that miRs-34 are not responsive to ELF-MF-induced oxidative stress. By contrast, we show that miRs-34 control reactive oxygen species production and affect mitochondrial oxidative stress triggered by ELF-MFs, likely by modulating mitochondria-related miR-34 targets identified by in silico analysis. We finally demonstrate that ELF-MFs alter the expression of the α-synuclein, which is specifically stimulated upon ELF-MFs exposure via both direct miR-34 targeting and oxidative stress. Altogether, our data highlight the potential of the ELF-MFs to tune redox homeostasis and epigenetic control of gene expression in vitro and shed light on the possible mechanism(s) producing detrimental effects and predisposing neurons to degeneration.

(NE) (IV, AE) Consales C, Panatta M, Butera A, Filomeni G, Merla C, Carrì MT, Marino C, Benassi B. 50-Hz magnetic field impairs the expression of iron-related genes in the in vitro SOD1^{G93A} model of amyotrophic lateral sclerosis. Int J Radiat Biol. 95(3):368-377, 2019.

PURPOSE: we characterized the response to the extremely low frequency magnetic field (ELF-MF) in an in vitro model of familial Amyotrophic Lateral Sclerosis (fALS), carrying two mutant variants of the superoxide dismutase 1 (SOD1) gene. MATERIALS AND METHODS: SH-SY5Y human neuroblastoma cells, stably over-expressing the wild type, the G93A or the H46R mutant SOD1 cDNA, were exposed to either the ELF-MF (50 Hz, 1 mT) or the sham control field, up to 72 hours. Analysis of i) viability, proliferation and apoptosis, ii) reactive oxygen species generation, and iii) assessment of the iron metabolism, were carried out in all clones in response to the MF exposure. RESULTS: we report that 50-Hz MF exposure induces: i) no change in proliferation and viability; ii) no modulation of the intracellular superoxide and H_2O_2 levels; iii) a significant deregulation in the expression of iron-related genes IRP1, MFRN1 and TfR1, this evidence being exclusive for the $SOD1^{G93A}$ clone and associated with a slight ($P = 0.0512$) difference in the total iron content. CONCLUSIONS: 50-Hz MF affects iron homeostasis in the in vitro $SOD1^{G93A}$ ALS model.

(E) (VO, CE, IFR, IOD) Coşkun S, Balabanli B, Canseven A, Seyhan N. Effects of continuous and intermittent magnetic fields on oxidative parameters in vivo. Neurochem Res. 34(2):238-243, 2009.

Continuous and intermittent 50 Hz, 1.5 mT magnetic field with the exposure period of 4 h/day for 4 days was used to investigate its possible effect on adult guinea pigs. Tissues and plasma specimens were assessed by biochemical parameters. Malondialdehyde (MDA), glutathione (GSH), nitric oxide (NO) levels and myeloperoxidase activity (MPO) were examined in plasma, liver and brain tissues. All parameters were determined by spectrophotometer. While intermittent magnetic field was effective on plasma lipid peroxidation, continuous magnetic field was found to be effective on plasma MPO activity and NO levels. Augmentation of lipid peroxidation was also observed in liver tissue both intermittent and continuous magnetic field exposures. These results indicate that both the intermittent and continuous magnetic field exposures affect various tissues in a distinct manner because of having different tissue antioxidant status and responses.

(E) (VO, CE, IOD, DAO) Cui Y, Ge Z, Rizak JD, Zhai C, Zhou Z, Gong S, Che Y. Deficits in water maze performance and oxidative stress in the hippocampus and striatum induced by extremely low frequency magnetic field exposure. PLoS One. 7(5):e32196, 2012.

The exposures to extremely low frequency magnetic field (ELF-MF) in our environment have dramatically increased. Epidemiological studies suggest that there is a possible association between ELF-MF exposure and increased risks of cardiovascular disease, cancers and neurodegenerative disorders. Animal studies show that ELF-MF exposure may interfere with the activity of brain cells, generate behavioral and cognitive disturbances, and produce deficits in attention, perception and spatial learning. Although, many research efforts have been focused on the interaction between ELF-MF exposure and the central nervous system, the mechanism of interaction is still unknown. In this study, we examined the effects of ELF-MF exposure on learning in mice using two water maze tasks and on some parameters indicative of oxidative stress in the hippocampus and striatum. We found that ELF-MF exposure (1 mT, 50 Hz) induced serious oxidative stress in the hippocampus and striatum and impaired hippocampal-dependent spatial learning and striatum-dependent habit learning. This study provides evidence for the association between the impairment of learning and the oxidative stress in hippocampus and striatum induced by ELF-MF exposure.

(E) (VT, AE, DFR) da Costa CC, Martins LAM, Koth AP, Ramos JMO, Guma FTCR, de Oliveira CM, Pedra NS, Fischer G, Helena ES, Gioda CR, Sanches PRS, Junior ASV, Soares MSP, Spanevello RM, Gamaro GD, de Souza ICC. Static Magnetic Stimulation Induces Changes in the Oxidative Status and Cell Viability Parameters in a Primary Culture Model of Astrocytes. Cell Biochem Biophys. 79(4):873-885, 2021.

Astrocytes play an important role in the central nervous system function and may contribute to brain plasticity response during static magnetic fields (SMF) brain therapy. However, most studies evaluate SMF stimulation in brain plasticity while few studies evaluate the consequences of SMF at the cellular level. Thus, we here evaluate the effects of SMF at 305 mT (medium-intensity) in a primary culture of healthy/normal cortical astrocytes obtained from neonatal (1 to 2-day-old) Wistar rats. After reaching confluence, cells were daily subjected to SMF stimulation for 5 min, 15 min, 30 min, and 40 min during 7 consecutive days. Oxidative stress parameters, cell cycle, cell viability, and mitochondrial function were analyzed. The antioxidant capacity was reduced in groups stimulated for 5 and 40 min. Although no difference was observed in the enzymatic activity of superoxide dismutase and catalase or the total thiol content, lipid peroxidation was increased in all stimulated groups. The cell cycle was changed after 40 min of SMF stimulation while 15, 30, and 40 min led cells to death by necrosis. Mitochondrial function was reduced after SMF stimulation, although imaging analysis did not reveal substantial changes in the mitochondrial network. Results mainly revealed that SMF compromised healthy astrocytes' oxidative status and viability. This finding reveals how important is to understand the SMF stimulation at the cellular level since this therapeutic approach has been largely used against neurological and psychiatric diseases.

(NE) (VT, AE) de Groot MW, Kock MD, Westerink RH. Assessment of the neurotoxic potential of exposure to 50 Hz extremely low frequency electromagnetic fields (ELF-EMF) in naïve and chemically-stressed PC12 cells. Neurotoxicology. 44:358-364, 2014.

Increasing exposure to extremely low frequency electromagnetic fields (ELF-EMF), generated by power lines and electric appliances, raises concern about potential adverse health effects of ELF-EMF. The central nervous system is expected to be particularly vulnerable to ELF-EMF as its function strongly depends on electrical excitability. We therefore investigated effects of acute (30min) and sub-chronic (48h) exposure to 50Hz ELF-EMF on naïve and chemically-stressed pheochromocytoma (PC12) cells. The latter have higher levels of iron and/or reactive oxygen species (ROS) and display increased vulnerability to environmental insults. Effects of ELF-EMF on Ca^{2+}-homeostasis, ROS production and membrane integrity were assessed using Fura-2 single cell fluorescence microscopy, H_2-DCFDA and CFDA assays, respectively. Our data demonstrate that acute exposure of naïve PC12 cells to 50 Hz ELF-EMF up to 1000 μT fails to affect basal or depolarization-evoked $[Ca^{2+}]_i$. Moreover, sub-chronic ELF-EMF exposure up to 1000μT has no consistent effects on Ca^{2+}-homeostasis in naïve PC12 cells and does not affect ROS production and membrane integrity. Notably, in chemically-stressed PC12 cells both acute and sub-chronic ELF-EMF exposure also failed to exert consistent effects on Ca^{2+}-homeostasis, ROS production and membrane integrity. Our combined findings thus indicate that exposure to 50Hz ELF-EMF up to 1000 μT, i.e. 10,000 times above background exposure, does not induce neurotoxic effects in vitro, neither in naïve nor in chemically-stressed PC12 cells. Though our data require confirmation, e.g. in developing neuronal cells in vitro or (developing) animals, it appears that the neurotoxic risk of ELF-EMF exposure is limited.

(NE) (VT, AE, IX) De Mattei M, Pasello M, Pellati A, Stabellini G, Massari L, Gemmati D, Caruso A. Effects of electromagnetic fields on proteoglycan metabolism of bovine articular cartilage explants. Connect Tissue Res. 44(3-4):154-159, 2003.

Electromagnetic field (EMF) exposure has been proposed for the treatment of osteoarthritis. In this study, we investigated the effects of EMF (75 Hz, 2,3 mT) on proteoglycan (PG) metabolism of bovine articular cartilage explants cultured in vitro, both under basal conditions and in the presence of interleukin-1beta (IL-1beta) in the culture medium. Proteoglycan synthesis and the residual PG tissue content resulted significantly higher in EMF-exposed explants than in controls, whereas no effect was observed on PG release and nitric oxide (NO) production. IL-1beta induced both a reduction in PG synthesis and an increase in PG release, related to a strong stimulation of NO production, which resulted in a net loss of tissue PG content. In IL-1beta-treated explants, EMF increased PG synthesis, whereas in spite of a slight stimulation of NO production EMF did not modify PG release. This resulted in the residual PG tissue content being maintained at the control level. In both experimental conditions, the effects of EMF were associated with an increase in lactate production. The results of our study show that EMFs are able to promote anabolic activities and PG synthesis in bovine articular cartilage explants. This effect also is maintained in the presence of IL-1beta, thus counteracting the catabolic activity of the cytokine. Altogether, these data suggest that EMF exposure exerts a chondroprotective effect on articular cartilage in vitro.

(E)(VT, AE, IFR, IAO) De Nicola M, Cordisco S, Cerella C, Albertini MC, D'Alessio M, Accorsi A, Bergamaschi A, Magrini A, Ghibelli L. Magnetic fields protect from apoptosis via redox alteration. Ann N Y Acad Sci. 1090:59-68, 2006.

Magnetic fields (MFs) are receiving much attention in basic research due to their emerging ability to alter intracellular signaling. We show here that static MFs with intensity of 6 mT significantly alter the intracellular redox balance of U937 cells. A strong increase of reactive oxygen species (ROS) and a decrease of glutathione (GSH) intracellular levels were found after 2 h of MF exposure and maintained thereafter. We found that also other types of MFs, such as extremely-low-frequency (ELF) MFs affect intracellular GSH starting from a threshold at 0.09 mT. We previously reported that static MFs in the intensity range of 0.3-60 mT reduce apoptosis induced by damaging agents (Fanelli et al., 1998). Here, we show that ELF-MFs are also able to protect U937 from apoptosis. Interestingly, this ability is limited to the ELF intensities able to alter redox equilibrium, indicating a link between MF's antiapoptotic effect and the MF alteration of intracellular redox balance. This suggests that MF-produced redox alterations may be part of the signaling pathway leading to apoptosis antagonism. Thus, we tested whether MFs may still exert an antiapoptotic action in cells where the redox state was artificially altered in both directions, that is, by creating an oxidative (via GSH depletion with BSO) or a reducing (with DTT) cellular environment. In both instances, MFs fail to affect apoptosis. Thus, a correct intracellular redox state is required in order for MFs to exert their antiapoptotic effect.

(E) (VT, VO, AE, IOD, DAO, IX) Deng B, Xu H, Zhang J, Wang J, Han LC, Li LY, Wu GL, Hou YN, Guo GZ, Wang Q, Sang HF, Xu LX. Neuroprotective effects of sevoflurane against electromagnetic pulse-induced brain injury through inhibition of neuronal oxidative stress and apoptosis. PLoS One. 9(3):e91019, 2014.

Electromagnetic pulse (EMP) causes central nervous system damage and neurobehavioral disorders, and sevoflurane protects the brain from ischemic injury. We investigated the effects of sevoflurane on EMP-induced brain injury. Rats were exposed to EMP and immediately treated with sevoflurane. The protective effects of sevoflurane were assessed by Nissl staining, Fluoro-Jade C staining and electron microscopy. The neurobehavioral effects were assessed using the open-field test and the Morris water maze. Finally, primary cerebral cortical neurons were exposed to EMP and incubated with different concentration of sevoflurane. The cellular viability, lactate dehydrogenase (LDH) release, superoxide dismutase (SOD) activity and malondialdehyde (MDA) level were assayed. TUNEL staining was performed, and the expression of apoptotic markers was determined. The cerebral cortexes of EMP-exposed rats presented neuronal abnormalities. Sevoflurane alleviated these effects, as well as the learning and memory deficits caused by EMP exposure. In vitro, cell viability was reduced and LDH release was increased after EMP exposure; treatment with sevoflurane ameliorated these effects. Additionally, sevoflurane increased SOD activity, decreased MDA levels and alleviated neuronal apoptosis by regulating the expression of cleaved caspase-3, Bax and Bcl-2. These findings demonstrate that Sevoflurane conferred neuroprotective effects against EMP radiation-induced brain damage by inhibiting neuronal oxidative stress and apoptosis.

(E) (VO, CE, IOD, DAO) Deng Y, Zhang Y, Jia S, Liu J, Liu Y, Xu W, Liu L. Effects of aluminum and extremely low frequency electromagnetic radiation on oxidative stress and memory in brain of mice. Biol Trace Elem Res. 156(1-3):243-252, 2013.

This study was aimed to investigate the effect of aluminum and extremely low-frequency magnetic fields (ELF-MF) on oxidative stress and memory of SPF Kunming mice. Sixty male SPF Kunming mice were divided randomly into four groups: control group, ELF-MF group (2 mT, 4 h/day), load aluminum group (200 mg aluminum/kg, 0.1 ml/10 g), and ELF-MF + aluminum group (2 mT, 4 h/day, 200 mg aluminum/kg). After 8 weeks of treatment, the mice of three experiment groups (ELF-MF group, load aluminum group, and ELF-MF + aluminum group) exhibited firstly the learning memory impairment, appearing that the escaping latency to the platform was prolonged and percentage in the platform quadrant was reduced in the Morris water maze (MWM) task. Secondly are the pathologic abnormalities including neuronal cell loss and overexpression of phosphorylated tau protein in the hippocampus and cerebral cortex. On the other hand, the markers of oxidative stress were determined in mice brain and serum. The results showed a statistically significant decrease in superoxide dismutase activity and increase in the levels of malondialdehyde in the ELF-MF group ($P < 0.05$ or $P < 0.01$), load aluminum group ($P < 0.01$), and ELF-MF + aluminum group ($P < 0.01$). However, the treatment with ELF-MF + aluminum induced no more damage than ELF-MF and aluminum did, respectively. In conclusion, both aluminum and ELF-MF could impact on learning memory and pro-oxidative function in Kunming mice. However, there was no evidence of any association between ELF-MF exposure with aluminum loading.

(E) (VO, CE, IOD) Di G, Xiang J, Dong L, Wu J. Testosterone synthesis in testicular Leydig cells after long-term exposure to a static electric field (SEF). Toxicology 2021;458:152836.

China's clean energy and resources are mainly located in the west and north while electric load center is concentrated in the middle and east. Thus, these resources and energy need to be converted into electrical energy in situ and transported to electric load center through ultra-high voltage direct current (UHVDC) transmissions. China has built 25,000 km UHVDC transmission lines of 800 kV and 1100 kV, near which the impact of electric field on health has attracted public attention. Previous studies showed that time-varying electromagnetic field exposure could disturb testosterone secretion. To study the effect of non-time-varying electric field caused by direct current transmission lines on testosterone synthesis, male ICR mice were continually (24 h/d) exposed to static electric field of 56.3 ± 1.4 kV/m. Results showed that on the 3rd day of exposure and on the 7th day after ceasing the exposure of 28 d, serum testosterone level and testicular oxidative stress indicators didn't change significantly. On the 28th day of exposure, serum testosterone levels, testicular glutathione peroxidase (GSH-Px) activity, the mRNA and protein levels of testicular StAR, PBR, CYP11A1 decreased significantly, and testicular malondialdehyde (MDA) content increased significantly. Meanwhile, electron-dense edges and vacuolation appeared in lipid droplets of Leydig cells. The gap between inner mitochondrial membrane (IMM) and outer mitochondrial membrane (OMM) enlarged, which would cause the swelling of mitochondria, the rupture and deficiency of mitochondrial membranes. Analysis showed that testicular oxidative stress could induce the damage of mitochondrial structure in Leydig cells, which would decrease the rate of cholesterol transport from cytoplasm to mitochondria. Since cholesterol is the necessary precursor of testosterone synthesis, testosterone synthesis was inhibited. The decrease of the mRNA and protein expression

levels of StAR and PBR in testes could diminish the cholesterol transported from OMM to IMM. The decrease of the mRNA and protein expression levels of CYP11A1 could reduce the pregnenolone required in testosterone synthesis and inhibit testosterone synthesis consequently

(E) (VT, AE, DRF) Di S, Tian Z, Qian A, Li J, Wu J, Wang Z, Zhang D, Yin D, Brandi ML, Shang P. Large gradient high magnetic field affects FLG29.1 cells differentiation to form osteoclast-like cells. Int J Radiat Biol. 88(11):806-813, 2012.

PURPOSE: We aimed to investigate the effects of different apparent gravities (μ g, 1 g and 2 g) produced by large gradient high magnetic field (LGHMF) on human preosteoclast FLG29.1 cells. MATERIALS AND METHODS: FLG29.1 cells were cultured in Roswell Park Memorial Institute (RPMI)-1640 medium. Cells were exposed to LGHMF for 72 h. On culture day 1, 2, 3, cell proliferation was detected by 3-(4,5)-dimethylthiahi-azo (-z-y1)-3,5-di-phenytetrazoliumromide (MTT) method. On day 3, cell apoptosis and necrosis were assayed by Hoechst and propidium iodide (PI) staining. After cells were exposed to LGHMF for 72 h with the induction of 12-o-tetradecanoylphorbol 13-acetate (TPA), Tartrate-Resistant Acid Phosphatase (TRAP) positive cells and nitric oxide (NO) release were detected by TRAP staining and Griess method, respectively. Intracellular TRAP activity was measured using nitrophenylphosphate (pNPP) as the substrate. RESULTS: MTT detection revealed that compared to control, FLG 29.1 cell proliferation in the μ g and 2 g groups were promoted. However, there is no obvious difference between the 1 g and control groups. Hoechst-PI staining showed that LGHMF promoted cell apoptosis and necrosis, especially in the 2 g group. Exposure to LGHMF inhibited the NO concentration of supernatant. Both the TRAP activity and the number of TRAP positive cells were higher in cells of μ g group than those in 2 g group. In the 1 g group, they were decreased significantly compared to control. CONCLUSIONS: These findings indicate that LGHMF could directly affect human preosteoclast FLG29.1 cells survival and differentiation. High magnetic flux inhibited osteoclasts formation and differentiation while reduced apparent gravity enhanced osteoclastogenesis.

(NE) (VT, CE) Di Loreto S, Falone S, Caracciolo V, Sebastiani P, D'Alessandro A, Mirabilio A, Zimmitti V, Amicarelli F. Fifty hertz extremely low-frequency magnetic field exposure elicits redox and trophic response in rat-cortical neurons. J Cell Physiol. 219(2):334-343, 2009.

Large research activity has raised around the mechanisms of interaction between extremely low-frequency magnetic fields (ELF-MFs) and biological systems. ELF-MFs may interfere with chemical reactions involving reactive oxygen species (ROS), thus facilitating oxidative damages in living cells. Cortical neurons are particularly susceptible to oxidative stressors and are also highly dependent on the specific factors and proteins governing neuronal development, activity and survival. The aim of the present work was to investigate the effects of exposures to two different 50 Hz sinusoidal ELF-MFs intensities (0.1 and 1 mT) in maturing rat cortical neurons' major anti-oxidative enzymatic and non-enzymatic cellular protection systems, membrane peroxidative damage, as well as

growth factor, and cytokine expression pattern. Briefly, our results showed that ELF-MFs affected positively the cell viability and concomitantly reduced the levels of apoptotic death in rat neuronal primary cultures, with no significant effects on the main anti-oxidative defences. Interestingly, linear regression analysis suggested a positive correlation between reduced glutathione (GSH) and ROS levels in 1 mT MF-exposed cells. On this basis, our hypothesis is that GSH could play an important role in the antioxidant defence towards the ELF-MF-induced redox challenge. Moreover, the GSH-based cellular response was achieved together with a brain-derived neurotrophic factor over-expression as well as with the interleukin 1beta-dependent regulation of pro-survival signaling pathways after ELF-MF exposure.

(E) (VO, CE, IOD) Dinčić M, Krstić DZ, Čolović MB, Nešović Ostojić J, Kovačević S, De Luka SR, Djordjević DM, Ćirković S, Brkić P, Todorović J. Modulation of rat synaptosomal ATPases and acetylcholinesterase activities induced by chronic exposure to the static magnetic field. Int J Radiat Biol. 94(11):1062-1071, 2018

PURPOSE: It is considered that exposure to static magnetic fields (SMF) may have both detrimental and therapeutic effect, but the mechanism of SMF influence on the living organisms is not well understood. Since the adenosine triphosphatases (ATPases) and acetylcholinesterase (AChE) are involved in both physiological and pathological processes, the modulation of Na^+/K^+-ATPase, ecto-ATPases and AChE activities, as well as oxidative stress responses were followed in synaptosomes isolated from rats after chronic exposure toward differently oriented SMF. MATERIAL AND METHODS: Wistar albino rats were randomly divided into three experimental groups (six animals per group): Up and Down group - exposed to upward and downward oriented SMF, respectively, and Control group. After 50 days, the rats were sacrificed, and synaptosomes were isolated from the whole rat brain and used for testing the enzyme activities and oxidative stress parameters. RESULTS: Chronic exposure to 1 mT SMF significantly increased ATPases, AChE activities, and malondialdehyde (MDA) level in both exposed groups, compared to control values. The significant decrease in synaptosomal catalase activity (1.48 ± 0.17 U/mg protein) induced by exposure to the downward oriented field, compared to those obtained for Control group (2.60 ± 0.29 U/mg protein), and Up group.

(E) (VT, AE, IX) Ding GR, Nakahara T, Hirose H, Koyama S, Takashima Y, Miyakoshi J. Extremely low frequency magnetic fields and the promotion of H2O2-induced cell death in HL-60 cells. Int J Radiat Biol. 80(4):317-324, 2004.

PURPOSE: To test whether exposure to an extremely low frequency magnetic field (60 Hz, 5 mT) affects hydrogen peroxide (H2O2)-induced cell death in human leukaemia HL-60 cells. MATERIALS AND METHODS: Cells were treated with H2O2 with or without exposure to an extremely low frequency magnetic fields. Viable cells, apoptotic and necrotic cells were determined by annexin V flow cytometry assay. The levels of apoptosis-related proteins (caspase-3, caspase-7, Bcl-2 and Bax) and poly(ADP-ribose) polymerase were detected using Western blotting. RESULTS: Simultaneous treatment with exposure to the magnetic field and H2O2 (85 or 100

microM) for 24 h increased the number of apoptotic and necrotic cells significantly, and significantly decreased the number of viable cells compared with cells treated with H2O2 alone. The protein levels of Bax and Bcl-2 showed no differences between H2O2-treated cells and those treated with both H2O2 and an extremely low frequency magnetic field. Exposure to the magnetic field also had no effect on H2O2-induced caspase-3 activation. However, the protein levels of active caspase-7 in cells simultaneously exposed to an extremely low frequency magnetic field and H2O2 for 2 and 8 h was higher than that of H2O2 treatment alone. In addition, simultaneous exposure to an extremely low frequency magnetic field and H2O2 caused poly(ADP-ribose) polymerase cleavage and induced early inactivation at 2 h, while H2O2 treatment alone did not produce this effect until 4 h. CONCLUSIONS: The data suggest that although the magnetic field itself cannot induce apoptosis and necrosis, it exerts a promoting effect on H2O2-induced cell death, and it demonstrates that caspase-7 as well as poly(ADP-ribose) polymerase might be involved in this process.

(E) (VO, CE, IFR) Djordjevic NZ, Paunović MG, Peulić AS. Anxiety-like behavioural effects of extremely low-frequency electromagnetic field in rats. Environ Sci Pollut Res Int. 24(27):21693-21699, 2017.

In recent years, extremely low-frequency electromagnetic field (ELF-EMF) has received considerable attention for its potential biological effects. Numerous studies have shown the role of ELF-EMF in behaviour modulation. The aim of this study was to investigate the effect of short-term ELF-EMF (50 Hz) in the development of anxiety-like behaviour in rats through change hypothalamic oxidative stress and NO. Ten adult male rats (Wistar albino) were divided in two groups: control group-without exposure to ELF-EMF and experimental group-exposed to ELF-EMF during 7 days. After the exposure, time open field test and elevated plus maze were used to evaluate the anxiety-like behaviour of rats. Upon completion of the behavioural tests, concentrations of superoxide anion ($O_2^{\cdot -}$), nitrite (NO_2^-, as an indicator of NO) and peroxynitrite ($ONOO^-$) were determined in the hypothalamus of the animals. Obtained results show that ELF-EMF both induces anxiety-like behaviour and increases concentrations of $O_2^{\cdot -}$ and NO, whereas it did not effect on $ONOO^-$ concentration in hypothalamus of rats. In conclusion, the development of anxiety-like behaviour is mediated by oxidative stress and increased NO concentration in hypothalamus of rats exposed to ELF-EMF during 7 days.

Dodson CA, Hore PJ, Wallace MI. A radical sense of direction: signalling and mechanism in cryptochrome magnetoreception. Trends Biochem Sci. 38(9):435-446, 2013. (Review)

The remarkable phenomenon of magnetoreception in migratory birds and other organisms has fascinated biologists for decades. Much evidence has accumulated to suggest that birds sense the magnetic field of the Earth using photochemical transformations in cryptochrome flavoproteins. In the last 5 years this highly interdisciplinary field has seen advances in structural biology, biophysics, spin chemistry, and genetic studies in model organisms. We review these developments and consider how this chemical signal can be integrated into the cellular response.

(E) (VT, AE, DFR) Dong D, Yang J, Zhang G, Huyan T, Shang P.16 T high static magnetic field inhibits receptor activator of nuclear factor kappa-B ligand-induced osteoclast differentiation by regulating iron metabolism in Raw264.7 cells. J Tissue Eng Regen Med. 13(12):2181-2190, 2019.

High static magnetic fields (HiSMFs) are usually defined as those SMFs with intensities ≥1 T. Although many studies have indicated that SMFs have positive effects on bone tissue, there were limited studies that investigate the effects of cells, including osteoclasts, to illustrate the effect of HiSMF on osteoclast differentiation, and whether iron involve in the altered osteoclast formation and resorption ability under HiSMF. 16 T HiSMF generated from a superconducting magnet was used. Osteoclastogenesis, bone resorption, acting ring formation, messenger ribonucleic acid expression, and protein expression were determined by tartrate-resistant acid phosphatase staining, pits formation assay, rhodamine-conjugated phalloidine staining, quantitative real-time polymerase chain reaction, and western blot, respectively. The changes induced by HiSMF in the level of iron and the concentration of mitochondrial protein, adenosine triphosphate, reactive oxygen species, malonaldehyde, and glutathione were examined by atomic absorption spectrometry and corresponding commercial kits, respectively. The results showed that HiSMF significantly inhibited osteoclastic formation and resorption ability and reduced cellular iron content during osteoclast differentiation. Mitochondrial concentration and oxidative stress levels in osteoclasts were decreased under HiSMF. Mechanistically, HiSMF markedly blocked the expression of osteoclast-associated transcription factors and osteoclast marker genes and inhibited iron absorption and iron storage-related protein expression. These findings demonstrated that the effect of HiSMF on iron metabolism of osteoclasts was involved in the inhibition of HiSMF on osteoclast differentiation.

(E) (VO, CE, IFR, IAO) Dong L, Xiang J, Guo J, Chen G, Di G. Can static electric fields increase the activity of nitric oxide synthase and induce oxidative stress and damage of spleen? Environ Sci Pollut Res Int. 29(3):4093-4100, 2022.

With the rapid development of ultra-high-voltage (UHV) direct-current (DC) transmissions, the impact of static electric fields (SEF) in the vicinity of overhead UHV DC transmission lines on health has aroused much public concern. This study explored the effects of 56.3kV/m SEF on the spleen of mice. Results showed that SEF exposure of 21days significantly increased malonic dialdehyde content, superoxide dismutase activity, calcineurin activity, nitric oxide synthase (NOS) activity, and the mRNA expression levels of tumor necrosis factor-α (TNF-α) and nuclear factor-κB (NF-κB) in the spleen and caused the separation of nucleus and nuclear membrane, the disappearance of mitochondrial membrane, and the deficiency of mitochondrial cristae in splenic lymphocytes. By analysis and discussion, it was deduced that SEF could induce oxidative stress of the spleen by increasing the activity of NOS.

Oxidative stress could further cause ultrastructural changes of splenic lymphocytes. Moreover, oxidative stress could cause the increase of the mRNA expression levels of TNF-α and NF-κB, which contributed to the occurrence of spleen inflammation.

(E) (IV, AE, IFR, DFR, IAO, DAO, IOD) Dornelles EB, Goncalves BD, Schott KL, Barbisan F, Unfer TC, Glanzner WG, Machado AK, Cadona FC, Azzolin VF, Montano MA, Griner J, da Cruz IB. Cytotoxic effects of moderate static magnetic field exposure on human periphery blood mononuclear cells are influenced by Val16Ala-MnSOD gene polymorphism. Environ Sci Pollut Res Int. 24(5):5078-5088, 2017.

Technological advancement has increasingly exposed humans to magnetic fields (MFs). However, more insights are necessary into the potential toxicity of MF exposure as a result of genetic variations related to oxidative metabolism. Therefore, the following study has assessed an in vitro cytotoxic effect of static magnetic field (SMF) (5 mT) on cells with Val16Ala polymorphism (AA, VA, and VV) in the manganese superoxide dismutase gene. Homozygous Val16Ala-superoxide dismutase 2 (SOD2) genotypes present oxidative imbalance that is associated with risk to several chronic degenerative diseases (VV produces less efficient and AA more efficient SOD2 enzyme). Blood samples from healthy adult subject carriers with different Val16Ala-SOD2 genotypes were obtained and exposed to MF at different times (0, 1, 3, 6 h). The cytotoxic effect as well as oxidative stress was evaluated after incubation of 24 h at 37 °C. In addition, apoptosis induction has been analyzed by flow cytometry as well as Bcl-2-associated X protein (BAX), B-cell lymphoma 2 (BCL-2), and caspases 8 and 3 gene expression. SMF cytotoxic effect has been observed in AA cells at all times of exposure, whereas AV cells presented higher mortality only after 6 h of exposure at SMF. Higher apoptosis induction has been observed in AA cells when compared to VV and AV cells. These results suggest a toxicogenetic SMF effect related to an imbalance in SOD2 activity.

(E) (VO, CE, IFR, DAO, IX) Duan Y, Wang Z, Zhang H, He Y, Lu R, Zhang R, Sun G, Sun X. The preventive effect of lotus seedpod procyanidins on cognitive impairment and oxidative damage induced by extremely low frequency electromagnetic field exposure. Food Funct. 4(8):1252-1262, 2013.

The present study investigated the effects of lotus seedpod procyanidins (LSPCs) administered by oral gavage on the cognitive deficits and oxidative damage of mice at extremely low frequency electromagnetic field (ELF-EMF) exposure (50 Hz, 8 mT, 28 days). The results showed that 90 mg kg^{-1} LSPCs treatment significantly increased body weight compared with the ELF-EMF group at ELF-EMF exposure and effectively maintained liver index, thymus index, kidney index and spleen index close to normal. A water maze test indicated that learning and memory abilities of the ELF-EMF group deteriorated significantly with ELF-EMF exposure when compared with the control group, but the ELF-EMF + LSPCs90 group had remarkably improved learning and memory abilities

compared with the ELF-EMF group. Malondialdehyde (MDA), reactive oxygen species (ROS), nitric oxide (NO) and nitric oxide synthase (NOS) mostly exhibited significant increases, while the activities of glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) decreased significantly under ELF-EMF exposure in the ELF-EMF group. LSPCs (especially 60, 90 mg kg^{-1}) administration decreased MDA, ROS, NO content and lowered NOS activity in LSPCs treatment groups. Furthermore, LSPCs (60, 90 mg kg^{-1}) treatment significantly augmented GPx, CAT, SOD activity in the hippocampus and serum. Pathological observation showed that number of pyramidal cells of the CA1 and CA3 regions of the hippocampus of the LSPCs treatment groups was significantly greater than the ELF-EMF group. All the data suggested that the LSPCs can effectively prevent learning and memory damage and oxidative damage caused by the ELF-EMF, most likely through the ability of LSPCs to scavenge oxygen free radicals and to stimulate antioxidant enzyme activity.

(NE) (VT, AE) Duan W, Liu C, Zhang L, He M, Xu S, Chen C, Pi H, Gao P, Zhang Y, Zhong M, Yu Z, Zhou Z. Comparison of the genotoxic effects induced by 50 Hz extremely low-frequency electromagnetic fields and 1800 MHz radiofrequency electromagnetic fields in GC-2 cells. Radiat Res. 183(3):305-314, 2015.

Extremely low-frequency electromagnetic fields (ELF-EMF) and radiofrequency electromagnetic fields (RF-EMF) have been considered to be possibly carcinogenic to humans. However, their genotoxic effects remain controversial. To make experiments controllable and results comparable, we standardized exposure conditions and explored the potential genotoxicity of 50 Hz ELF-EMF and 1800 MHz RF-EMF. A mouse spermatocyte-derived GC-2 cell line was intermittently (5 min on and 10 min off) exposed to 50 Hz ELF-EMF at an intensity of 1, 2 or 3 mT or to RF-EMF in GSM-Talk mode at the specific absorption rates (SAR) of 1, 2 or 4 W/kg. After exposure for 24 h, we found that neither ELF-EMF nor RF-EMF affected cell viability using Cell Counting Kit-8. Through the use of an alkaline comet assay and immunofluorescence against γ-H2AX foci, we found that ELF-EMF exposure resulted in a significant increase of DNA strand breaks at 3 mT, whereas RF-EMF exposure had insufficient energy to induce such effects. Using a formamidopyrimidine DNA glycosylase (FPG)-modified alkaline comet assay, we observed that RF-EMF exposure significantly induced oxidative DNA base damage at a SAR value of 4 W/kg, whereas ELF-EMF exposure did not. Our results suggest that both ELF-EMF and RF-EMF under the same experimental conditions may produce genotoxicity at relative high intensities, but they create different patterns of DNA damage. Therefore, the potential mechanisms underlying the genotoxicity of different frequency electromagnetic fields may be different.

(E) (VT, AE, IX, DFR) Duong CN, Kim JY. Exposure to electromagnetic field attenuates oxygen-glucose deprivation-induced microglial cell death by reducing intracellular Ca2+ and ROS. Int J Radiat Biol. 92(4):195-201, 2016.

Purpose: The aim of this research was to demonstrate the protective effects of electromagnetic field (EMF) exposure on the human microglial cell line, HMO6, against ischemic cell death induced by in vitro oxygen-glucose deprivation (OGD). Materials and

methods: HMO6 cells were cultured for 4 h under OGD with or without exposure to EMF with different combinations of frequencies and intensities (10, 50, or 100 Hz/1 mT and 50 Hz/0.01, 0.1, or 1 mT). Cell survival, intracellular calcium and reactive oxygen species (ROS) levels were measured. Results: OGD caused significant HMO6 cell death as well as elevation of intracellular Ca^{2+} and ROS levels. Among different combinations of EMF frequencies and intensities, 50 Hz/1 mT EMF was the most potent to attenuate OGD-induced cell death and intracellular Ca^{2+} and ROS levels. A significant but less potent protective effect was also found at 10 Hz/1 mT, whereas no protective effect was found at other combinations of EMF. A xanthine oxidase inhibitor reversed OGD-induced ROS production and cell death, while NADPH oxidase and mitochondrial respiration chain complex II inhibitors did not affect cell death. Conclusions: 50 Hz/1 mT EMF protects human microglial cells from OGD-induced cell death by interfering with OGD-induced elevation of intracellular Ca^{2+} and ROS levels, and xanthine oxidase is one of the main mediators involved in OGD-induced HMO6 cell death. Non-invasive treatment of EMF radiation may be clinically useful to attenuate hypoxic-ischemic brain injury.

(E) (IV, AE, CE, IFR, DFR, IAO) Ehnert S, Fentz AK, Schreiner A, Birk J, Wilbrand B, Ziegler P, Reumann MK, Wang H, Falldorf K, Nussler AK. Pulsed electromagnetic fields cause antioxidative defense mechanisms in human osteoblasts via induction of $\bullet O_2^-$ and H_2O_2. Sci Rep. 7(1):14544, 2017.

Recently, we identified a specific extremely low-frequency pulsed electromagnetic field (ELF-PEMF) that supports human osteoblast (hOBs) function in an ERK1/2-dependent manner, suggesting reactive oxygen species (ROS) being key regulators in this process. Thus, this study aimed at investigating how ELF-PEMF exposure can modulate hOBs function via ROS. Our results show that single exposure to ELF-PEMF induced ROS production in hOBs, without reducing intracellular glutathione. Repetitive exposure (>3) to ELF-PEMF however reduced ROS-levels, suggesting alterations in the cells antioxidative stress response. The main ROS induced by ELF-PEMF were $\bullet O_2^-$ and H_2O_2, therefore expression/activity of antioxidative enzymes related to these ROS were further investigated. ELF-PEMF exposure induced expression of GPX3, SOD2, CAT and GSR on mRNA, protein and enzyme activity level. Scavenging $\bullet O_2^-$ and H_2O_2 diminished the ELF-PEMF effect on hOBs function (AP activity and mineralization). Challenging the hOBs with low amounts of H_2O_2 on the other hand improved hOBs function. In summary, our data show that ELF-PEMF treatment favors differentiation of hOBs by producing non-toxic amounts of ROS, which induces antioxidative defense mechanisms in these cells. Thus, ELF-PEMF treatment might represent an interesting adjunct to conventional therapy supporting bone formation under oxidative stress conditions, e.g. during fracture healing.

(E) (VT, AE, IFR) Elexpuru-Zabaleta M, Raffaella Lazzarini , Maria Fiorella Tartaglione, Francesco Piva, Veronica Ciarapica, Elena Marinelli Busilacchi, Antonella Poloni, Matteo Valentino, Lory Santarelli, Massimo Bracc.i A 50 Hz magnetic field influences the viability of breast cancer cells 96 h after exposure. Mol Biol Rep 2022 Nov 15. doi: 10.1007/s11033-022-08069-7. Online ahead of print.

Background: The exposure of breast cancer to extremely low frequency magnetic fields (ELF-MFs) results in various biological responses. Some studies have suggested a possible cancer-enhancing effect, while others showed a possible therapeutic role. This study investigated the effects of in vitro exposure to 50 Hz ELF-MF for up to 24 h on the viability and cellular response of MDA-MB-231 and MCF-7 breast cancer cell lines and MCF-10A breast cell line. **Methods and results:** The breast cell lines were exposed to 50 Hz ELF-MF at flux densities of 0.1 mT and 1.0 mT and were examined 96 h after the beginning of ELF-MF exposure. The duration of 50 Hz ELF-MF exposure influenced the cell viability and proliferation of both the tumor and nontumorigenic breast cell lines. In particular, short-term exposure (4-8 h, 0.1 mT and 1.0 mT) led to an increase in viability in breast cancer cells, while long and high exposure (24 h, 1.0 mT) led to a decrease in viability and proliferation in all cell lines. Cancer and normal breast cells exhibited different responses to ELF-MF. Mitochondrial membrane potential and reactive oxygen species (ROS) production were altered after ELF-MF exposure, suggesting that the mitochondria are a probable target of ELF-MF in breast cells. **Conclusions:** The viability of breast cells in vitro is influenced by ELF-MF exposure at magnetic flux densities compatible with the limits for the general population and for workplace exposures. The effects are apparent after 96 h and are related to the ELF-MF exposure time.

(E) (VO, CE, IOD, IAO) Emre M, Cetiner S, Zencir S, Unlukurt I, Kahraman I, Topcu Z. Oxidative stress and apoptosis in relation to exposure to magnetic field. Cell Biochem Biophys. 59(2):71-77, 2011.

We investigated the effect of extremely low-frequency electromagnetic field (ELF-EMF) with pulse trains exposure on lipid peroxidation, and, hence, oxidative stress in the rat liver tissue. The parameters that we measured were the levels of plasma alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase as well as plasma albumin, bilirubin, and total protein levels in 30 adult male Wistar rats exposed to ELF. We also determined the percentage of apoptotic and necrotic cells of the kidney extracts from the animals by flow cytometry method. Apoptotic cell death was further characterized by monitoring DNA degradation using gel electrophoresis. The results showed an increase in the levels of oxidative stress indicators, and the flow cytometric data suggested a possible relationship between the exposure to magnetic field and the cell death. We showed significantly lower necrotic cell percentages in experimental animals compared to either unexposed or sham control groups. However, DNA ladder analyses did not differentiate between the groups. Our results were discussed in relation to the response of biological systems to EMF.

(E) (VO, CE, IFR) Erdal N, Gürgül S, Tamer L, Ayaz L. Effects of long-term exposure of extremely low frequency magnetic field on oxidative/nitrosative stress in rat liver. J Radiat Res (Tokyo). 49(2):181-187, 2008.

Thirty-two adult Wistar-Albino female and male rats were used to investigate the long-term (45 days) effects of extremely low frequency magnetic field (ELF-MF; 50Hz, 1mT, 4h/day) exposure on oxidative/nitrosative stress in liver tissues of rats. The rats were divided randomly into four groups: female control (FC; n = 8) and MF-exposed female rats (F-MF; n = 8); male control (MC; n = 8)

and MF-exposed male rats (M-MF; n = 8). Liver tissue from each animal was harvested and utilized for malondialdehyde (MDA) and 3-nitrotyrosine (3-NT) detection. MDA levels were measured by MDA-TBA method, while the 3-NT levels were determined by the HPLC-UV system. There were no significant differences between the MDA levels of the control (FC; MC) and MF-exposed (F-MF; M-MF) rats ($P > 0.05$). In the F-MF rats, 3-NT levels were significantly increased when compared to those of the FC rats ($P < 0.05$). There were no significant differences between the 3-NT levels of the MC and M-MF rats. In conclusion, our study suggests that the long-term ELF-MF exposure may enhance the oxidative/nitrosative stress in liver tissue of the female rats and could have a deteriorative effect on cellular proteins rather than lipids by enhancing 3-NT formation.

(E) (VT, AE, IAO, IX) Errico Provenzano A, Amatori S, Nasoni MG, Persico G, Russo S, Mastrogiacomo AR, Gambarara A, Fanelli M. Effects of fifty-hertz electromagnetic fields on granulocytic differentiation of ATRA-treated acute promyelocytic leukemia NB4 cells. Cell Physiol Biochem. 46(1):389-400, 2018.

BACKGROUND/AIMS: Life on Earth is constantly exposed to electromagnetic fields (EMFs) and the effects induced by EMFs on biological systems have been extensively studied producing different and sometimes contradictory results. Extremely low-frequency electromagnetic fields (ELF-EMFs) have shown to play a role in regulating cell proliferation and differentiation, although how EMFs influence these processes remains unclear. Human acute promyelocytic leukemia (APL) cells are characterized by the arrest of differentiation at the promyelocytic stage due to epigenetic perturbations induced by PML/RARα fusion protein (Promyelocytic Leukemia protein - PML/Retinoic Acid Receptor alpha - RARα). Therapeutic administration of all-trans retinoic acid (ATRA) re-establishes the leukemogenic mechanism re-inducing the normal differentiation processes. METHODS: We studied the effects of ELF-EMFs (50 Hz, 2 mT) on the ATRA-mediated granulocytic differentiation process of APL NB4 cells (a cell line established from the bone marrow of a patient affected by the acute promyelocytic leukemia) by monitoring cellular proliferation and morphology, nitrob lue tetrazolium (NBT) reduction and the expression of differentiation surface markers. Finally, we investigated mechanisms focusing on reactive oxygen species (ROS) generation and related molecular pathways. RESULTS:
ELF-EMF exposure decreases cellular proliferation potential and helps ATRA-treated NB4 cells to mature. Furthermore, the analysis of ROS production and the consequent extracellular signal regulated kinases (ERK1/2) phosphorylation suggest that a changed intracellular oxidative balance may influence the biological effects of ELF-EMFs. CONCLUSIONS: These results indicate that the exposure to ELF-EMF promotes ATRA-induced granulocytic differentiation of APL cells.

(E) (VO, CE, IOD, DAO) Ersoy N, Acikgoz B, Aksu I, Kiray A, Bagriyanik HA, Kiray M. The Effects of Prenatal and Postnatal Exposure to 50-Hz and 3 mT Electromagnetic Field on Rat Testicular Development. Medicina (Kaunas) 59(1):71, 2022.

Background and objectives: It has been shown that electromagnetic fields (EMFs) have negative effects on the reproductive system. The biological effects of EMF on the male reproductive system are controversial and vary depending on the frequency and exposure time. Although a limited number of studies have focused on the structural and functional effects of EMF, the effects of prenatal and postnatal EMF exposure on testes are not clear. We aimed to investigate the effects of 50-Hz, 3-mT EMF exposure (5 days/wk, 4 h/day) during pre- and postnatal periods on testis development. *Materials and Methods:* Pups from three groups of Sprague-Dawley pregnant rats were used: Sham, EMF-28 (EMF-exposure applied during pregnancy and until postnatal day 28), EMF-42 (EMF-exposure applied during pregnancy and until postnatal day 42). The testis tissues and blood samples of male offspring were collected on the postnatal day 42. *Results:* Morphometric analyses showed a decrease in seminiferous tubule diameter as a result of testicular degeneration in the EMF-42 group. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were decreased in the EMF-42 group. Lipid peroxidation levels were increased in both EMF groups, while antioxidant levels were decreased only in the EMF-28 group. We found decreased levels of vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF1) in the EMF-42 group, and decreased levels of the SRC homology 3 (SH3) and multiple ankyrin repeat domain (SHANK3) in the EMF-28 group in the testis tissue. *Conclusions:* EMF exposure during pre- and postnatal periods may cause deterioration in the structure and function of testis and decrease in growing factors that would affect testicular functions in male rat pups. In addition to the oxidative stress observed in testis, decreased SHANK3, VEGF, and IGF1 protein levels suggests that these proteins may be mediators in testis affected by EMF exposure. This study shows that EMF exposure during embryonic development and adolescence can cause apoptosis and structural changes in the testis.

(E) (IV, AE, IAO, IX, MC) Falone S, Grossi MR, Cinque B, D'Angelo B, Tettamanti E, Cimini A, Di Ilio C, Amicarelli F. Fifty hertz extremely low-frequency electromagnetic field causes changes in redox and differentiative status in neuroblastoma cells. Int J Biochem Cell Biol. 39(11):2093-2106, 2007.

The current study was designed to establish whether extremely low-frequency electromagnetic fields might affect neuronal homeostasis through redox-sensitive mechanisms. To this end, intracellular reactive oxygen species production, antioxidant and glutathione-based detoxifying capability and genomic integrity after extremely low-frequency electromagnetic fields exposure were investigated. Moreover, we also studied potential extremely low-frequency electromagnetic fields-dependent changes in the proliferative and differentiative cellular status. Results seem to support redox-mediated extremely low-frequency electromagnetic fields effects on biological models as, although no major oxidative damage was detected, after exposure we observed a positive

modulation of antioxidant enzymatic expression, as well as a significant increase in reduced glutathione level, indicating a shift of cellular environment towards a more reduced state. In addition, extremely low-frequency electromagnetic fields treatment induced a more differentiated phenotype as well as an increased expression in peroxisome proliferators-activated receptor isotype beta, a class of transcription factors related to neuronal differentiation and cellular stress response. As second point, to deepen how extremely low-frequency electromagnetic fields treatment could affect neuroblastoma cell antioxidant capacity, we examined the extremely low-frequency electromagnetic fields-dependent modifications of cell susceptibility to pro-oxidants. Results clearly showed that 50 Hz extremely low-frequency electromagnetic fields exposure reduces cell tolerance towards oxidative attacks.

(E) (VO, CE, IAO, DAO) Falone S, Mirabilio A, Carbone MC, Zimmitti V, Di Loreto S, Mariggiò MA, Mancinelli R, Di Ilio C, Amicarelli F. Chronic exposure to 50 Hz magnetic fields causes a significant weakening of antioxidant defence systems in aged rat brain. Int J Biochem Cell Biol. 40(12):2762-2770, 2008.

Several studies suggest that extremely low-frequency magnetic fields (ELF-MFs) may enhance the free radical endogenous production. It is also well known that one of the unavoidable consequences of ageing is an overall oxidative stress-based decline in several physiological functions and in the general resistance to stressors. On the basis of these assumptions, the aim of this study was to establish whether the ageing process can increase susceptibility towards widely present ELF-MF-mediated pro-oxidative challenges. To this end, female Sprague-Dawley rats were continuously exposed to a sinusoidal 50 Hz, 0.1 mT magnetic field for 10 days. Treatment-induced changes in the major antioxidant protection systems and in the neurotrophic support were investigated, as a function of the age of the subjects. All analyses were performed in brain cortices, due to the high susceptibility of neuronal cells to oxidative injury. Our results indicated that ELF-MF exposure significantly affects anti-oxidative capability, both in young and aged animals, although in opposite ways. Indeed, exposed young individuals enhanced their neurotrophic signalling and anti-oxidative enzymatic defence against a possible ELF-MF-mediated increase in oxygen radical species. In contrast, aged subjects were not capable of increasing their defences in response to ELF-MF treatment but, on the contrary, they underwent a significant decrease in the major antioxidant enzymatic activities. In conclusion, our data seem to suggest that the exposure to ELF-MFs may act as a risk factor for the occurrence of oxidative stress-based nervous system pathologies associated with ageing.

(E) (VT, AE, IAO, IX) Falone S, Marchesi N, Osera C, Fassina L, Comincini S, Amadio M, Pascale A. Pulsed electromagnetic field (PEMF) prevents pro-oxidant effects of H_2O_2 in SK-N-BE(2) human neuroblastoma cells. Int J Radiat Biol. 92(5):281-286, 2016.

Purpose: The redox milieu, together with reactive oxygen species (ROS) accumulation, may play a role in mediating some biological effects of extremely-low-frequency electromagnetic fields (ELF-EMF). Some of us have recently reported that a pulsed EMF (PEMF) improves the antioxidant response of a drug-sensitive human neuroblastoma SH-SY5Y cell line to pro-oxidants. Since drug resistance may affect cell sensitivity to redox-based treatments, we wanted to verify whether drug-resistant human neuroblastoma SK-N-BE(2) cells respond to a PEMF in a similar fashion. Materials and methods: SK-N-BE(2) cells were exposed to repeated 2 mT, 75 Hz PEMF (15 min each, repeated 3 times over 5 days), and ROS production, Mn-dependent superoxide dismutase (MnSOD)-based antioxidant protection and viability were assessed after 10 min or 30 min 1 mM hydrogen peroxide. Sham controls were kept at the same time in identical cell culture incubators. Results: The PEMF increased the MnSOD-based antioxidant protection and reduced the ROS production in response to a pro-oxidant challenge. Conclusions: Our work might lay foundation for the development of non-invasive PEMF-based approaches aimed at elevating endogenous antioxidant properties in cellular or tissue models.

(E) (VT, AE, IAO) Falone S, Santini S Jr, Cordone V, Cesare P, Bonfigli A, Grannonico M, Di Emidio G, Tatone C, Cacchio M, Amicarelli F. Power frequency magnetic field promotes a more malignant phenotype in neuroblastoma cells via redox-related mechanisms. Sci Rep. 7(1):11470, 2017.

In accordance with the classification of the International Agency for Research on Cancer, extremely low frequency magnetic fields (ELF-MF) are suspected to promote malignant progression by providing survival advantage to cancer cells through the activation of critical cytoprotective pathways. Among these, the major antioxidative and detoxification defence systems might be targeted by ELF-MF by conferring cells significant resistance against clinically-relevant cytotoxic agents. We investigated whether the hyperproliferation that is induced in SH-SY5Y human neuroblastoma cells by a 50 Hz, 1 mT ELF magnetic field was supported by improved defence towards reactive oxygen species (ROS) and xenobiotics, as well as by reduced vulnerability against both H_2O_2 and anti-tumor ROS-generating drug doxorubicin. ELF-MF induced a proliferative and survival advantage by activating key redox-responsive antioxidative and detoxification cytoprotective pathways that are associated with a more aggressive behavior of neuroblastoma cells. This was coupled with the upregulation of the major sirtuins, as well as with increased signaling activity of the erythroid 2-related nuclear transcription factor 2 (NRF2). Interestingly, we also showed that the exposure to 50 Hz MF as low as 100 μT may still be able to alter behavior and responses of cancer cells to clinically-relevant drugs.

Falone S, Santini S Jr, Cordone V, Di Emidio G, Tatone C, Cacchio M, Amicarelli F. Extremely low-frequency magnetic fields and redox-responsive pathways linked to cancer drug resistance: Insights from co-exposure-based *In Vitro* studies. Front Public Health. 6:33, 2018. (Review)

Electrical devices currently used in clinical practice and common household equipments generate extremely low-frequency magnetic fields (ELF-MF) that were classified by the International Agency for Research on Cancer as "possible carcinogenic." Assuming that

ELF-MF plays a role in the carcinogenic process without inducing direct genomic alterations, ELF-MF may be involved in the promotion or progression of cancers. In particular, ELF-MF-induced responses are suspected to activate redox-responsive intracellular signaling or detoxification scavenging systems. In fact, improved protection against oxidative stress and redox-active xenobiotics is thought to provide critical proliferative and survival advantage in tumors. On this basis, an ever-growing research activity worldwide is attempting to establish whether tumor cells may develop multidrug resistance through the activation of essential cytoprotective networks in the presence of ELF fields, and how this might trigger relevant changes in tumor phenotype. This review builds a framework around how the activity of redox-responsive mediators may be controlled by co-exposure to ELF-MF and reactive oxygen species-generating agents in tumor and cancer cells, in order to clarify whether and how such potential molecular targets could help to minimize or neutralize the functional interaction between ELF-MF and malignancies.

(E) (VO, CE, IAO, IOD, IER) Faraji N, Salehi I, Alizadeh A, Pourgholaminejad A, Komaki A, Taheri Azandaryani M, Sadeghian R, Golipoor Z . Comparing the Effects of Long-term Exposure to Extremely Low-frequency Electromagnetic Fields With Different Values on Learning, Memory, Anxiety, and β-amyloid Deposition in Adult Rats. Basic Clin Neurosci. 12:849-860, 2021.

Introduction: Extremely Low-Frequency Electromagnetic Fields (ELF-EMFs) have gathered significant consideration for their possible pathogenicity. However, their effects on the nervous system's functions were not fully clarified. This study aimed to assay the impact of ELF-EMFs with different intensities on memory, anxiety, antioxidant activity, β-amyloid (Aβ) deposition, and microglia population in rats. Methods: Fifty male adult rats were randomly separated into 5 groups; 4 were exposed to a flux density of 1, 100, 500, and 2000 microtesla (μT), 50 Hz frequency for one h/day for two months, and one group as a control group. The control group was without ELF-EMF stimulation. After 8 weeks, passive avoidance and Elevated Plus Maze (EPM) tests were performed to assess memory formation and anxiety-like behavior, respectively. Total free thiol groups and the index of lipid peroxidation were evaluated. Additionally, for detection of Aβ deposition and stained microglia in the brain, anti-β-amyloid and anti-Iba1 antibodies were used. Results: The step-through latency in the retention test in ELF-EMF exposure groups (100, 500 & 2000 μT) was significantly greater than the control group ($P<0.05$). Furthermore, the frequency of the entries into the open arms in ELF-EMF exposure groups (especially 2000 μT) decreased than the control group ($P<0.05$). No Aβ depositions were detected in the hippocampus of different groups. An increase in microglia numbers in the 100, 500, and 2000 μT groups was observed compared to the control and one μT group. Conclusion: Exposure to ELF-EMF had an anxiogenic effect on rats, promoted memory, and induced oxidative stress. No Aβ depositions were detected in the brain. Moreover, the positive impact of ELF-EMF was observed on the microglia population in the brain.

(VT, AE, IFR, AO) Feng B, Qiu L, Ye C, Chen L, Fu Y, Sun W. Exposure to a 50-Hz magnetic field induced mitochondrial permeability transition through the ROS/GSK-3β signaling pathway. Int J Radiat Biol. 92:148-155, 2016a.

Purpose To investigate the biological effects of a 50-Hz magnetic field (MF) on mitochondrial permeability. Materials and methods Human amniotic epithelial cells were exposed to MF (50 Hz, 0.4 mT) for different durations. Mitochondrial permeability, mitochondrial membrane potential (ΔΨm), cytochrome c (Cyt-c) release and the related mechanisms were explored. Results Exposure to the MF at 0.4 mT for 60 min transiently induced mitochondrial permeability transition (MPT) and Cyt-c release, although there was no significant effect on mitochondrial membrane potential (ΔΨm). Other than decreasing the total Bcl-2 associated X protein (Bax) level, MF exposure did not significantly affect the levels of Bax and B-cell lymphoma-2 (Bcl-2) in mitochondria. In addition, cells exposed to the MF showed increased intracellular reactive oxidative species (ROS) levels and glycogen synthase kinase-3β (GSK-3β) dephosphorylation at 9 serine residue (Ser^9). Moreover, the MF-induced MPT was attenuated by ROS scavenger (N-acetyl-L-cysteine, NAC) or GSK-3β inhibitor, and NAC pretreatment prevented GSK-3β dephosphorylation (Ser^9) caused by MF exposure. Conclusion MPT induced by MF exposure was mediated through the ROS/GSK-3β signaling pathway.

(E) (VT, AE, IFR) Feng B, Dai A, Chen L, Qiu L, Fu Y, Sun W. NADPH oxidase-produced superoxide mediated a 50-Hz magnetic field-induced epidermal growth factor receptor clustering. Int J Radiat Biol. 92:596-602, 2016b.

PURPOSE: A 50-Hz magnetic field (MF) was found to induce epidermal growth factor receptor (EGFR) clustering in our previous study. The aim of this work was to investigate the molecular mechanisms that mediated MF-induced EGFR clustering. MATERIALS AND METHODS: Human amniotic epithelial (FL) cells were exposed to a 50-Hz MF. Total reactive oxygen species (ROS), cytoplasmic and mitochondrial superoxide production were detected by DCFH-DA, DHE and MitoSOX, respectively. EGFR clustering was analyzed using confocal microscopy after indirect immunofluorescence staining. RESULTS: Results showed that exposing FL cells to MF at intensity higher than 0.2 mT for 15 min enhanced total ROS production. Additionally, enhanced total ROS and cytoplasmic superoxide production were observed after exposing cells to MF at 0.4 mT for 5, 15, or 30 min, while mitochondrial superoxide production for 15 or 30 min. Pretreatment with Nox inhibitor, DPI, effectively inhibited MF-induced cytoplasmic superoxide production and subsequent EGFR clustering while mitochondrial superoxide production was not affected. CONCLUSIONS: Nox-produced superoxide mediated a 50-Hz magnetic field-induced EGFR clustering.

(E) (VT, AE, IFR, MC) Feng B, Ye C, Qiu L, Chen L, Fu Y, Sun W. Mitochondrial ROS release and subsequent Akt Activation potentially mediated the anti-apoptotic effect of a 50-Hz magnetic field on FL cells. Cell Physiol Biochem. 38(6):2489-2499, 2016c.

BACKGROUND/AIMS: Our previous study showed that exposure to a 50-Hz magnetic field (MF) could induce transient mitochondrial permeability transition (MPT) in cells. In the present study, the aim was to explore the possible biological implications of MF-induced transient MPT. MATERIALS AND METHODS: Human amniotic (FL) cells were exposed to MF for different durations or intensities followed by incubation with staurosporine for 4 h. After MF exposure, cell early apoptosis, cell viability, mitochondrial ROS and the level of phosphorylated Akt were assessed. After MF exposure followed by incubation with staurosporine, cell early apoptosis was assessed. RESULTS: MF exposure had a protective effect against early apoptosis induced by staurosporine, which could be abolished by MPT inhibitors, although MF exposure alone had no significant effect on early apoptosis or viability of cells. In addition, exposing cells to MF increased the level of mitochondrial ROS which were released into cytoplasm through mitochondrial permeability transition pores (mPTP), and induced ROS-dependent phosphorylation of Akt. Furthermore, the anti-apoptotic effect of MF exposure was completely eliminated when Akt was inhibited. CONCLUSIONS: The present study indicated a possibility that mitochondrial ROS release through mPTP and subsequent Akt activation were necessary for the anti-apoptotic effect of MF.

(E) (VT, VO, CE, DOD, DFR) Feng C, Yu B, Song C, Wang J, Zhang L, Ji X, Wang Y, Fang Y, Liao Z, Wei M, Zhang X. Static Magnetic Fields Reduce Oxidative Stress to Improve Wound Healing and Alleviate Diabetic Complications. Cells 11(3):443, 2022.

Although some studies have shown that some static magnetic fields (SMFs) can promote wound healing in diabetic mice, it is not clear whether the other diabetes complications, such as liver disease and diabetic nephropathy, can also be alleviated. Here, we constructed two simple magnetic plates using neodymium permanent magnets to examine the comprehensive effects of moderate SMFs on genetically obese leptin receptor-deficient db/db diabetic mice. We found that although the blood glucose was not obviously reduced by these two SMF settings, both of the glycated serum protein (GSP) and malondialdehyde (MDA) levels were significantly decreased (Cohen's d = 2.57-3.04). Moreover, the wound healing, liver lipid accumulation, and renal defects were all significantly improved by SMF treatment (Cohen's d = 0.91-2.05). Wound tissue examination showed obvious nuclear factor erythroid 2-related factor 2 (NRF2) level decrease (Cohen's d = 2.49-5.40) and Ki-67 level increase (Cohen's d = 2.30-3.40), indicating decreased oxidative stress and increased cell proliferation. In vitro cellular studies with fibroblast NIH3T3 cells showed that SMFs could reduce high glucose-induced NRF2 nucleus translocation (Cohen's d = 0.87-1.15) and cellular reactive oxygen species (ROS) elevation (Cohen's d = 0.92), indicating decreased oxidative stress. Consequently, high glucose-induced impairments in cell vitality, proliferation, and migration were all improved by SMF treatment. Therefore, our results demonstrate that these simple SMF devices could effectively reduce oxidative stress in diabetic mice and may provide a cost-effective physical therapy strategy to alleviate multiple diabetic complications in the future.

(E) (VO, CE, DAO) Fernie KJ, Bird DM. Evidence of oxidative stress in American kestrels exposed to electromagnetic fields. Environ Res. 86(2):198-207, 2001.

Exposure to electromagnetic fields (EMFs) alters melatonin, behavior, growth, and reproduction of captive American kestrels (Falco sparverius), particularly of males. EMF exposure is a "possible" human carcinogen and associated with some neurodegenerative diseases. Oxidative stress contributes to cancer, neurodegenerative diseases, and immune disorders. We tested whether EMF exposure elicits an avian immune response and alters oxidative stress levels. Captive male kestrels were bred under control or EMF conditions equivalent to those experienced by wild kestrels. Short-term EMF exposure (one breeding season) suppressed plasma total proteins, hematocrits, and carotenoids in the first half of the breeding season. It also suppressed erythrocyte cells and lymphocyte proportions, but elevated granulosa proportions at the end of the breeding season. Long-term EMF exposure (two breeding seasons) suppressed hematocrits in the first half of the reproductive period too. Results indicate that only short-term EMF birds experience an immune response, particularly during the early half of the breeding season. The elevation of granulocytes, and the suppression of carotenoids, total proteins, and previously melatonin in the same kestrels, signifies that the short-term EMF male kestrels had higher levels of oxidative stress, due to an immune response and/or EMF exposure. Long-term EMF exposure may be linked to higher levels of oxidative stress through EMF exposure only.

(E) (VT, AE, IX) Fiorani M, Biagiarelli B, Vetrano F, Guidi G, Dachà M, Stocchi V. In vitro effects of 50 Hz magnetic fields on oxidatively damaged rabbit red blood cells. Bioelectromagnetics. 18(2):125-131, 1997.

The aim of this study was to investigate the effects of 50 Hz magnetic fields (0.2-0.5 mT) on rabbit red blood cells (RBCs) that were exposed simultaneously to the action of an oxygen radical-generating system, Fe(II)/ascorbate. Previous data obtained in our laboratory showed at the exposure of rabbit erythrocytes or reticulocytes to Fe(II)/ascorbate hexokinase inactivation, whereas the other glycolytic enzymes do not show any decay. We also observed depletion of reduced glutathione (GSH) content with a concomitant intracellular and extracellular increase in oxidized glutathione (GSSG) and a decrease in energy charge. In this work we investigated whether 50 Hz magnetic fields could influence the intracellular impairments that occur when erythrocytes or reticulocytes are exposed to this oxidant system, namely, inactivation of hexokinase activity, GSH depletion, a change in energy charge, and hemoglobin oxidation. The results obtained indicate the a 0.5 mT magnetic field had no effect on intact RBCs, whereas it increased the damage with Fe(II)/ascorbate to a 0.5 mT magnetic field induced a significant further decay in hexokinase activity (about 20%) as well as a twofold increase in methemoglobin production compared with RBCs that were exposed to the oxidant system alone. Although further studies will be needed to determine the physiological implications of these data, the results reported in this study demonstrate that the effects of the magnetic fields investigated are able to potentiate the cellular damage induced in vitro by oxidizing agents.

(E) (VT, AE, IFR) Fitzsimmons RJ, Gordon SL, Kronberg J, Ganey T, Pilla AA. A pulsing electric field (PEF) increases human chondrocyte proliferation through a transduction pathway involving nitric oxide signaling. J Orthop Res. 26(6):854-859, 2008.

A potential treatment modality for joint pain due to cartilage degradation is electromagnetic fields (EMF) that can be delivered, noninvasively, to chondrocytes buried within cartilage. A pulsed EMF in clinical use for recalcitrant bone fracture healing has been modified to be delivered as a pulsed electric field (PEF) through capacitive coupling. It was the objective of this study to determine whether the PEF signal could have a direct effect on chondrocytes in vitro. This study shows that a 30-min PEF treatment can increase DNA content of chondrocyte monolayer by approximately 150% at 72 h poststimulus. Studies intended to explore the biological mechanism showed this PEF signal increased nitric oxide measured in culture medium and cGMP measured in cell extract within the 30-min exposure period. Increasing calcium in the culture media or adding the calcium ionophore A23187, without PEF treatment, also significantly increased short-term nitric oxide production. The inhibitor W7, which blocks calcium/calmodulin, prevented the PEF-stimulated increase in both nitric oxide and cGMP. The inhibitor L-NAME, which blocks nitric oxide synthase, prevented the PEF-stimulated increase in nitric oxide, cGMP, and DNA content. An inhibitor of guanylate cyclase (LY83583) blocked the PEF-stimulated increase in cGMP and DNA content. A nitric oxide donor, when present for only 30 min, increased DNA content 72 h later. Taken together, these results suggest the transduction pathway for PEF-stimulated chondrocyte proliferation involves nitric oxide and the production of nitric oxide may be the result of a cascade that involves calcium, calmodulin, and cGMP production.

(E) (VT, AE, IFR) Frahm J, Lantow M, Lupke M, Weiss DG, Simkó M. Alteration in cellular functions in mouse macrophages after exposure to 50 Hz magnetic fields. J Cell Biochem. 99(1):168-177, 2006.

The aim of the present study is to investigate whether extremely low frequency electromagnetic fields (ELF-EMF) affect certain cellular functions and immunologic parameters of mouse macrophages. In this study, the influence of 50 Hz magnetic fields (MF) at 1.0 mT was investigated on the phagocytic activity and on the interleukin-1beta (IL-1beta) production in differentiated macrophages. MF-exposure led to an increased phagocytic activity after 45 min, shown as a 1.6-fold increased uptake of latex beads in MF-exposed cells compared to controls. We also demonstrate an increased IL-1beta release in macrophages after 24 h exposure (1.0 mT MF). Time-dependent IL-1beta formation was significantly increased already after 4 h and reached a maximum of 12.3-fold increase after 24 h compared to controls. Another aspect of this study was to examine the genotoxic capacity of 1.0 mT MF by analyzing the micronucleus (MN) formation in long-term (12, 24, and 48 h) exposed macrophages. Our data show no significant differences in MN formation or irregular mitotic activities in exposed cells. Furthermore, the effects of different flux densities (ranging from 0.05 up to 1.0 mT for 45 min) of 50 Hz MF was tested on free radical formation as an endpoint of cell activation in mouse macrophage precursor cells. All tested flux densities significantly stimulated the formation of free radicals. Here, we demonstrate the capacity of ELF-EMF

to stimulate physiological cell functions in mouse macrophages shown by the significantly elevated phagocytic activity, free radical release, and IL-1beta production suggesting the cell activation capacity of ELF-EMF in the absence of any genotoxic effects.

(E) (VT, AE, IFR) Frahm J, Mattsson MO, Simkó M. Exposure to ELF magnetic fields modulate redox related protein expression in mouse macrophages. Toxicol Lett. 192(3):330-336, 2010.

The interaction of extremely low frequency (ELF) magnetic fields (MF) with cells can induce alterations in various cell physiological processes. Here, we present evidence that exposure of mouse macrophages to 50 Hz, 1.0 mT MF lead to immune cell activation seen as increased production of reactive oxygen species (ROS), and also to modulation on the expression level of important proteins acting in redox regulatory processes and thus explaining the noted changes in ROS levels seen after exposure. The MF exposure caused slight and transient decreases after short term exposures (2h or less) of clathrin, adaptin, PI3-kinase, protein kinase B (PKB) and PP2A, whereas longer exposures had no effect. The levels of the NAD(P)H oxidase subunit gp91phox oscillated between increased and normal levels compared to controls. The stress proteins Hsp70 and Hsp110 exhibited increased levels at certain time points, but not generally. The effects of MF on protein levels are different from the effects exerted by 12-O-tetradecanolyphobol-13-acetate (TPA) or LPS, although all three factors cause increases in ROS release. This suggests that ELF MF interacts with other cellular constituents than these chemicals, although induced pathways at least partially converge.

(E) (VT, AE, IFR) Garip AI, Akan Z. Effect of ELF-EMF on number of apoptotic cells; correlation with reactive oxygen species and HSP. Acta Biol Hung. 61(2):158-167, 2010.

It is by now accepted that extremely low frequency electromagnetic fields ELF-EMF (0-300 Hz) affect biological systems although the mechanism has not been elucidated yet. In this study the effect of ELFEMF on the number of apoptotic cells of K562 human leukemia cell line induced or not with oxidative stress and the correlation with heat-shock protein 70 (hsp70) levels was investigated. One sample was treated with H 2 O 2 while the other was left untreated. ELF-EMF (1 mT, 50 Hz) was applied for 3 hours. ELF-EMF alone caused a decrease in the number of apoptotic cells and a slight increase in viability. However, it increased the number of apoptotic cells. In cells treated with H 2 O 2 . hsp70 and reactive oxygen species (ROS) levels were increased by ELF-EMF. These results show that the effect of ELF-EMF on biological systems depends on the status of the cell: while in cells not exposed to oxidative stress it is able to decrease the number of apoptotic cells by inducing an increase in hsp levels, it increases the number of apoptotic cells in oxidative stress-induced cells.

(E)(VO, CE, IAO, IX) Ghodbane S, Amara S, Arnaud J, Garrel C, Faure H, Favier A, Sakly M, Abdelmelek H. Effect of selenium pre-treatment on plasma antioxidant vitamins A (retinol) and E (α-tocopherol) in static magnetic field-exposed rats. Toxicol Ind Health. 27(10):949-955, 2011a.

In the present study, we evaluate the effect of the co-exposure to static magnetic field (SMF) and selenium (Se) on the antioxidant vitamins A and E levels and some other parameters of oxidative stress in rat. Sub-acute exposure of male adult rats to a uniform SMF (128 mT, 1 h/day during 5 consecutive days) increased plasma activity of glutathione peroxidase (+35%) but decreased α-tocopherol (-67%) and retinol levels (-41%). SMF exposure failed to alter the plasmatic thiobarbituric acid-reactive species (TBARs), total thiol groups and selenium concentrations. Sub-chronic administration of Se (Na(2)SeO(3), 0.2 mg/L, for 30 consecutive days, per os) ameliorated the antioxidant capacities in SMF-treated rats. Our investigation demonstrated that sub-acute exposure to SMF induced oxidative stress, which may be prevented by a pretreatment with selenium.

(E) (VO, CE, IAO, DAO) Ghodbane S, Amara S, Garrel C, Arnaud J, Ducros V, Favier A, Sakly M, Abdelmelek H. Selenium supplementation ameliorates static magnetic field-induced disorders in antioxidant status in rat tissues. Environ Toxicol Pharmacol. 31(1):100-106, 2011b.

The aim of this study was to investigate the effect of selenium supplementation on the antioxidant enzymatic system (such as GPx, GR and SOD), GSH and selenium level in liver, kidney, muscle and brain of static magnetic field (SMF) exposed rats. Male adult rats were divided into control rats (n=6), SMF-exposed rats (128 mT; 1h/day for 5 days), selenium-treated rats (Na(2)SeO(3), 0.2mg/l, in drinking water for 4 weeks) and co-exposed rats (selenium for 4 weeks and SMF during the last 5 consecutive days). Sub-acute exposure to SMF induces a decrease of selenium levels in kidney, muscle and brain. Our results also revealed a decrease of GPx activities in kidney and muscle. By contrast, SMF exposure increased total GSH levels and total SOD activities in liver, while glutathione reductase activity is unaffected. Selenium supplementation in SMF-exposed rats restored selenium levels in kidney, muscle and brain and elevated the activities of GPx in kidney and muscle to those of control group. In the liver, selenium supplementation failed to bring down the elevated levels of total GSH and SOD activity. Our investigations suggested that sub-acute exposure to SMF altered the antioxidant response by decreasing the level of total selenium in kidney, muscle and brain. Interestingly, selenium supplementation ameliorates antioxidant capacity in rat tissues exposed to SMF.

Ghodbane S, Lahbib A, Sakly M, Abdelmelek H. Bioeffects of static magnetic fields: oxidative stress, genotoxic effects, and cancer studies. Biomed Res Int. 2013:602987, 2013. (review)

The interaction of static magnetic fields (SMFs) with living organisms is a rapidly growing field of investigation. The magnetic fields (MFs) effect observed with radical pair recombination is one of the well-known mechanisms by which MFs interact with biological systems. Exposure to SMF can increase the activity, concentration, and life time of paramagnetic free radicals, which might cause oxidative stress, genetic mutation, and/or apoptosis. Current evidence suggests that cell proliferation can be influenced by a treatment with both SMFs and anticancer drugs. It has been recently found that SMFs can enhance the anticancer effect of chemotherapeutic drugs; this may provide a new strategy for cancer therapy. This review focuses on our own data and other data from the literature of

SMFs bioeffects. Three main areas of investigation have been covered: free radical generation and oxidative stress, apoptosis and genotoxicity, and cancer. After an introduction on SMF classification and medical applications, the basic phenomena to understand the bioeffects are described. The scientific literature is summarized, integrated, and critically analyzed with the help of authoritative reviews by recognized experts; international safety guidelines are also cited.

(E) (VO, CE, IX) Ghodbane S1, Amara S, Lahbib A, Louchami K, Sener A, Sakly M, Abdelmelek H. Vitamin E prevents glucose metabolism alterations induced by static magnetic field in rats. Environ Sci Pollut Res Int. 21(22):12731-12738, 2014.

In the present study, we investigate the effects of a possible protective role of vitamin E (vit E) or selenium (Se) on glucose metabolism disruption induced by static magnetic field (SMF) in rats. Rats have been exposed to SMF (128 mT, 1 h/day during 5 days). Our results showed that SMF failed to alter body weight and relative liver weight. Our data demonstrated that exposure to SMF increased (+21 %) blood glucose level and caused a decrease (-15 %) in liver glycogen content. Moreover, the same treatment induced a reduction of pancreatic islet area. Interestingly, supplementation with vit E (DL α-tocopherol acetate, 150 mg/kg per os during 5 days) prevented alterations induced by SMF on glucose metabolism and liver glycogen content, whereas supplementation with Se (Na_2SeO_3, 0.20 mg/l, in drinking water for 4 weeks) restored only hepatic glycogen contents. By contrast, both vit E and Se failed to correct the area of pancreatic islets.

(E) (VO, CE, IAO, AO) Ghodbane S, Ammari M, Lahbib A, Sakly M, Abdelmelek H. Static magnetic field exposure-induced oxidative response and caspase-independent apoptosis in rat liver: effect of selenium and vitamin E supplementations. Environ Sci Pollut Res Int. 22(20):16060-16066, 2015a.

In the present study, we investigated the implication of oxidative stress and apoptosis under static magnetic field (SMF) in the brain and liver. Moreover, we estimated the protective role of selenium and vitamin E in rat tissues against disorders induced by SMF. Exposure of rats to SMF (128 mT, 1 h/day during five consecutive days) increased the activity of catalase (CAT) (+24 %) in the liver but not in the brain. By contrast, the same treatment failed to alter malondialdehyde (MDA) concentration in the brain and liver. Exposure to SMF also induced hepatocyte apoptosis through a caspase-independent pathway involving mitochondrial apoptosis-inducing factor (AIF) but not in the brain. Selenium and vitamin E supplementations to SMF-exposed rats restored liver CAT activity but failed to minimize liver apoptosis.

(E) (VO, CE, IAO, IOD, AO) Ghodbane S, Lahbib A, Ammari M, Sakly M, Abdelmelek H. Does static magnetic field-exposure induced oxidative stress and apoptosis in rat kidney and muscle? Effect of vitamin E and selenium supplementations. Gen Physiol Biophys. 34(1):23-32, 2015b.

Static magnetic fields (SMFs) effect observed with radical pair recombination is one of the well-known mechanisms by which SMFs interact with biological systems. Our aim was to study whether SMF induces oxidative stress and apoptosis in rat tissues and to evaluate the possible protector effect of selenium (Se) and vitamin E (vit E) supplementations. Rats were randomly divided into control, SMF-exposed, Se-treated, vit E-treated, SMF exposed rats and co-treated with Se, and SMF exposed rats and co-treated with vit E. After animal sacrifice, catalase (CAT) activity and malondialdehyde (MDA) concentration were measured and apoptosis inducing factor (AIF) immunohistochemical labeling was performed in kidney and muscle. Exposure of rats to SMF (128 mT, 1 h/day for 5 days) increased the MDA concentrations (+25%) and CAT activities (+34%) in kidney but not in muscle. By contrast, the same treatment failed to induce a caspase-independent pathway apoptosis in both tissues. Interestingly, Se pre-treatment inhibited the increase of MDA concentrations and CAT activities in kidney in SMF-exposed rats. However, vit E administration corrected only MDA levels in rat kidney. In conclusion, exposure to SMF induced oxidative stress in kidney that can be prevented by treatment with Se or vit E.

(NE)(VT, AE, IX) Giorgi G, Lecciso M, Capri M, Lukas Yani S, Virelli A, Bersani F, Del Re B. An evaluation of genotoxicity in human neuronal-type cells subjected to oxidative stress under an extremely low frequency pulsed magnetic field. Mutat Res Genet Toxicol Environ Mutagen. 775-776:31-37, 2014.

The possible genotoxicity of extremely low frequency magnetic field (ELF-MF) exposure is still a controversial topic. The most of the reported data suggests that it alone does not affect DNA integrity, but several recent reports have suggested that sinusoidal ELF-MF may increase the effect of known genotoxic agents. Only a few studies deal with non sinusoidal ELF-MF, including pulsed magnetic field (PMF), which are produced by several devices. The aim of this study is to investigate whether PMF exposure can interfere with DNA damage and repair in the presence of a genotoxic oxidative agent in neuronal type cells. To this purpose gamma-H2AX foci formation, which is a sensitive marker of DNA double strand breaks (DSB), was investigated at different points of time (1, 24, 48, 72h) after the H2O2 treatment (300μM for 1h) under PMF exposure (1mT, 50Hz) in human neuroblastoma BE(2)C cells. Moreover, cytotoxicity evaluation, by MTT assay and cell cycle analysis, was performed at various points of time after the treatment. Taken together, results suggest that PMF exposure does not interfere with genotoxicity and cytotoxicity induced by oxidative stress.

(E) (VT, AE, IOD, IX) Giorgi G, Pirazzini C, Bacalini MG, Giuliani C, Garagnani P, Capri M, Bersani F, Del Re B. Assessing the combined effect of extremely low-frequency magnetic field exposure and oxidative stress on LINE-1 promoter methylation in human neural cells. Radiat Environ Biophys. 56(2):193-200, 2017.

Extremely low frequency magnetic fields (ELF-MF) have been classified as "possibly carcinogenic", but their genotoxic effects are still unclear. Recent findings indicate that epigenetic mechanisms contribute to the genome dysfunction and it is well known that they are affected by environmental factors. To our knowledge, to date the question of whether exposure to ELF-MF can influence

epigenetic modifications has been poorly addressed. In this paper, we investigated whether exposure to ELF-MF alone and in combination with oxidative stress (OS) can affect DNA methylation, which is one of the most often studied epigenetic modification. To this end, we analyzed the DNA methylation levels of the 5'untranslated region (5'UTR) of long interspersed nuclear element-1s (LINE-1 or L1), which are commonly used to evaluate the global genome methylation level. Human neural cells (BE(2)C) were exposed for 24 and 48 h to extremely low frequency pulsed magnetic field (PMF; 50 Hz, 1 mT) in combination with OS. The methylation levels of CpGs located in L1 5'UTR region were measured by MassARRAY EpiTYPER. The results indicate that exposures to the single agents PMF and OS induced weak decreases and increases of DNA methylation levels at different CpGs. However, the combined exposure to PMF and OS lead to significant decrease of DNA methylation levels at different CpG sites. Most of the changes were transient, suggesting that cells can restore homeostatic DNA methylation patterns. The results are discussed and future research directions outlined.

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(E) (VO, CE, DOD, IAO) Glinka M, Sieroń A, Birkner E, Cieślar G. Influence of extremely low-frequency magnetic field on the activity of antioxidant enzymes during skin wound healing in rats. Electromagn Biol Med. 32(4):463-470, 2013.

The aim of this study was to evaluate the activity of the antioxidant enzymes mitochondrial and cytosolic superoxide dismutase (EC 1.15.1.1), glutathione peroxidase (POX, EC 1.11.1.9) and glutathione S-transferase (EC 3.1.2.7), as well as the concentration of malone dialdehyde (MDA), as an indicator of lipid peroxidation rate in the liver tissue homogenates and blood serum of male rats exposed to extremely low-frequency magnetic field (ELF-MF) in order to improve the healing process of an experimental cut wound on the back of each animal. The exposure to ELF-MF with frequency 40 Hz and magnetic flux density 10 mT induced an increase in POX serum activity and a decrease in MDA contents in the liver tissue, which suggests the inhibition of phospholipid peroxidation and subsequent stabilization of cellular membranes, as a result of ELF-MF action. Based on the results obtained, it seems that ELF-MF could be a useful supplement in the complex treatment of prolonged wound healing, due to the activation of endogenous enzymatic antioxidant system.

(E) (IV, AE, DAO) Glinka M, Gawron S, Sieroń A, Pawłowska-Góral K, Cieślar G, Sieroń K. Impact of Static Magnetic Field on the Antioxidant Defence System of Mice Fibroblasts. Biomed Res Int. 2018:5053608, 2018.

Results of research assessing the biological impact of static magnetic fields are controversial. So far, they have not provided a clear answer to their influence on cell functioning. Since the use of permanent magnets both in everyday life and in industry becomes more and more widespread, the investigations are continued in order to explain these controversies and to evaluate positive applications. The goal of current work was to assess the impact of static magnetic field of different intensities on redox homeostasis in cultures of fibroblasts. The use of permanent magnets allowed avoiding the thermal effects which are present in electromagnets. During the

research we used 6 chambers, designed exclusively by us, with different values of field flux density (varying from 0.1 to 0.7 T). We have noted the decrease in the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx). The static magnetic fields did not modify the energy state of fibroblasts- adenosine triphosphate (ATP) concentration was stable, as well as the generation of malondialdehyde (MDA)-which is a marker of oxidative stress. Results of research suggest that static magnetic fields generated by permanent magnets do not cause oxidative stress in investigated fibroblasts and that they may show slight antioxidizing activity.

Ghodbane S, Lahbib A, Sakly M, Abdelmelek H. Bioeffects of static magnetic fields: oxidative stress, genotoxic effects, and cancer studies. Biomed Res Int. 2013:602987, 2013. (review)

The interaction of static magnetic fields (SMFs) with living organisms is a rapidly growing field of investigation. The magnetic fields (MFs) effect observed with radical pair recombination is one of the well-known mechanisms by which MFs interact with biological systems. Exposure to SMF can increase the activity, concentration, and life time of paramagnetic free radicals, which might cause oxidative stress, genetic mutation, and/or apoptosis. Current evidence suggests that cell proliferation can be influenced by a treatment with both SMFs and anticancer drugs. It has been recently found that SMFs can enhance the anticancer effect of chemotherapeutic drugs; this may provide a new strategy for cancer therapy. This review focuses on our own data and other data from the literature of SMFs bioeffects. Three main areas of investigation have been covered: free radical generation and oxidative stress, apoptosis and genotoxicity, and cancer. After an introduction on SMF classification and medical applications, the basic phenomena to understand the bioeffects are described. The scientific literature is summarized, integrated, and critically analyzed with the help of authoritative reviews by recognized experts; international safety guidelines are also cited.

(E) (VO, CE, IOD) Gok DK, Akpinar D, Hidisoglu E, Ozen S, Agar A, Yargicoglu P. The developmental effects of extremely low frequency electric fields on visual and somatosensory evoked potentials in adult rats. Electromagn Biol Med. 35(3):245-259, 2016.

The purpose of our study was to investigate the developmental effects of extremely low frequency electric fields (ELF-EFs) on visual evoked potentials (VEPs) and somatosensory-evoked potentials (SEPs) and to examine the relationship between lipid peroxidation and changes of these potentials. In this context, thiobarbituric acid reactive substances (TBARS) levels were determined as an indicator of lipid peroxidation. Wistar albino female rats were divided into four groups; Control (C), gestational (prenatal) exposure (Pr), gestational+ postnatal exposure (PP) and postnatal exposure (Po) groups. Pregnant rats of Pr and PP groups were exposed to 50 Hz electric field (EF) (12 kV/m; 1 h/day), while those of C and Po groups were placed in an inactive system during pregnancy. Following

parturition, rats of PP and Po groups were exposed to ELF-EFs whereas rats of C and Pr groups were kept under the same experimental conditions without being exposed to any EF during 68 days. On postnatal day 90, rats were prepared for VEP and SEP recordings. The latencies of VEP components in all experimental groups were significantly prolonged versus C group. For SEPs, all components of PP group, P2, N2 components of Pr group and P1, P2, N2 components of Po group were delayed versus C group. As brain TBARS levels were significantly increased in Pr and Po groups, retina TBARS levels were significantly elevated in all experimental groups versus C group. In conclusion, alterations seen in evoked potentials, at least partly, could be explained by lipid peroxidation in the retina and brain.

(E) (VT, CE, IRF, IOD, DAO) Goraca A, Ciejka E, Piechota A. Effects of extremely low frequency magnetic field on the parameters of oxidative stress in heart. J Physiol Pharmacol. 61(3):333-338, 2010.

Increasing production of free radicals in organisms is one of the putative mechanisms by which a extremely low frequency magnetic field (ELF-MF) may affect biological systems. The present study was designated to assess if ELF-MF applied in the magnetotherapy, affects generation of reactive oxygen species (ROS) in heart tissue and antioxidant capacity of plasma according to its working time. The experiments were performed on 3 groups of animals: group I - control; group II - exposed to 40 Hz, 7 mT, 30 min/day for 14 days (this field is commonly applied in magnetotherapy); group III - exposed to 40 Hz, 7 mT, 60 min/day for 14 days. Control rats were housed in a separate room without exposure to ELF-MF. Immediately after the last exposure, blood was taken from the tail vein and hearts were removed under anesthesia. The effect of the exposure to ELF-MF on oxidative stress was assessed on the basis of the measurements of thiobarbituric acid reactive substances (TBARS), hydrogen peroxide (H(2)O(2)), total free sulphydryl groups (-SH groups) and reduced glutathione (GSH) concentrations in heart homogenates. The total antioxidant capacity of plasma was measured using ferric reducing ability method (FRAP). Exposure to ELF-MF (40 Hz, 7 mT, 30 min/day for 2 weeks) did not significantly alter tissue TBARS, H(2)O(2), total free -SH groups, reduced glutathione (GSH) and total antioxidant capacity of plasma. By contrast, ELF-MF with the same frequency and induction but used for 60 min/day for 14 days caused significant increase in TBARS and H(2)O(2) concentration ($P<0.01$) and decrease in the concentration of GSH ($P<0.05$) and total free -SH groups in heart homogenates. Moreover, exposure of rats to ELF-MF (40 Hz, 7 mT, 60 min/day for 2 weeks) resulted in the decrease of plasma antioxidant capacity. Our results indicate that effects of ELF-MF on ROS generation in the heart tissue and antioxidant capacity of plasma depend on its working time.

(E) (VT, AE, IFR, cell type dependent) Groiss S, Lammegger R, Brislinger D. Anti-Oxidative and Immune Regulatory Responses of THP-1 and PBMC to Pulsed EMF Are Field-Strength Dependent. Int J Environ Res Public Health 18(18):9519m 2021.

Innate immune cells react to electromagnetic fields (EMF) by generating reactive oxygen species (ROS), crucial intracellular messengers. Discrepancies in applied parameters of EMF studies, e.g., flux densities, complicate direct comparison of downstream anti-oxidative responses and immune regulatory signaling. We therefore compared the impact of different EMF flux densities in human leukemic THP1 cells and peripheral blood mononuclear cells (PBMC) of healthy donors to additionally consider a potential disparate receptivity based on medical origin. ROS levels increased in THP1 cells stimulated with lipopolysaccharide (LPS) after one hour of EMF exposure. Moreover, weak EMF mitigated the depletion of the reducing agent NAD(P)H in THP1. Neither of these effects occurred in PBMC. Landscaping transcriptional responses to varied EMF revealed elevation of the anti-oxidative enzymes PRDX6 (2-fold) and DHCR24 (6-fold) in THP1, implying involvement in lipid metabolism. Furthermore, our study confirmed anti-inflammatory effects of EMF by 6-fold increased expression of IL10. Strikingly, THP1 responded to weak EMF, while PBMC were primarily affected by strong EMF, yet with severe cellular stress and enhanced rates of apoptosis, indicated by HSP70 and caspase 3 (CASP3). Taken together, our results emphasize an altered susceptibility of immune cells of different origin and associate EMF-related effects with anti-inflammatory signaling and lipid metabolism.

(E) (VO, CE, IOD, DAO) Guleken Z, Kula-Maximenko M, Depciuch J, Kılıç AM, Sarıbal D. Detection of the chemical changes in blood, liver, and brain caused by electromagnetic field exposure using Raman spectroscopy, biochemical assays combined with multivariate analyses. Photodiagnosis Photodyn Ther 38:102779, 2022.

The effects of the electromagnetic field on living organisms have been studied for several years. In this article, we showed what kind of cold change an extremely low-frequency electromagnetic field (ELF-MF) exposure 500 μT 50 Hz by using a Meritt Coil System causes in the samples of the brain and liver samples. To measure oxidative load, we measured malondialdehyde (MDA) and glutathione (GSH) levels. To identify the chemical changes, we collected Raman spectra of cerebellum, left brain, right brain and liver tissue from the control group of animals and from the animal, which were exposed to an electromagnetic field (ELF-MF group). Obtained results showed, that lipid peroxidation was increased and the antioxidant response was decreased. In the brain samples the shift of peaks corresponding to the amide III vibrations existed after ELF-MF exposure. Structural changes were detected in CH_2 vibrations originating from lipids in both hemispheres. Additionally, the number of amide III bonds was increased with ELF-MF exposure in the cerebellum and left-brain tissue. In liver tissue higher Raman intensities were visible in the tissues from the ELF-MF group. In this group electromagnetic field also caused structural changes in lipids. Principal component analysis (PCA) showed, that it is possible to distinguish ELF-MF and control groups. Consequently, hierarchical component analysis (HCA) showed that tissues from ELF-MF and control groups separately created similarity with the groups. Obtained results suggest that the electromagnetic field caused structural and quantitative chemical changes in brain and liver tissue. Additionally, present data suggest that ELF-MF plays an important role in the regulation of enzyme activity and has effects on biochemical processes, possibly improved by production of ROS.

(E) (VO, CE, IFR, IOD, DAO) Guler G, Turkozer Z, Tomruk A, Seyhan N. The protective effects of N-acetyl-L-cysteine and epigallocatechin-3-gallate on electric field-induced hepatic oxidative stress. Int J Radiat Biol. 84(8):669-680, 2008.

PURPOSE: To investigate the effects of 12 kV/m electric (E) field sourced by power lines on oxidative and nitrosative stress, and antioxidant status. Furthermore, the study aimed to examine the protective effects of N-Acetyl-L-cysteine (NAC) and epigallocatechin-gallate (EGCG) in the liver tissues of guinea pigs against the possible detriments of electromagnetic field exposure. MATERIALS AND METHODS: Guinea pigs were exposed to 50 Hz 12 kV/m E-field. NAC and EGCG were administered intraperitoneally. Malonedialdehyde (MDA), a product of lipid peroxidation (LPO), and nitric oxide derivatives (nitrate (NO(3)), nitrite (NO(2)), total level of nitric oxide (NO(x)) were estimated as biomarkers of oxidative and nitrosative stress, respectively. Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and myeloperoxidase (MPO) were evaluated as endogenous antioxidant enzymes in liver tissues of the guinea pigs. RESULTS: The results of our study indicated a significant increase in the levels of oxidant products (MDA, NO(3), NO(2), NO(x)), and a significant decrease in antioxidant enzyme (SOD, GSH-Px and MPO) activities. We also found that the individual or plus application of NAC and EGCG resulted in the reduction of oxidative stress prior to E field application. CONCLUSION: To conclude, extremely low frequency (ELF) electric field has potential harmful effects on the living organisms by enhancing the free radical production. NAC and EGCG might have hepatoprotective effects in ELF-E field induced oxidative and nitrosative stress.

(NE) (VO, CE) Güler G, Türközer Z, Ozgur E, Tomruk A, Seyhan N, Karasu C. Protein oxidation under extremely low frequency electric field in guinea pigs. Effect of N-acetyl-L-cysteine treatment. Gen Physiol Biophys. 28(1):47-55, 2009a.

Modern age exposes humans to an increasing level of electromagnetic activity in their environment due to overhead power lines and transformers around residential areas. Studies have shown that treatment with antioxidants can suppress the oxidative damage induced by electromagnetic fields in various frequencies of the non-ionizing radiation band. In this study, we detected protein carbonyl content (PCO), advanced oxidation protein products (AOPP) in liver and 3-nitrotyrosine (3-NT) levels in plasma of guinea pigs in order to investigate the effects of N-acetyl-L-cysteine (NAC) administration on oxidative protein damage induced by power frequency electric (E) field (50 Hz, 12 kV/m, 7 days/8 h/day). We also analyzed hepatic hydroxyproline level to study protein synthesis. According to the findings of the present study, no statistically significant changes occurred in PCO, AOPP and 3-NT levels of the guinea pigs that were exposed to the E field with respect to the control group. However, liver hydroxyproline level was significantly diminished in the E field exposure group compared to the control and PCO, hydroxyproline and 3-NT levels changed significantly in the NAC-administrated groups.

(NE) (VO, CE) Güler G, Türközer Z, Ozgur E, Seyhan N. Antioxidants alleviate electric field-induced effects on lung tissue based on assays of heme oxygenase-1, protein carbonyl content, malondialdehyde, nitric oxide, and hydroxyproline. Sci Total Environ. 407(4):1326-1332, 2009b.

In order to test whether antioxidants have beneficiary effects on electric field induced damage, we determined the pulmonary levels of heme oxygenase-1 (HO-1), protein carbonyl content (PCO), malondialdehyde (MDA), nitric oxide (NO) and hydroxyproline (HP) under extremely low frequency (ELF) electric (E) field exposure (50 Hz, 12 kV/m, 7 days/for 8 h/day). While PCO levels significantly increased ($p<0.05$), insignificant changes ($p>0.05$) were observed in HO-1, MDA, NO and HP levels for electric field exposure groups compared to the control group. We have not observed any significant change in these parameters on the electric field group compared to the group where NAC and EGCG were separately applied along with electric field. However, during our previous studies, we have concluded that NAC and EGCG are potent antioxidants and we believe that new studies should be established by way of setting up different experimental conditions.

(E) (VO, CE, AO) Guo, Y., FU, Y, Sun W. 50 Hz Magnetic Field Exposure Inhibited Spontaneous Movement of Zebrafish Larvae through ROS-Mediated syn2a Expression. Int. J. Mol. Sci. 24(8), 7576, 2023.

Extremely low frequency electromagnetic field (ELF-EMF) exists widely in public and occupational environments. However, its potential adverse effects and the underlying mechanism on nervous system, especially behavior are still poorly understood. In this study, zebrafish embryos (including a transfected synapsin IIa (syn2a) overexpression plasmid) at 3 h post-fertilization (hpf) were exposed to a 50-Hz magnetic field (MF) with a series of intensities (100, 200, 400 and 800 μT, respectively) for 1 h or 24 h every day for 5 days. Results showed that, although MF exposure did not affect the basic development parameters including hatching rate, mortality and malformation rate, yet MF at 200 μT could significantly induce spontaneous movement (SM) hypoactivity in zebrafish larvae. Histological examination presented morphological abnormalities of the brain such as condensed cell nucleus and cytoplasm, increased intercellular space. Moreover, exposure to MF at 200 μT inhibited syn2a transcription and expression, and increased reactive oxygen species (ROS) level as well. Overexpression of syn2a could effectively rescue MF-induced SM hypoactivity in zebrafish. Pretreatment with N-acetyl-L-cysteine (NAC) could not only recover syn2a protein expression which was weakened by MF exposure, but also abolish MF-induced SM hypoactivity. However, syn2a overexpression did not affect MF-increased ROS. Taken together, the findings suggested that exposure to a 50-Hz MF inhibited spontaneous movement of zebrafish larvae via ROS-mediated syn2a expression in a nonlinear manner.

(E) (VT, AE, IFR, DFR) Gurhan H, Bruzon R, Kandala S, Greenebaum B, Barnes F. Effects Induced by a Weak Static Magnetic Field of Different Intensities on HT-1080 Fibrosarcoma Cells. Bioelectromagnetics 42:212-223, 2021.

In this study, we investigated the effects of weak static magnetic fields (SMFs) on HT-1080 human fibrosarcoma cells. Exposures to SMFs for four consecutive days were varied from 0.5 to 600 μT for treated units, while exposures to control units were held at 45 μT. Growth rates were measured by comparing cell counts, whereas membrane potentials, mitochondrial calcium, mitochondrial superoxide (O_2^-), nitric oxide (NO), hydrogen peroxide (H_2O_2), intercellular pH, and oxidative stress were measured by using fluorescent dyes. The relative cell growth rates vary with the angle of the SMFs. Increases in the magnitude of the SMFs increased concentrations of mitochondrial calcium and membrane potential and decreased intracellular pH. H_2O_2, an important reactive oxygen species (ROS), increases at 100 and 200 μT, decreases at 300 and 400 μT and increases again at 500 and 600 μT. Overall, oxidative stress increases slightly with increasing SMFs, while superoxide and NO concentrations decrease. These results indicate that weak SMFs can accelerate and inhibit cell growth rates and induce alterations in ROS. Changes in ROS and oxidative stress are important for various cell functions. Calcium influx into mitochondria was one of the initial steps into the corresponding changes.

(E) (VO, CE, IFR, IAO) Haghighat N, Abdolmaleki P, Ghanati F, Behmanesh M, Payez A.Modification of catalase and MAPK in Vicia faba cultivated in soil with high natural radioactivity and treated with a static magnetic field. J Plant Physiol. 171(5):99-103, 2014.

The effects of a static magnetic field (SMF) and high natural radioactivity (HR) on catalase and MAPK genes in Vicia faba were investigated. Soil samples with high natural radioactivity were collected from Ramsar in north Iran where the annual radiation absorbed dose from background radiation is higher than 20mSv/year. The specific activity of the radionuclides of (232)Th, (236)Ra, and (40)K was measured using gamma spectrometry. The seeds were planted either in the soil with high natural radioactivity or in the control soils and were then exposed to a SMF of 30mT for 8 days; 8h/day. Levels of expression of catalase and MAPK genes, catalase activity and H2O2 content were evaluated. The results demonstrated significant differences in the expression of catalase and MAPK genes in SMF- and HR-treated plants compared to the controls. An increase in catalase activity was accompanied by increased expression of its gene and accumulation of H2O2. Relative expression of the MAPK gene in treated plants, however, was lower than those of the controls. The results suggest that the response of V. faba plants to SMF and HR may be mediated by modification of catalase and MAPK.

(E) (VT, AE, IAO, IFC, IX) Hajipour Verdom B, Abdolmaleki P, Behmanesh M. The static magnetic field remotely boosts the efficiency of doxorubicin through modulating ROS behaviors. Sci Rep. 8(1):990, 2018.

Exposure to magnetic field (MF) can affect cellular metabolism remotely. Cardio-toxic effects of Doxorubicin (DOXO) have limited clinical uses at high dose. MF due to its effect on reactive oxygen species (ROS) lifetime, may provide a suitable choice to boost the efficacy of this drug at low dose. Here, we investigated the potential effects of homogenous static magnetic field (SMF) on DOXO-

induced toxicity and proliferation rate of cancer cells. The results indicated that SMF similar to DOXO decreased the cell viability as well as the proliferation rate of MCF-7 and HFF cells. Moreover, combination of 10 mT SMF and 0.1 µM DOXO decreased the viability and proliferation rate of cancer and normal cells in a synergetic manner. In spite of high a GSH level in cancer cell, SMF boosts the generation and lifetime of ROS at low dose of DOXO, and overcame to GSH mediated drug resistance. The results also confirmed that SMF exposure decreased 50% iron content of cells, which is attributed to iron homeostasis. In conclusion, these findings suggest that SMF can decrease required dose of chemotherapy drug s such as DOXO and thereby decrease their side effect.

(E) (VO, CE, IAO, LI) Hajnorouzi A, Vaezzadeh M, Ghanati F, Jamnezhad H, Nahidian B. Growth promotion and a decrease of oxidative stress in maize seedlings by a combination of geomagnetic and weak electromagnetic fields. J Plant Physiol. 168(10):1123-1128, 2011.

In the present study, we hypothesized that an appropriate combination of a geomagnetic field (as a static field) and an alternative magnetic field may result in the promotion of maize seedling growth by an alleviation of an excess production of reactive oxygen species. First, we determined the applicable range of frequencies by theoretical calculations, and a combined magnetic field was designed. The seeds were germinated in the magnetic field for 4 days, and the seedlings were allowed to grow in a nutrient solution for another 4 days. The magnetic field-treated maize seeds produced seedlings with a faster growth rate than the control seeds. The activity of superoxide dismutase in the magnetic field-treated seedlings was lower, while the total antioxidant capacity of these seedlings was higher than that of the control group. The maintenance of membrane integrity and a decrease of iron content in the magnetic field-treated seedlings suggest that a combination of both static and alternative magnetic fields promotes the growth of the plants by lowering iron absorption, a reduction in the Fenton chemistry, and lowering the risk of oxidative burst.

(E) (VT, AE, IFR, AO, MC) Hambarde S, Manalo JM, Baskin DS, Sharpe MA, Helekar SA. Spinning magnetic field patterns that cause oncolysis by oxidative stress in glioma cells. Sci Rep. 13(1):19264, 2023.

Raising reactive oxygen species (ROS) levels in cancer cells to cause macromolecular damage and cell death is a promising anticancer treatment strategy. Observations that electromagnetic fields (EMF) elevate intracellular ROS and cause cancer cell death, have led us to develop a new portable wearable EMF device that generates spinning oscillating magnetic fields (sOMF) to selectively kill cancer cells while sparing normal cells in vitro and to shrink GBM tumors in vivo through a novel mechanism. Here, we characterized the precise configurations and timings of sOMF stimulation that produce cytotoxicity due to a critical rise in superoxide in two types of human glioma cells. We also found that the antioxidant Trolox reverses the cytotoxic effect of sOMF on glioma cells indicating that ROS play a causal role in producing the effect. Our findings clarify the link between the physics of magnetic stimulation and its

mechanism of anticancer action, facilitating the development of a potential new safe noninvasive device-based treatment for GBM and other gliomas.

(E) (VO, AE, IOD, IAO) Hanini R, Chatti A, Ghorbel SB, Landoulsi A. Role of SOD gene in response to static magnetic fields in Pseudomonas aeruginosa. Curr Microbiol. 74(8):930-937, 2017.

The protective role of superoxide dismutase (SOD) against non-ionizing radiation such as static electromagnetic field (200 mT) has been studied in wild-type and mutant strain of Pseudomonas aeruginosa lacking cytosolic Mn-SOD (sodM), Fe-SOD (sodB), or both SODs (sodMB). Our results showed that inactivation of sodM and/or sodB genes increases the sensitivity of P. aeruginosa toward stress induced by the static magnetic field (200 mT). Furthermore, our results showed an enhancement of SOD, catalase, and peroxidases after exposure to the magnetic field. However, wild-type cells maintained significantly higher activities of antioxidant enzymes than mutant strains. The malondialdehyde produced by the oxidative degradation of unsaturated lipids and fatty acids showed significant increase in mutant strains compared to the wild-type. The overall results showed that the SOD has a protective role against a stress induced by static electromagnetic field in P. aeruginosa.

(NE) (VO, CE) Harakawa S, Inoue N, Hori T, Tochio K, Kariya T, Takahashi K, Doge F, Suzuki H, Nagasawa H. Effects of a 50 Hz electric field on plasma lipid peroxide level and antioxidant activity in rats. Bioelectromagnetics. 26(7):589-594, 2005.

The effects of exposure to extremely low frequency electric fields (ELF EFs) on plasma lipid peroxide levels and antioxidant activity (AOA) in Sprague-Dawley rats were studied. The test was based on comparisons among rats treated with a combination of the oxidizing agent, 2,2'-azobis(2-aminopropane) dihydrochloride (AAPH) and 50 Hz EF of 17.5 kV/m intensity for 15 min per day for 7 days, AAPH alone, EF alone or no treatment. EF significantly decreased the plasma peroxide level in rats treated with AAPH, similar to treatment by ascorbic acid or the superoxide dismutase. Ascorbic acid increased AOA; however, EF and superoxide dismutase did not change AOA compared with sham exposure in stressed rats. No influence on the lipid peroxide level and AOA in unstressed rats was observed with EF exposure alone. Although the administration of AAPH decreased AOA, this decrease did not change when EF was added. These data indicate that the ELF EF used in this study influenced the lipid peroxide level in an oxidatively stressed rat.

(E) (VO, CE, IOD, DAO) Hashish AH, El-Missiry MA, Abdelkader HI, Abou-Saleh RH. Assessment of biological changes of continuous whole body exposure to static magnetic field and extremely low frequency electromagnetic fields in mice. Ecotoxicol Environ Saf. 71(3):895-902. 2008.

The question whether static magnetic fields (SMFs) and extremely low frequency electromagnetic fields (ELF-EMF) cause biological effects is of special interest. We investigated the effects of continuous whole body exposure to both fields for 30 days on some liver

and blood parameters in mice. Two exposure systems were designed; the first produced a gradient SMF while the second generated uniform 50Hz ELF-EMF. The results showed a gradual body weight loss when mice were exposed to either field. This is coupled with a significant decrease ($P<0.05$) in the levels of glucose, total protein and the activity of alkaline phosphatase in serum. A significant increase in lactate dehydrogenase activity was demonstrated in serum and liver paralleled with a significant elevation in hepatic gamma-glutamyl transferase activity. The glutathione-S-transferase activity and lipid peroxidation level in the liver were significantly increased while a significant decrease in hepatic gluthathione content was recorded. A significant decrease in the counts of monocytes, platelets, peripheral lymphocytes as well as splenic total, T and B lymphocytes levels was observed for SMF and ELF-EMF exposed groups. The granulocytes percentage was significantly increased. The results indicate that there is a relation between the exposure to SMF or ELF-EMF and the oxidative stress through distressing redox balance leading to physiological disturbances.

(E) (VT, CE, IFR) He W-F, Qin R, Gao Y-H, Zhou J, Wei J-J, Liu J, X Hou X-F, Ma H-P, Xian CJ, Li X-Y, Chen K-M. The interdependent relationship between the nitric oxide signaling pathway and primary cilia in pulse electromagnetic field-stimulated osteoblastic differentiation. FASEB J 2022, 36(6):e22376.

Pulsed electromagnetic fields (PEMFs) have long been recognized being safe and effective in treating bone fracture nonunion and osteoporosis. However, the mechanism of osteogenic action of PEMFs is still unclear. While primary cilia are reported to be a sensory organelle for PEMFs, and nitric oxide (NO) plays an indispensable role in osteogenic effect of PEMFs, the relationship between NO and primary cilia is unknown. In this study, effects of treatment with 50 Hz 0.6 mT PEMFs on osteogenic differentiation and mineralization, NO secretion, and ciliary location of specific proteins were examined in rat calvarial osteoblasts (ROBs) with normal or abrogated primary cilia. It was found that PEMFs stimulated the osteogenic differentiation by activating the NOS/NO/sGC/cGMP/PKG signaling pathway, which need the existence of primary cilia. All components of the signaling pathway including iNOS, eNOS, sGC, PKG-1, and PKG-2 were localized to primary cilia, and eNOS was phosphorylated inside the primary cilia. Besides, primary cilia were elongated significantly by PEMF treatment and changed dynamically with the activation NO/cGMP pathway. When the pathway was blocked by L-NAME, PEMFs could no longer elongate the primary cilia and stimulate the osteoblastic differentiation. Thus, this study for the first time observed activation of the NO/cGMP signaling pathway in ciliary compartment of osteoblasts, and PEMFs could not stimulate the osteoblastic differentiation if the NO signaling pathway was blocked or the ciliogenesis was inhibited. Our findings indicate the interdependent relationship between NO and primary cilia in the PEMF-promoted osteogenesis.

(E) (VT, AE, IOD, IFR, IAO, DAO) Henrykowska G, Jankowski W, Pacholski K, Lewicka M, Smigielski J, Dziedziczak-Buczyńska M, Buczyński A. The effect of 50 Hz magnetic field of different shape on oxygen metabolism in blood platelets: in vitro studies. Int J Occup Med Environ Health. 22(3):269-276, 2009.

OBJECTIVES: The aim of the study was to assess the influence that the shape of low frequency magnetic field may have on catalase and superoxide dismutase activity, malondialdehyde concentration and free radicals generation in human blood platelets. MATERIALS AND METHODS: The suspension of human blood platelets was exposed for 15 min to 50 Hz magnetic field of different shape, and flux density of 10 mT. RESULTS: The determinations of free radicals, malondialdehyde and catalase showed increased values compared with the initial level, regardless of the shape of the magnetic field applied. In contrast, superoxide dismutase activity was lower than at the onset of the experiment. CONCLUSIONS: The findings indicate that the oxidative stress resulting from exposure to 50 Hz magnetic field of 10 mT induction may produce a number of adverse effects within the cell and thus may lead to systemic disturbances in the human body.

(NE) (VT, AE) Hong MN, Han NK, Lee HC, Ko YK, Chi SG, Lee YS, Gimm YM, Myung SH, Lee JS. Extremely low frequency magnetic fields do not elicit oxidative stress in MCF10A cells. Radiat Res. 53(1):79-86, 2012.

The aim of this study was to determine whether extremely low frequency magnetic fields (ELF-MF) could affect intracellular reactive oxygen species (ROS) levels and antioxidant enzyme activity. After MCF10A human breast epithelial cells were exposed to 1 mT of 60 Hz ELF-MF for 4 hours, intracellular ROS level, superoxide dismutase (SOD) activity, and reduced to oxidized glutathione (GSH/GSSG) ratio were measured. The cells exposed to ELF-MF did not evidence statistically significant changes in the above-mentioned biological parameters as compared to either the incubator controls or sham-exposed cells. By way of contrast, the IR-exposed cells exhibited marked changes in ROS level, SOD activity, and GSH/GSSG ratio. When we assessed morphological changes and senescence-associated beta-galactosidase (SA-β-Gal) activity, only the IR-exposed cells were positive. According to our results, it could be concluded that ELF-MF has no effect on intracellular ROS level, SOD activity, and GSH/GSSG ratio under our exposure condition.

(E) (HU, CE, IOD, IAO) Hosseinabadi MB, Khanjani N. The effect of extremely low-frequency electromagnetic fields on the prevalence of musculoskeletal disorders and the role of oxidative stress. Bioelectromagnetics. 40(5):354-360, 2019.

Extremely low-frequency electromagnetic fields (ELF-EMFs) may cause negative health effects. This study aimed to investigate the direct and indirect effects of chronic exposure to extremely low-frequency electric and magnetic fields on the prevalence of musculoskeletal disorders (MSDs). In this cross-sectional study, 152 power plant workers were enrolled. The exposure level of employees was measured based on the IEEE Std C95.3.1 standard. Superoxide dismutase (SOD), catalase (Cat), glutathione peroxidase (GPx), total antioxidant capacity (TAC), and malondialdehyde (MDA) (independent variables) were measured in the serum of subjects. The Nordic musculoskeletal questionnaire was used to assess MSDs (dependent variable). The mean exposure of electric and magnetic fields were 4.09 V/m (standard deviation [SD] = 4.08) and 16.27 μT (SD = 22.99), respectively. Increased levels of SOD, Cat, GPx, and MDA had a direct significant relation with MSDs. In the logistic regression model, SOD (odds ratio

[OR] = 0.952, P = 0.026), GPx (OR = 0.991, P = 0.048), and MDA (OR = 0.741, P = 0.021) were significant predictors of MSDs. ELF-EMFs were not related to MSDs directly; however, increased levels of oxidative stress may cause MSDs.

(E) (HU, CE, AO) Hosseinabadi MB, Narges Khanjani , Pirasteh Norouzi, Ali Faghihi-Zarandi, Davood Darban-Sarokhalil, Seyed Sajjad Khoramrooz, Seyed Reza Mirbadie , Mehdi Mirzaii. The Effects of Antioxidant Vitamins on Proinflammatory Cytokines and Some Biochemical Parameters of Power Plant Workers: A Double-Blind Randomized Controlled Clinical Trial. Bioelectromagnetics 42(1): 18-26, 2020.

Some epidemiological studies have suggested that exposure to extremely low-frequency magnetic fields (ELF-MFs) can affect the immune system. This study aimed to investigate the effects of antioxidant vitamin consumption on proinflammatory cytokines and biochemical parameters changes. In this randomized, controlled double-blinded trial study, power plant workers exposed to ELF-MFs were enrolled based on inclusion criteria. Ninety-one eligible subjects were randomly divided into four groups: the first group (400 units of vitamin E/day), second group (1,000 mg of vitamin C/day), third group (400 units of vitamin E and 1,000 mg of vitamin C/day), and control group. The intervention was conducted for 3 months. Proinflammatory cytokines interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), and biochemical parameters (fasting blood sugar, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol [HDL-c], total protein, and albumin) were measured among the participants' serums, before and after the intervention. The mean level of IL-6 in all vitamin-receiving groups, the mean level of IL-1β in vitamin C and E&C groups, and the mean level of TNF-α in the vitamin C group, decreased significantly after intervention. The arithmetic means of the effect sizes for IL-1β, IL-6, and TNF-α were 0.71, 0.57, and 0.2, respectively. The level of HDL-c in the vitamin E and vitamin E&C groups and the level of triglyceride in the vitamin C group significantly increased after the intervention. Taking antioxidant vitamins can prevent an increase of proinflammatory cytokines induced by prolonged exposure to ELF-MFs.

(E) (HU, CE, IOD, IAO) Hosseinabadi MB, Khanjani N, Norouzi P, Mirbadie SR, Fazli M, Mirzaii M. Oxidative stress associated with long term occupational exposure to extremely low frequency electric and magnetic fields. Work 2021;68(2):379-386.

Background: Occupational exposure to extremely low frequency electromagnetic fields (ELF-EMFs) may have harmful effects on biologic systems and has raised many concerns in the last decades. **Objective:** The aim of this study was to determine the effects of exposure to extremely low frequency electric and magnetic fields on lipid peroxidation and antioxidant enzyme activities. **Methods:** This study was conducted on 115 power plant workers as the exposed group and 145 office workers as the non-exposed group. The levels of Malondialdehyde (MDA), superoxide dismutase (SOD), Catalase (Cat), and total antioxidant capacity (TAC) were measured in the serum of all subjects. Exposure to ELF-EMFs was measured based on spot measurements and the IEEE Std C95.3.1 standard. **Results:** The levels of MDA, SOD, and Cat in the exposed group were significantly higher than in the non-exposed group. However, the level of TAC was not significantly different between the exposed (2.45±1.02) and non-exposed (2.21±1.07)

groups. The levels of MDA and SOD were higher among workers with higher exposure to electric fields than workers with low exposure. All oxidative stress indicators increased with increased exposure to magnetic fields, except TAC. **Conclusions:** The antioxidant system imbalance among power plant workers may be related to long term occupational exposure to electromagnetic fields.

(E) (VT, AE, IFR) Höytö A, Herrala M, Luukkonen J, Juutilainen J, Naarala J. Cellular detection of 50 Hz magnetic fields and weak blue light: effects on superoxide levels and genotoxicity. Int J Radiat Biol. 7:1-7, 2017.

PURPOSE: We tested the hypothesis that the effects of 50 Hz magnetic fields (MFs) on superoxide levels and genotoxicity depend on the presence of blue light. MATERIALS AND METHODS: Human SH-SY5Y neuroblastoma cells were exposed to a 50 Hz, 100 μT MF with or without non-phototoxic level of blue light for 24 h. We also studied whether these treatments alter responses to menadione, an agent that induces mitochondrial superoxide ($O_2^{\bullet -}$) production and DNA damage. Micronuclei, proliferation, viability, cytosolic and mitochondrial $O_2^{\bullet -}$ levels were assessed. RESULTS: MF (without blue light) increased cytosolic $O_2^{\bullet -}$ production and blue light suppressed this effect. Mitochondrial $O_2^{\bullet -}$ production was reduced by both MF and blue light, but these effects were not additive. Micronucleus frequency was not affected by blue light or MF alone, but blue light (significantly when combined with MF) enhanced menadione-induced micronuclei. CONCLUSIONS: The original simple hypothesis (blue light is needed for MF effects) was not supported, but interaction of MF and blue light was nevertheless observed. The results are consistent with MF effects on light-independent radical reactions.

(E) (VO, CE, DFR) Hu Y, Lai J, Wan B, Liu X, Zhang Y, Zhang J, Sun D, Ruan G, Liu E, Liu GP, Chen C, Wang DW. Long-term exposure to ELF-MF ameliorates cognitive deficits and attenuates tau hyperphosphorylation in 3xTg AD mice. Neurotoxicology 53:290-300, 2016.

Although numerous studies have reported the influence of extremely low frequency magnetic field (ELF-MF) exposure on human health, its effects on cognitive deficits in Alzheimer's disease (AD) have remained under debate. Moreover, the influence of ELF-MF on hyperphosphorylated tau, which is one of the most common pathological hallmarks of AD, has not been reported to date. Therefore, transgenic mice (3xTg) were used in the present study. 3xTg mice, which express an APP/PS1 mutation combined with a tau (P301L) mutation and that develop cognitive deficits at 6 months of age, were subjected to ELF-MF (50Hz, 500μT) exposure or sham exposure daily for 3 months. We discovered that ELF-MF exposure ameliorated cognitive deficits and increased synaptic proteins in 3xTg mice. The protective effects of ELF-MF exposure may have also been caused by the inhibition of apoptosis and/or decreased oxidative stress levels that were observed in the hippocampus tissues of treated mice. Furthermore, tau hyperphosphorylation was decreased in vivo because of ELF-MF exposure, and this decrease was induced by the inhibition of GSK3β

and CDK5 activities and activation of PP2Ac. We are the first to report that exposure to ELF-MF can attenuate tau phosphorylation. These findings suggest that ELF-MF exposure could act as a valid therapeutic strategy for ameliorating cognitive deficits and attenuating tau hyperphosphorylation in AD.

(E) (VT, AE, IX, AO) Jajte J, Zmyślony M, Palus J, Dziubałtowska E, Rajkowska E. Protective effect of melatonin against in vitro iron ions and 7 mT 50 Hz magnetic field-induced DNA damage in rat lymphocytes. Mutat Res. 483(1-2):57-64, 2001.

We have previously shown that simultaneous exposure of rat lymphocytes to iron ions and 50Hz magnetic field (MF) caused an increase in the number of cells with DNA strand breaks. Although the mechanism of MF-induced DNA damage is not known, we suppose that it involves free radicals. In the present study, to confirm our hypothesis, we have examined the effect of melatonin, an established free radicals scavenger, on DNA damage in rat peripheral blood lymphocytes exposed in vitro to iron ions and 50Hz MF. The alkaline comet assay was chosen for the assessment of DNA damage. During pre-incubation, part of the cell samples were supplemented with melatonin (0.5 or 1.0mM). The experiments were performed on the cell samples incubated for 3h in Helmholtz coils at 7mT 50Hz MF. During MF exposure, some samples were treated with ferrous chloride (FeCl2, 10microg/ml), while the rest served as controls. A significant increase in the number of cells with DNA damage was found only after simultaneous exposure of lymphocytes to FeCl2 and 7mT 50Hz MF, compared to the control samples or those incubated with FeCl2 alone. However, when the cells were treated with melatonin and then exposed to iron ions and 50Hz MF, the number of damaged cells was significantly reduced, and the effect depended on the concentration of melatonin. The reduction reached about 50% at 0.5mM and about 100% at 1.0mM. Our results indicate that melatonin provides protection against DNA damage in rat lymphocytes exposed in vitro to iron ions and 50Hz MF (7mT). Therefore, it can be suggested that free radicals may be involved in 50Hz magnetic field and iron ions-induced DNA damage in rat blood lymphocytes. The future experimental studies, in vitro and in vivo, should provide an answer to the question concerning the role of melatonin in the free radical processes in the power frequency magnetic field.

(E) (VT, AE, IX) Jajte J, Grzegorczyk J, Zmyślony M, Rajkowska E. Effect of 7 mT static magnetic field and iron ions on rat lymphocytes: apoptosis, necrosis and free radical processes. Bioelectrochemistry. 57(2):107-111, 2002.

Simultaneous exposure of rat lymphocytes to 7 mT static magnetic field (SMF) and iron ions caused an increase in the number of cells with DNA damage. The mechanism by which MF induces DNA damage and the possible cytotoxic consequences are not known. However, we suppose that free radicals are involved. Potentially, the deterioration of DNA molecules by simultaneous exposure to 7 mT SMF and iron ions may lead to cell death: apoptosis or necrosis. The possible prooxidative properties of these two agents may result in an induction of the lipid peroxidation process as a marker of free radical mechanism in the cells. Experiments were performed on rat blood lymphocytes incubated for 3 h in Helmholtz coils at SMF of flux density 7 mT. During SMF exposure, some samples were treated with ferrous chloride (10 microg/ml), the rest serving as controls. We used the dye exclusion method with the DNA-

fluorochromes: ethidium bromide and acridine orange. No significant differences were observed between unexposed lymphocytes incubated with medium alone and lymphocytes exposed to 7 mT SMF. Three-hour incubation with FeCl(2) (10 microg/ml) did not affect cell viability. However, when lymphocytes were exposed to 7 mT SMF and simultaneously treated with FeCl(2), there was a significant increase in the percentage of apoptotic and necrotic cells accompanied by significant alterations in cell viability. As compared to lipid peroxidation, there is a significant increase in the amount of lipid peroxidation end products MDA+4 HNE in rat lymphocytes after simultaneous exposure to 7 mT SMF and FeCl(2) (vs. to the control samples and those exposed to SMF alone). This suggests that 7 mT static magnetic field in the presence of Fe(2+) ions can increase the concentration of oxygen free radicals and thus may lead to cell death.

(E) (VT, AE, IX, AO) Jajte J, Zmyślony M, Rajkowska E. [Protective effect of melatonin and vitamin E against prooxidative action of iron ions and static magnetic field]. Med Pr. 54(1):23-28, 2003. [Article in Polish]

The purpose of this study was to examine the effect of melatonin and vitamin E (trolox) on the level of lipid peroxidation in rat blood lymphocytes after in vitro (3 h) exposure to iron ions and/or 7mT static magnetic field (SMF). The lipid peroxidation process was chosen as a marker of free radical mechanism of SMF in cells. The cells were supplemented with (0.5 mM) melatonin or (0.1 mM) vitamin E (trolox) in preincubation. During SMF exposure in Helmholtz coils some samples were treated with ferrous chloride (10 mg/ml or 20 mg/ml), while the rest served as controls. There is a significant increase in the amount of lipid peroxidation end-products (4-HNE + MDA) in rat lymphocytes after simultaneous exposure to 7 mT SMF and iron ions (versus control samples and those exposed to SMF alone). Instead, when the cells were treated with melatonin or trolox and then exposed to iron ions and 7 mT SMF, the level of lipid peroxidation was significantly reduced. The results also indicated that melatonin is less effective than vitamin E (trolox) in inhibiting lipid peroxidation under the experimental conditions used.

(E) (VO, CE, IOD) Jakubowska-Lehrmann M, Białowąs M, Otremba Z, Hallmann A, Śliwińska-Wilczewska S, Urban-Malinga B. Do magnetic fields related to submarine power cables affect the functioning of a common bivalve? Mar Environ Res 179:105700, 2022.

The aim of the study was to determine the effect of static magnetic field (SMF) and electromagnetic field (EMF), of values usually recorded near submarine cables, on the bioenergetics, oxidative stress, and neurotoxicity in the cockle Cerastoderma glaucum. Bivalves maintained a positive energy balance, but the filtration rate and energy available for individual production were significantly lower in SMF-exposed animals compared to the control treatment. No changes in the respiration were noted but ammonia excretion rate was significantly lower after exposure to EMF. Changes in the activities of antioxidant enzymes and the lipid peroxidation were not observed however, exposure to both fields resulted in increased protein carbonylation. After exposure to EMF a significant

inhibition of acetylcholinesterase activity was observed. As the present study for the first time revealed the oxidative damage and neurotoxicity in marine invertebrate after exposure to artificial magnetic fields, the need for further research is highlighted.

(E) (VT, AE, IFR, DFR) (cell type-dependent) Jedrzejczak-Silicka M, Kordas M, Konopacki M, Rakoczy R. Modulation of Cellular Response to Different Parameters of the Rotating Magnetic Field (RMF)-An In Vitro Wound Healing Study. Int J Mol Sci 22(11):5785, 2021.

Since the effect of MFs (magnetic fields) on various biological systems has been studied, different results have been obtained from an insignificant effect of weak MFs on the disruption of the circadian clock system. On the other hand, magnetic fields, electromagnetic fields, or electric fields are used in medicine. The presented study was conducted to determine whether a low-frequency RMF (rotating magnetic field) with different field parameters could evoke the cellular response in vitro and is possible to modulate the cellular response. The cellular metabolic activity, ROS and Ca^{2+} concentration levels, wound healing assay, and gene expression analyses were conducted to evaluate the effect of RMF. It was shown that different values of magnetic induction (*B*) and frequency (*f*) of RMF evoke a different response of cells, e.g., increase in the general metabolic activity may be associated with the increasing of ROS levels. The lower intracellular Ca^{2+} concentration (for 50 Hz) evoked the inability of cells to wound closure. It can be stated that the subtle balance in the ROS level is crucial in the wound for the effective healing process, and it is possible to modulate the cellular response to the RMF in the context of an in vitro wound healing.

(E) (VO, CE, IFR, IOD, IAO) Jelenković A, Janać B, Pesić V, Jovanović DM, Vasiljević I, Prolić Z. Effects of extremely low-frequency magnetic field in the brain of rats. Brain Res Bull. 68(5):355-360, 2006.

An extremely low-frequency magnetic field (50 Hz, 0.5 mT) was used to investigate its possible effect on the brain of adult male Wistar rats following a 7-day exposure. The control rats were sham-exposed. Superoxide dismutase activities and production of superoxide radicals, lipid peroxidation, and nitric oxide were examined in the frontal cortex, striatum, basal forebrain, hippocampus, brainstem, and cerebellum. Significantly increased superoxide radical contents were registered in all the structures examined. Production of nitric oxide, which can oppose superoxide radical activities, was significantly increased in some structures: the frontal cortex, basal forebrain, hippocampus, and brainstem. Augmentation of lipid peroxydation was also observed, with significance only in the basal forebrain and frontal cortex, in spite of the significantly increased superoxide dismutase activities and nitric oxide production in the basal forebrain, and increased production of nitric oxide in the frontal cortex. The results obtained indicate that a 7-day exposure to extremely low-frequency magnetic field can be harmful to the brain, especially to the basal forebrain and frontal cortex due to development of lipid peroxidation. Also, high production of superoxide anion in all regions may compromise nitric oxide signaling processes, due to nitric oxide consumption in the reaction with the superoxide radical.

(E) (VO, AE, IFR) Jeong JH, Kum C, Choi HJ, Park ES, Sohn UD. Extremely low frequency magnetic field induces hyperalgesia in mice modulated by nitric oxide synthesis. Life Sci. 78(13):1407-1412, 2006.

We investigated an effect of extremely low frequency magnetic field (ELF-MF, 60 Hz) on hyperalgesia using hot plate test. The level of nitric oxide (NO) and the expression of nitric oxide synthase (NOS) were measured to determine if ELF-MF is engaged in NO mediated pain mechanism. Additionally, the involvement of Ca2+-dependent NO pathway in ELF-MF induced hyperalgesia was evaluated by blocking Ca2+ sources with NMDA receptor antagonist and Ca2+ channel blocker. The exposure of mice to ELF-MF lowered pain threshold and elevated NO synthesis in brain and spinal cord. An NOS inhibitor blocked these effects of ELF-MF with attenuating the reduction of pain threshold and the rise of NO level in brain and spine by the exposure of ELF-MF. The hyperalgesic effects of ELF-MF were also blocked by a Ca2+ channel blocker, nimodipine, but not by a NMDA receptor antagonist, MK-801. The expression of Ca2+ -dependent nNOS and eNOS and Ca2+ -independent iNOS were not changed by ELF-MF. These results indicated that the exposure of ELF-MF might cause Ca2+ -dependent NOS activation, which then induces hyperalgesia with the increase in NO synthesis. In conclusion, ELF-MF may produce hyperalgesia by modulating NO synthesis via Ca2+ -dependent NOS.

(NE) (VT, AE) Jin H, Yoon HE, Lee JS, Kim JK, Myung SH, Lee YS. Effects on g2/m phase cell cycle distribution and aneuploidy formation of exposure to a 60 Hz electromagnetic field in combination with ionizing radiation or hydrogen peroxide in l132 nontumorigenic human lung epithelial cells. Korean J Physiol Pharmacol. 19(2):119-124, 2015.

The aim of the present study was to assess whether exposure to the combination of an extremely low frequency magnetic field (ELF-MF; 60 Hz, 1 mT or 2 mT) with a stress factor, such as ionizing radiation (IR) or H2O2, results in genomic instability in non-tumorigenic human lung epithelial L132 cells. To this end, the percentages of G2/M-arrested cells and aneuploid cells were examined. Exposure to 0.5 Gy IR or 0.05 mM H2O2 for 9 h resulted in the highest levels of aneuploidy; however, no cells were observed in the subG1 phase, which indicated the absence of apoptotic cell death. Exposure to an ELF-MF alone (1 mT or 2 mT) did not affect the percentages of G2/M-arrested cells, aneuploid cells, or the populations of cells in the subG1 phase. Moreover, when cells were exposed to a 1 mT or 2 mT ELF-MF in combination with IR (0.5 Gy) or H2O2 (0.05 mM), the ELF-MF did not further increase the percentages of G2/M-arrested cells or aneuploid cells. These results suggest that ELF-MFs alone do not induce either G2/M arrest or aneuploidy, even when administered in combination with different stressors.

(NE) (VT, AE) Jin YB, Kang GY, Lee JS, Choi JI, Lee JW, Hong SC, Myung SH, Lee YS. Effects on micronuclei formation of 60-Hz electromagnetic field exposure with ionizing radiation, hydrogen peroxide, or c-Myc overexpression. Int J Radiat Biol. 88(4):374-80, 2012.

PURPOSE: Epidemiological studies have demonstrated a possible correlation between exposure to extremely low-frequency magnetic fields (ELF-MF) and cancer. However, this correlation has yet to be definitively confirmed by epidemiological studies. The principal objective of this study was to assess the effects of 60 Hz magnetic fields in a normal cell line system, and particularly in combination with various external factors, via micronucleus (MN) assays. MATERIALS AND METHODS: Mouse embryonic fibroblast NIH3T3 cells and human lung fibroblast WI-38 cells were exposed for 4 h to a 60 Hz, 1 mT uniform magnetic field with or without ionizing radiation (IR, 2 Gy), H(2)O(2) (100 μM) and cellular myelocytomatosis oncogene (c-Myc) activation. RESULTS: The results obtained showed no significant differences between the cells exposed to ELF-MF alone and the unexposed cells. Moreover, no synergistic effects were observed when ELF-MF was combined with IR, H(2)O(2), and c-Myc activation. CONCLUSIONS: Our results demonstrate that ELF-MF did not enhance MN frequency by IR, H(2)O(2) and c-Myc activation.

(NE) (VT, AE) Jin YB, Choi SH, Lee JS, Kim JK, Lee JW, Hong SC, Myung SH, Lee YS. Absence of DNA damage after 60-Hz electromagnetic field exposure combined with ionizing radiation, hydrogen peroxide, or c-Myc overexpression. Radiat Environ Biophys. 53(1):93-101, 2014.

The principal objective of this study was to assess the DNA damage in a normal cell line system after exposure to 60 Hz of extremely low frequency magnetic field (ELF-MF) and particularly in combination with various external factors, via comet assays. NIH3T3 mouse fibroblast cells, WI-38 human lung fibroblast cells, L132 human lung epithelial cells, and MCF10A human mammary gland epithelial cells were exposed for 4 or 16 h to a 60-Hz, 1 mT uniform magnetic field in the presence or absence of ionizing radiation (IR, 1 Gy), H_2O_2 (50 μM), or c-Myc oncogenic activation. The results obtained showed no significant differences between the cells exposed to ELF-MF alone and the unexposed cells. Moreover, no synergistic or additive effects were observed after 4 or 16 h of pre-exposure to 1 mT ELF-MF or simultaneous exposure to ELF-MF combined with IR, H_2O_2, or c-Myc activation.

(E) (VO, CE, IOD, DAO) Jouni FJ, Abdolmaleki P, Ghanati F. Oxidative stress in broad bean (Vicia faba L.) induced by static magnetic field under natural radioactivity. Mutat Res. 741(1-2):116-121, 2012.

The investigation was performed to evaluate the influence of the static magnetic field on oxidative stress in Vicia faba cultivated in soil from high background natural radioactivity in Iran. Soil samples were collected from Ramsar, Iran where the annual radiation absorbed dose from background radiation is substantially higher than 20 mSv/year. The soil samples were then divided into 2 separate groups including high and low natural radioactivity. The plants were continuously exposed to static magnetic field of 15 mT for 8 days, each 8h/day. The results showed that in the plants cultivated in soils with high background natural radioactivity and low background natural radioactivity the activity of antioxidant enzymes as well as flavonoid content were lower than those of the control. Treatment of plants with static magnetic field showed similar results in terms of lowering of antioxidant defense system and increase of peroxidation of membrane lipids. Accumulation of ROS also resulted in chromosomal aberration and DNA damage. This

phenomenon was more pronounced when a combination of natural radiation and treatment with static magnetic field was applied. The results suggest that exposure to static magnetic field causes accumulation of reactive oxygen species in V. faba and natural radioactivity of soil exaggerates oxidative stress.

(E) (VT, AE, IFR, IX) Kamalipooya S, Abdolmaleki P, Salemi Z, Javani Jouni F, Zafari J, Soleimani H. Simultaneous application of cisplatin and static magnetic field enhances oxidative stress in HeLa cell line. In Vitro Cell Dev Biol Anim. 53(9):783-790, 2017.

In this study, we reported the effects of simultaneous application of static magnetic field (SMF) and cisplatin as an anticancer drug on the oxidative stress in human cervical cancer (HeLa) cell line and normal skin fibroblast cells (Hu02). The cells were exposed to different SMF intensities (7, 10, and 15 mT) for 24 and 48 h. IC_{50} concentrations of cisplatin were obtained by MTT assay. The cytotoxic effects of combined treatment were studied by measuring the intracellular reactive oxygen species content using flow cytometric method and estimation of membrane lipid peroxidation by spectrophotometry. Statistical analysis was assessed using one-way repeated measures analysis of variance (ANOVA) followed by Tukey's test. Based on the obtained results, the highest and lowest death rate, respectively, in HeLa and Hu02 cell lines was observed at the intensity of 10 mT. Also, we found that membrane lipid peroxidation in cancer cells is higher than that of normal counterparts. SMF potently sensitized human cervical cancer cells to cisplatin through reactive oxygen species (ROS) accumulation while it had small effects on normal cells. The combination of both treatments for 48 h led to a marked decrease in the viability percentage of HeLa cells by about 89% compared to untreated cells. This study suggests that conjugation of both physical and chemical treatments could increase the oxidative stress in HeLa cell line and among three optional intensities of SMF, the intensity of 10 mT led to the higher damage to cancer cells in lower doses of drug.

(E) (VO, CE, IOD) Kantar Gok D, Akpinar D, Yargicoglu P, Ozen S, Aslan M, Demir N, Derin N, Agar A. Effects of extremely low-frequency electric fields at different intensities and exposure durations on mismatch negativity. Neuroscience. 272C:154-166, 2014.

The effects of extremely low-frequency electric fields (ELF-EFs, 3-300Hz) on lipid peroxidation levels and antioxidant enzyme activities have been shown in many tissues and plasma after exposure to 50-Hz alternating current (AC) electric fields. However, similar studies investigating brain lipid peroxidation status are limited. Moreover and as far as we know, no study has been conducted to examine mismatch negativity (MMN) response in rats following exposure to a 50-Hz AC electric field. Therefore, the purpose of the study was to investigate different intensities and exposure durations of ELF-EFs on MMN component of event-related potentials (ERPs) as well as apoptosis and oxidative brain damage in rats. Ninety male rats, aged 3months were used in our study. A total of six groups, composed of 15 animals each, was formed as follows: sham-exposed rats for 2weeks (C2), sham-exposed rats for 4weeks

(C4), rats exposed to 12-kV/m and 18-kV/m electric fields for 2weeks (E12-2 and E18-2), rats exposed to 12- and 18-kV/m electric fields for 4weeks (E12-4 and E18-4). At the end of the experimental period, MMN responses were recorded in urethane-anesthetized rats by electrodes positioned stereotaxically to the surface of the dura. After MMN recordings, animals were killed by exsanguination and their brain tissues were removed for 4-hydroxy-2-nonenal (4-HNE), protein carbonyl and TUNEL analysis. In the current study, different change patterns in ERP parameters were observed dependent on the intensity and exposure duration of ELF-EFs. There were differences in the amplitudes of ERP between the responses to the standard and the deviant tones in all groups. When peak-to-peak amplitude of the difference curves was evaluated, MMN amplitude was significantly decreased in the E18-4 group compared with the C4 group. Additionally, the amount of 4-HNE was increased in all experimental groups compared with the control group. Consequently, it could be concluded that electric field decreased MMN amplitudes possibly induced by lipid peroxidation.

(E) (VO, CE, IFR, IAO, IOD) Karimi SA, Salehi I, Shykhi T, Zare S, Komaki A. Effects of exposure to extremely low-frequency electromagnetic fields on spatial and passive avoidance learning and memory, anxiety-like behavior and oxidative stress in male rats. Behav Brain Res. 359:630-638, 2019.

There are many controversies about the safety of extremely low-frequency electromagnetic field (ELF-EMF) on body health and cognitive performance. In the present study, we explored the effects of ELF-EMF on oxidative stress and behaviors of rats. Seventy-two adult male Wistar rats were randomly divided into following groups, control, sham exposure group and the ELF-EMF exposure groups (1 μT, 100 μT, 500 μT, and 2000 μT). After 60 days exposure (2 h/day), elevated plus maze (EPM), Morris water maze (MWM) and Passive avoidance learning (PAL) tasks were used to evaluate the anxiety-like behavior, spatial and passive learning and memory, respectively. Some days after behavioral examination, oxidative stress markers were measured. During spatial reference memory test, animals in ELF-EMF exposure groups (100, and 2000 μT) spent more time in target zone ($F(4, 55) = 5.699$, $P = 0.0007$, One-way ANOVA). In PAL retention, the step through latency in the retention test (STLr) in ELF-EMF exposure groups (100,500, and 2000 μT) was significantly greater than control group ($F(4, 55) = 29.13$, $P < 0.0001$, One-way ANOVA). In EPM test, ELF-EMF exposure (500 and 2000 μT) decreased the percentage of the entries into the open arms ($F(4, 55) = 26.31$, $P < 0.0001$, one-way ANOVA). ELF-EMF exposure (100, and 500 μT) increased Malondialdehyde (MDA) concentration ($F(4, 25) = 79.83$, $P < 0.0001$, One-way ANOVA). Our results may allow the conclusion that exposure to ELF-EMFs can improve memory retention (but not acquisition) in the adult male rats. Although exposure to ELF-EMFs could be a factor in the development of anxious state or oxidative stress.

(E) (VO, AE, IFR, MC) Kataria S, Jain M, Tripathi DK, Singh VP. Involvement of nitrate reductase-dependent nitric oxide production in magnetopriming-induced salt tolerance in soybean. Physiol Plant. 168(2):422-436, 2020.

In the present study, experiments were performed to investigate the role of nitric oxide (NO) in magnetopriming-induced seed germination and early growth characteristics of soybean (Glycine max) seedlings under salt stress. The NO donor (sodium nitroprusside, SNP), NO scavenger (2-[4-carboxyphenyl]-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide, CPTIO), inhibitors of nitrate reductase (sodium tungstate, ST) or NO synthase (N-nitro-L-Arg-methyl ester, LNAME) and NADPH oxidase inhibitor (diphenylene iodonium, DPI) have been used to measure the role of NO in the alleviation of salinity stress by static magnetic field (SMF of 200 mT, 1 h). Salt stress (50 mM NaCl) significantly reduced germination and early growth of seedlings emerged from non-primed seeds. Pre-treatment of seeds with SMF positively stimulated the germination and consequently promoted the seedling growth. ST, LNAME, CPTIO and DPI significantly decreased the growth of seedling, activities of α-amylase, protease and nitrate reductase (NR), hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet-}$) and NO content in roots of seedlings emerged from non-primed and SMF-primed seeds. However, the extent of reduction was higher with ST in seedlings of SMF-primed seeds under both conditions, whereas SNP promoted all the studied parameters. Moreover, the generation of NO was also confirmed microscopically using a membrane permanent fluorochrome (4-5-diaminofluorescein diacetate [DAF-2 DA]). Further, analysis showed that SMF enhanced the NR activity and triggered the NO production and NR was maximally decreased by ST as compared to LNAME, CPTIO and DPI. Thus, in addition to ROS, NO might be one of the important signaling molecules in magnetopriming-induced salt tolerance in soybean and NR may be responsible for SMF-triggered NO generation in roots of soybean.

(E) (VO, AE, IFR) Kavaliers M, Choleris E, Prato FS, Ossenkopp K. Evidence for the involvement of nitric oxide and nitric oxide synthase in the modulation of opioid-induced antinociception and the inhibitory effects of exposure to 60-Hz magnetic fields in the land snail. Brain Res. 809(1):50-57, 1998.

The attenuation of opioid peptide-mediated antinociception is a well-established effect of extremely low frequency (ELF) electromagnetic fields with alterations in calcium channel function and/or calcium ion flux and protein kinase C activity being implicated in the mediation of these effects. The present study was designed to examine the effects of nitric oxide (NO) and calcium ion/calmodulin-dependent nitric oxide synthase (NOS) on opioid-induced antinociception and their involvement in mediating the inhibitory effects of exposure to ELF magnetic fields. We observed that enkephalinase (SCH 34826)-induced, and likely enkephalin-mediated, antinociception in the land snail, Cepaea nemoralis, as measured by the enhanced latency of a foot withdrawal response to a thermal (40 degreesC) stimulus, was reduced by the NO releasing agent, S-nitro-N-acetylpenicillamide (SNP), and enhanced by the NO synthase inhibitor, NG-nitro-l-arginine methyl ester (l-NAME). Exposure of snails to an ELF magnetic field (15 min, 60 Hz, 141 microT peak) also reduced the enkephalinase-induced antinociception. The inhibitory effects of the 60-Hz magnetic field were significantly reduced by the NO synthase inhibitor, l-NAME, and significantly enhanced by the NO releasing agent, SNP, at dosages which by themselves had no evident effects on nociceptive sensitivity. These results suggest that: (1) NO and NO synthase have antagonistic effects on opioid-induced analgesia in the snail, Cepaea and (2) the inhibitory effects of ELF magnetic fields on opioid analgesia involve alteration in NO and NO synthase activity.

(NE) (VT, AE) Kesari KK, Luukkonen J, Juutilainen J, Naarala J. Genomic instability induced by 50Hz magnetic fields is a dynamically evolving process not blocked by antioxidant treatment. Mutat Res Genet Toxicol Environ Mutagen. 794:46-51, 2015.

Increased level of micronuclei was observed in SH-SY5Y cells in a previous study at 8 and 15 days after exposure to extremely low frequency (ELF) magnetic fields (MF), indicating possible induction of genomic instability in the progeny of the exposed cells. The aim of this study was to further explore the induction of genomic instability by ELF MFs by increasing the follow-up time up to 45 days after exposure. Human SH-SY5Y neuroblastoma cells were exposed to a 50Hz, 100μT MF for 24h with or without co-exposure to menadione (MQ), a chemical agent that increases cellular superoxide production. Micronuclei, reactive oxygen species (ROS) and lipid peroxidation (LPO) were measured at 15, 30 and 45 days after exposure. To study the possible causal role of ROS in the delayed effects of MF, the antioxidant N-acetylcysteine (NAC) was administered before MF exposure. Consistently with the previous study, the level of micronuclei was statistically significantly elevated 15 days after exposure. A similar effect was observed at 30 days, but not at 45 days after exposure. The level of LPO was statically significantly decreased 30 and 45 days after exposure. Consistently with our previous findings, the MF effect did not depend on co-exposure to MQ. Treatment with NAC effectively decreased cellular ROS level and suppressed the effect of MQ on ROS, but it did not block the MF effect, indicating that increase in ROS is not needed as a causal link between MF exposure and induction of delayed effects. The results presented here are consistent with genomic instability that persists in the progeny of MF-exposed cells up to at least 30 days after exposure. Changes in LPO observed at 30 and 45 days after exposure indicates that the MF-initiated process may continue up to at least 45 days after exposure.

(E) (VT, AE, IFR) Kesari KK, Juutilainen J, Luukkonen J, Naarala J. Induction of micronuclei and superoxide production in neuroblastoma and glioma cell lines exposed to weak 50 Hz magnetic fields. J R Soc Interface. 2016 Jan;13(114). pii: 20150995.

Extremely low-frequency (ELF) magnetic fields (MF) have been associated with adverse health effects in epidemiological studies. However, there is no known mechanism for biological effects of weak environmental MFs. Previous studies indicate MF effects on DNA integrity and reactive oxygen species, but such evidence is limited to MFs higher (greater than or equal to 100 μT) than those generally found in the environment. Effects of 10 and 30 μT fields were studied in SH-SY5Y and C6 cells exposed to 50-Hz MFs for 24 h. Based on earlier findings, menadione (MQ) was used as a cofactor. Responses to MF were observed in both cell lines, but the effects differed between the cell lines. Micronuclei were significantly increased in SH-SY5Y cells at 30 μT. This effect was largest at the highest MQ dose used. Increased cytosolic and mitochondrial superoxide levels were observed in C6 cells. The effects on superoxide levels were independent of MQ, enabling further mechanistic studies without co-exposure to MQ. The micronucleus and mitochondrial superoxide data were consistent with a conventional rising exposure-response relationship. For cytosolic superoxide, the effect size was unexpectedly large at 10 μT. The results indicate that the threshold for biological effects of ELF MFs is 10 μT or less.

(E) (VT, AE, IFR) Khadir R, Morgan JL, Murray JJ. Effects of 60 Hz magnetic field exposure on polymorphonuclear leukocyte activation. Biochim Biophys Acta. 1472(1-2):359-367, 1999.

We have investigated the effects of a sinusoidal 60 Hz magnetic field on free radical (superoxide anion) production, degranulation (beta-glucuronidase and lysozyme release) and viability in human neutrophils (PMNs). Experiments were performed blindly in very controlled conditions to examine the effects of a magnetic field in resting PMNs and in PMNs stimulated with a tumor promoter: phorbol 12-myristate 13-acetate (PMA). Exposure of unstimulated human PMNs to a 60 Hz magnetic field did not affect the functions examined. In contrast, exposure of PMNs to a 22 milliTesla (mT), 60 Hz magnetic field induced significant increases in superoxide anion (O2-) production (26.5%) and in beta-glucuronidase release (53%) when the cells were incubated with a suboptimal stimulating dose of PMA. Release of lysozyme and lactate dehydrogenase was unchanged by the magnetic field, whether the cells were stimulated or not. A 60 Hz magnetic field did not have any effect on O2- generation by a cell-free system xanthine/xanthine oxidase, suggesting that a magnetic field could upregulate common cellular events (signal transduction) leading to O2- generation and beta-glucuronidase release. In conclusion, exposure of PMNs to a 22 mT, 60 Hz magnetic field potentiates the effect of PMA on O2- generation and beta-glucuronidase release. This effect could be the result of an alteration in the intracellular signaling.

(E) (VT, AE, IFR, AO) Kim SJ, Jang YW, Hyung KE, Lee DK, Hyun KH, Jeong SH, Min KH, Kang W, Jeong JH, Park SY, Hwang KW. Extremely low-frequency electromagnetic field exposure enhances inflammatory response and inhibits effect of antioxidant in RAW 264.7 cells. Bioelectromagnetics. 38(5):374-385, 2017.

In recent years, there has been a dramatic increase in the number and variety of electronic devices that emit electromagnetic waves. Because people live and work in close proximity to these pieces of electrical equipment, there is growing concern surrounding the destruction of homeostasis by electromagnetic field exposure. In the present study, the effects of 60 Hz 0.8 mT extremely low-frequency electromagnetic fields (ELF-EMF) on a macrophage cell line (RAW 264.7) were examined. Under defined ELF-EMF exposure conditions, the production of nitric oxide and pro-inflammatory cytokines, TNF-α, IL-1β, and IL-6, were increased in RAW 264.7 cells and the expression of those genes was also upregulated. However, cell proliferation was not altered. Translocation of NF-κB (nuclear factor kappa B), molecules that act downstream of the pro-inflammatory cytokines, were increased to the nucleus under ELF-EMF exposure conditions. In addition, we found that ELF-EMF exposure elevated activation of nuclear factor of activated T cells (NFAT) 2, as well as positively affected the influx of calcium. Furthermore, with both the presence of a potent antioxidant (Resveratrol) and downregulation of the antioxidant-related gene Prx-1 (Peroxiredoxin-1), ELF-EMF was associated with higher inflammatory responses of macrophages. These results suggest that an ELF-EMF amplifies inflammatory responses through enhanced macrophage activation and can decrease the effectiveness of antioxidants.

(E) (VT,AE, IX, MC) Kimsa-Dudek M, Synowiec-Wojtarowicz A, Derewniuk M, Gawron S, Paul-Samojedny M, Kruszniewska-Rajs C, Pawłowska-Góral K. Impact of fluoride and a static magnetic field on the gene expression that is associated with the antioxidant defense system of human fibroblasts. Chem Biol Interact. 287:13-19, 2018.

Fluoride cytotoxicity has been associated with apoptosis, oxidative stress, general changes in DNA and RNA and protein biosynthesis, whereas the results of studies on the effect of SMF on antioxidant activity of cells are contradictory. Therefore, the aim of our study was to evaluate the simultaneous exposure of human cells to fluoride SMF that are generated by permanent magnets on the expression profile of the genes that are associated with the antioxidant defense system. Control fibroblasts and fibroblasts that had been treated with fluoride were subjected to the influence of SMF with a moderate induction. In order to achieve our aims, we applied modern molecular biology techniques such as the oligonucleotide microarray. Among the antioxidant defense genes, five (SOD1, PLK3, CLN8, XPA, HAO1), whose expression was significantly altered by the action of fluoride ions and the exposure to SMF were normalized their expression was identified. We showed that fluoride ions cause oxidative stress, whereas exposure to SMF with a moderate induction can suppress their effects by normalizing the expression of the genes that are altered by fluoride. Our research may explain the molecular mechanisms of the influence of fluoride and SMF that are generated by permanent magnets on cells.

(E) (VT, AE, IFR, IOD) Kimsa-Dudek M, Synowiec-Wojtarowicz A, Krawczyk A, Kosowska A, Kimsa-Furdzik M, Francuz T. The Apoptotic Effect of Caffeic or Chlorogenic Acid on the C32 Cells That Have Simultaneously Been Exposed to a Static Magnetic Field. Int J Mol Sci 2022, 23(7):3859.

The induction of apoptosis is one of the main goals of the designed anti-cancer therapies. In recent years, increased attention has been paid to the physical factors such as magnetic fields and to the natural bioactive compounds and the possibilities using them in medicine. Hence, the aim of this study was to evaluate the anti-tumor effect of caffeic or chlorogenic acid in combination with a moderate-strength static magnetic field on C32 melanoma cells by assessing the effect of both factors on the apoptotic process. The apoptosis of the C32 cells was evaluated using a flow cytometry analysis. The expression of the apoptosis-associated genes was determined using the RT-qPCR technique. The caspase activity and the concentration of the oxidative damage markers were also measured. It was found that phenolic acids and a static magnetic field trigger the apoptosis of the C32 cells and also affect the expression of the genes encoding the apoptosis regulatory proteins. In conclusion, our study indicated that both of the phenolic acids and a static magnetic field can be used supportively in the treatment of melanoma and that caffeic acid is more pro-apoptotic than chlorogenic acid.

Kıvrak EG, Yurt KK, Kaplan AA, Alkan I, Altun G. Effects of electromagnetic fields exposure on the antioxidant defense system. J Microsc Ultrastruct. 5(4):167-176, 2017. (Review)

Technological devices have become essential components of daily life. However, their deleterious effects on the body, particularly on the nervous system, are well known. Electromagnetic fields (EMF) have various chemical effects, including causing deterioration in large molecules in cells and imbalance in ionic equilibrium. Despite being essential for life, oxygen molecules can lead to the generation of hazardous by-products, known as reactive oxygen species (ROS), during biological reactions. These reactive oxygen species can damage cellular components such as proteins, lipids and DNA. Antioxidant defense systems exist in order to keep free radical formation under control and to prevent their harmful effects on the biological system. Free radical formation can take place in various ways, including ultraviolet light, drugs, lipid oxidation, immunological reactions, radiation, stress, smoking, alcohol and biochemical redox reactions. Oxidative stress occurs if the antioxidant defense system is unable to prevent the harmful effects of free radicals. Several studies have reported that exposure to EMF results in oxidative stress in many tissues of the body. Exposure to EMF is known to increase free radical concentrations and traceability and can affect the radical couple recombination. The purpose of this review was to highlight the impact of oxidative stress on antioxidant systems.

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(E) (VO, CE, IOD, IAO) Klimek A, Nowakowska A, Kletkiewicz H, Wyszkowska J, Maliszewska J, Jankowska M, Peplowski L. Bidirectional Effect of Repeated Exposure to Extremely Low-Frequency Electromagnetic Field (50 Hz) of 1 and 7 mT on Oxidative/Antioxidative Status in Rat's Brain: The Prediction for the Vulnerability to Diseases. Oxid Med Cell Longev 2022, 2022:1031211.

Studies reported evidence for opposite effects of extremely low-frequency electromagnetic field (EMF): harmful, including the oxidative stress induction, and beneficial, such as the activation of antioxidant defense. People's exposure to EMF is often repeated or prolonged, and it is important to consider the cumulative effect of such kind of exposure on the organism. If changes evoked by repeated exposure to EMF are permanent, responsiveness to other stress factors can be modified. The aims of our study were (1) to evaluate changes in the levels of oxidative stress and antioxidant defense markers in the prefrontal cortex of adult rats after repeated exposure to 1 and 7 mT EMF and (2) to assess whether repeated EMF exposure can modify oxidative/antioxidative status in response to other stress factors. Rats were exposed to EMF 1 h/day for 7 days, one, twice, or three times. After each exposure, 8-isoprostanes, protein carbonyl groups, and the total antioxidant capacity were assessed. Part of the animals, after EMF treatment, was exposed to another stress factor-open field. Results showed that repeated exposure changed the oxidative/antioxidative status depending on the intensity of the EMF and the number of exposures. 1 mT EMF created weak changes in the oxidative status in the brain; however, 7 mT EMF moved the balance to a clearly higher level. The changes in the oxidative status after 1 mT EMF were enough to reduce, and after 7 mT EMF to intensify oxidative processes in response to the next stress. We concluded that the organism might adapt to "weak" EMF, while "strong" EMF exceeds the adaptive capacity of the organism and sensitizes it to subsequent stress, and thus may modulate

vulnerability to diseases. Our results also provide new insights into the possible therapeutic properties of the magnetic field, as 1 mT EMF appears to have a potentially protective impact on the brain.

(E) (VT, AE, IFR, AO) Koh EK, Ryu BK, Jeong DY, Bang IS, Nam MH, Chae KS. A 60-Hz sinusoidal magnetic field induces apoptosis of prostate cancer cells through reactive oxygen species. Int J Radiat Biol. 84(11):945-955, 2008.

PURPOSE: To explore the effects of power frequency magnetic fields (MF) on cell growth in prostate cancer, DU145, PC3, and LNCaP cells were examined in vitro. MATERIALS AND METHODS: The cells were exposed to various intensities and durations of 60-Hz sinusoidal MF in combination with various serum concentrations in the media. To analyze MF effects on cell growth, cell counting, trypan blue exclusion assay, Western blot analysis, flow cytometry, enzyme-linked immunosorbent assay (ELISA), semi-quantitative reverse transcriptase-polymerase chain reaction (RT-PCR), fluorescence microscopy, and spectrofluorometry were used. RESULTS: MF exposure induced significant cell growth inhibition and apoptosis in an intensity- and time-dependent manner, in which cell cycle arrest, cleaved Caspase-3, and reactive oxygen species (ROS) increased. Pretreatment with a Caspase-3 inhibitor or antioxidant, N-acetyl-L-cysteine (NAC), significantly attenuated MF-induced cell growth inhibition and cell death. Media replacement experiments failed to show any notable change in the MF effects. CONCLUSIONS: These results demonstrate 60-Hz sinusoidal MF-activated cell growth inhibition of prostate cancer in vitro. Apoptosis together with cell cycle arrest were the dominant causes of the MF-elicited cell growth inhibition, mediated by MF-induced ROS. These results suggest that a possibility of using 60-Hz MF in radiation therapy of prostate cancer could usefully be investigated.

(E) (VO, AE, IAO, MC) Kostyn K, Boba A, Kozak B, Sztafrowski D, Widuła J, Szopa J, Preisner M. Transcriptome profiling of flax plants exposed to a low-frequency alternating electromagnetic field. Front Genet 14:1205469, 2023.

All living organisms on Earth evolved in the presence of an electromagnetic field (EMF), adapted to the environment of EMF, and even learned to utilize it for their purposes. However, during the last century, the Earth's core lost its exclusivity, and many EMF sources appeared due to the development of electricity and electronics. Previous research suggested that the EMF led to changes in intercellular free radical homeostasis and further altered the expression of genes involved in plant response to environmental stresses, inorganic ion transport, and cell wall constituent biosynthesis. Later, CTCT sequence motifs in gene promoters were proposed to be responsible for the response to EMF. How these motifs or different mechanisms are involved in the plant reaction to external EMF remains unknown. Moreover, as many genes activated under EMF treatment do not have the CTCT repeats in their promoters, we aimed to determine the transcription profile of a plant exposed to an EMF and identify the genes that are directly involved in response to the treatment to find the common denominator of the observed changes in the plant transcriptome.

(E) (VT, AE, IX) Koyama S, Nakahara T, Hirose H, Ding GR, Takashima Y, Isozumi Y, Miyakoshi J. ELF electromagnetic fields increase hydrogen peroxide (H_2O_2)-induced mutations in pTN89 plasmids. Mutat Res. 560(1):27-32, 2004.

We have examined the mutational effects of hydrogen peroxide (H(2)O(2)) in the presence and absence of an extremely low-frequency magnetic field (ELFMF), using pTN89 plasmids. Mutations were detected in the supF gene carried by these plasmids in Escherichia coli. The plasmids were either treated with H(2)O(2) (1microM) alone at 37 degrees C for 4h, or were exposed to an ELFMF (60Hz, 5 millitesla (mT)) simultaneously with H(2)O(2) treatment. The mutation frequency was 2.28 x 10(-4) for H(2)O(2) treatment alone, and 5.81 x 10(-4) for ELFMF exposure with H(2)O(2) treatment. We did not observe any mutations using treatment with ELFMF exposure alone. This indicates that the ELFMF may potentiate H(2)O(2)-induced mutation. Sequence analysis of the supF mutant plasmids revealed that base substitutions, G: C-->A :T transitions and G:C-->T:A transversions were dominant in both treatment groups, and there was no difference in the mutation spectrum or the hotspots between the groups. Therefore, ELFMFs may interact and potentiate the damage induced by H(2)O(2), resulting in an increase in the number of mutations.

(E) (VT, AE, IX) Koyama S, Sakurai T, Nakahara T, Miyakoshi J. Extremely low frequency (ELF) magnetic fields enhance chemically induced formation of apurinic/apyrimidinic (AP)sites in A172 cells. Int J Radiat Biol. 84(1):53-59, 2008.

PURPOSE: To detect the effects of extremely low frequency (ELF) magnetic fields, the number of apurinic/apyrimidinic (AP) sites in human glioma A172 cells was measured following exposure to ELF magnetic fields. MATERIALS AND METHODS: The cells were exposed to an ELF magnetic field alone, to genotoxic agents (methyl methane sulfonate (MMS) and hydrogen peroxide (H2O2)) alone, or to an ELF magnetic field with the genotoxic agents. After exposure, DNA was extracted, and the number of AP sites was measured. RESULTS: There was no difference in the number of AP sites between cells exposed to an ELF magnetic field and sham controls. With MMS or H2O2 alone, the number of AP sites increased with longer treatment times. Exposure to an ELF magnetic field in combination with the genotoxic agents increased AP-site levels compared with the genotoxic agents alone. CONCLUSIONS: Our results suggest that the number of AP sites induced by MMS or H2O2 is enhanced by exposure to ELF magnetic fields at 5 millitesla (mT). This may occur because such exposure can enhance the activity or lengthen the lifetime of radical pairs.

Krylov VV, Osipova EA. Molecular Biological Effects of Weak Low-Frequency Magnetic Fields: Frequency-Amplitude Efficiency Windows and Possible Mechanisms. Int J Mol Sci. (13):10989, 2023.

This review covers the phenomenon of resonance-like responses of biological systems to low-frequency magnetic fields (LFMF). The historical development of this branch of magnetobiology, including the most notable biophysical models that explain the resonance-like responses of biological systems to LFMF with a specific frequency and amplitude, is given. Two groups can be distinguished among these models: one considers ion-cofactors of proteins as the primary targets for the LFMF influence, and the other regards the

magnetic moments of particles in biomolecules. Attention is paid to the dependence of resonance-like LFMF effects on the cell type. A radical-pair mechanism of the magnetic field's influence on biochemical processes is described with the example of cryptochrome. Conditions for this mechanism's applicability to explain the biological effects of LFMF are given. A model of the influence of LFMF on radical pairs in biochemical oscillators, which can explain the frequency-amplitude efficiency windows of LFMF, is proposed.

(E) (VO, AE, IAO, DAO, IOD) Kthiri A, Hidouri S, Wiem T, Jeridi R, Sheehan D, Landouls A. Biochemical and biomolecular effects induced by a static magnetic field in Saccharomyces cerevisiae: Evidence for oxidative stress. PLoS One. 14(1):e0209843, 2019.

Exposure to static magnetic fields (SMF) can cause changes in microorganism metabolism altering key subcellular functions. The purpose of this study was to investigate whether an applied SMF could induce biological effects on growth of Saccharomyces cerevisiae, and then to probe biochemical and bio-molecular responses. We found a decrease in growth and viability under SMF (250mT) after 6h with a significant decrease in colony forming units followed by an increase between 6 h and 9 h. Moreover, measurements of antioxidant enzyme activities (catalase, superoxide dismutase, glutathione peroxidase) demonstrated a particular profile suggesting oxidative stress. For instance, SOD and catalase activities increased in magnetized cultures after 9 h compared with unexposed samples. However, SMF exposure caused a decrease in glutathione peroxidase activity. Finally, SMF caused an increase in MDA levels as well as the content of protein carbonyl groups after 6 and 9 h of exposure.

(E) (HU, CE, IFR) Kunt H, Şentürk İ, Gönül Y, Korkmaz M, Ahsen A, Hazman Ö, Bal A, Genç A, Songur A. Effects of electromagnetic radiation exposure on bone mineral density, thyroid, and oxidative stress index in electrical workers. OncoTargets and Therapy. 2016(9):745-754, 2016.

Background: In the literature, some articles report that the incidence of numerous diseases increases among the individuals who live around high-voltage electric transmission lines (HVETL) or are exposed vocationally. However, it was not investigated whether HVETL affect bone metabolism, oxidative stress, and the prevalence of thyroid nodule. Methods: Dual-energy X-ray absorptiometry (DEXA) bone density measurements, serum free triiodothyronine (FT3), free thyroxine (FT4), RANK, RANKL, osteoprotegerin (OPG), alkaline phosphatase (ALP), phosphor, total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) levels were analyzed to investigate this effect. Results: Bone mineral density levels of L1–L4 vertebrae and femur were observed significantly lower in the electrical workers. ALP, phosphor, RANK, RANKL, TOS, OSI, and anteroposterior diameter of the left thyroid lobe levels were significantly higher, and OPG, TAS, and FT4 levels were detected significantly lower in the study group when compared with the control group. Conclusion: Consequently, it was observed that the balance between construction and

destruction in the bone metabolism of the electrical workers who were employed in HVETL replaced toward destruction and led to a decrease in OPG levels and an increase in RANK and RANKL levels. In line with the previous studies, long-term exposure to an electromagnetic field causes disorders in many organs and systems. Thus, it is considered that long-term exposure to an electromagnetic field affects bone and thyroid metabolism and also increases OSI by increasing the TOS and decreasing the antioxidant status

(E) (VT, CE, IX) Kurzeja E, Synowiec-Wojtarowicz A, Stec M, Glinka M, Gawron S, Pawłowska-Góral K. Effect of a static magnetic fields and fluoride ions on the antioxidant defense system of mice fibroblasts. Int J Mol Sci.14(7):15017-15028, 2013.

The results of studies on the biological influence of magnetic fields are controversial and do not provide clear answers regarding their impact on cell functioning. Fluoride compounds are substances that influence free radical processes, which occur when the reactive forms of oxygen are present. It is not known whether static magnetic fields (SMF) cause any changes in fluoride assimilation or activity. Therefore, the aim of this work was to determine the potential relationship between magnetic field exposure to, and the antioxidant system of, fibroblasts cultured with fluoride ions. Three chambers with static magnetic fields of different intensities (0.4, 0.6, and 0.7 T) were used in this work. Fluoride ions were added at a concentration of 0.12 mM, which did not cause the precipitation of calcium or magnesium. The results of this study show that static magnetic fields reduce the oxidative stress caused by fluoride ions and normalize the activities of antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Static magnetic fields modify the energy state of fibroblasts, causing an increase in the ATP concentration and a decrease in the MDA concentration. These results suggest that exposure to fluoride and an SMF improves the tolerance of cells to the oxidative stress induced by fluoride ions.

(E) (VO, CE, IFR, IOD, DAO) Kuzay D, Ozer C, Sirav B, Canseven AG, Seyhan N. Oxidative effects of extremely low frequency magnetic field and radio frequency radiation on testes tissues of diabetic and healthy rats. Bratisl Lek Listy. 118(5):278-282, 2017.

With the development of technology, people are increasingly under the exposure of electromagnetic fields. Individuals with chronic diseases such as diabetes are now long-term exposed to Radio Frequency-RF radiation and extremely low frequency (ELF) magnetic fields (MFs). The purpose of this present study is to investigate oxidative effects and antioxidant parameters of ELF MFs and RF radiation on testis tissue in diabetic and healthy rats. Wistar male rats were divided into 10 groups. Intraperitoneal single dose STZ (65 mg/kg) dissolved in citrate buffer (0.1M (pH 4.5)) was injected to diabetes groups. ELF MFs and RF radiation were used as an electromagnetic exposure for 20 min/day, 5 days/week for one month. Testis tissue oxidant malondialdehyde (MDA), and antioxidants glutathione (GSH), and total nitric oxide (NOx) levels were determined. The results of ANOVA and Mann-Whitney tests were compared; $p < 0.05$ was considered significant. ELF and RF radiation resulted in an increase in testicular tissue MDA and NOX levels

($p < 0.05$), and caused a decrease in GSH levels ($p < 0.05$) in both healthy and diabetic rats, yet more distinctively in diabetic rats. The most pronounced effect was recorded in D-RF + ELF group ($p < 0.005$). Both radiation practices increased the oxidative stress in testis tissue while causing a decrease in antioxidant level which was more distinctive in diabetic rats (Tab. 1, Fig. 3, Ref. 30).

Lahbib A, Ghodbane S, Sakly M, Abdelmelek H. Vitamins and glucose metabolism: The role of static magnetic fields. Int J Radiat Biol. 90(12):1240-1245, 2014. (review)

PURPOSE: This review focuses on our own data and other data from the literature of static magnetic fields (SMF) bioeffects and vitamins and glucose metabolism. Three main areas of investigation have been covered: Static magnetic field and glucose metabolism, static magnetic field and vitamins and the role of vitamins on glucose metabolism. CONCLUSION: Considering these articles comprehensively, the conclusions are as follows: The primary cause of changes in cells after incubation in external SMF is disruption of free radical metabolism and elevation of their concentration. Such disruption causes oxidative stress leading to an unsteadiness of glucose level and insulin release. Moreover, based on available data, it was concluded that exposure to SMF alters plasma levels of vitamin A, C, D and E; these parameters can take part in disorder of glucose homeostasis and insulin release.

Lai H. Exposure to Static and Extremely-Low Frequency Electromagnetic Fields and Cellular Free Radicals. Electromagn Biol Med. 2019;38(4):231-248. (review)

This paper summarizes studies on changes in cellular free radical activities from exposure to static and extremely-low frequency (ELF) electromagnetic fields (EMF), particularly magnetic fields. Changes in free radical activities, including levels of cellular reactive oxygen (ROS)/nitrogen (RNS) species and endogenous antioxidant enzymes and compounds that maintain physiological free radical concentrations in cells, is one of the most consistent effects of EMF exposure. These changes have been reported to affect many physiological functions such as DNA damage; immune response; inflammatory response; cell proliferation and differentiation; wound healing; neural electrical activities; and behavior. An important consideration is the effects of EMF-induced changes in free radicals on cell proliferation and differentiation. These cellular processes could affect cancer development and proper growth and development in organisms. On the other hand, they could cause selective killing of cancer cells, for instance, via the generation of the highly cytotoxic hydroxyl free radical by the Fenton Reaction. This provides a possibility of using these electromagnetic fields as a non-invasive and low side-effect cancer therapy. Static- and ELF-EMF probably play important roles in the evolution of living organisms. They are cues used in many critical survival functions, such as foraging, migration, and reproduction. Living organisms can detect and respond immediately to low environmental levels of these fields. Free radical processes are involved in some of these mechanisms. At this time, there is no credible hypothesis or mechanism that can adequately

explain all the observed effects of static- and ELF-EMF on free radical processes. We are actually at the impasse that there are more questions than answers.

(E) (VO, AE, AO) Lai H, Singh NP. Melatonin and N-tert-butyl-alpha-phenylnitrone block 60-Hz magnetic field-induced DNA single and double strand breaks in rat brain cells. J Pineal Res. 22(3):152-162, 1997.

In previous research, we have found an increase in DNA single- and double-strand breaks in brain cells of rats after acute exposure (two hours) to a sinusoidal 60-Hz magnetic field. The present experiment was carried out to investigate whether treatment with melatonin and the spin-trap compound N-tert-butyl-alpha-phenylnitrone (PBN) could block the effect of magnetic fields on brain cell DNA. Rats were injected with melatonin (1 mg/kg, sc) or PBN (100 mg/kg, ip) immediately before and after two hours of exposure to a 60-Hz magnetic field at an intensity of 0.5 mT. We found that both drug treatments blocked the magnetic field-induced DNA single- and double-strand breaks in brain cells, as assayed by a microgel electrophoresis method. Since melatonin and PBN are efficient free radical scavengers, these data suggest that free radicals may play a role in magnetic field-induced DNA damage.

(E) (VO, AE, AO) Lai H, Singh NP. Magnetic-field-induced DNA strand breaks in brain cells of the rat. Environ Health Perspect. 112(6):687-694, 2004.

In previous research, we found that rats acutely (2 hr) exposed to a 60-Hz sinusoidal magnetic field at intensities of 0.1-0.5 millitesla (mT) showed increases in DNA single- and double-strand breaks in their brain cells. Further research showed that these effects could be blocked by pretreating the rats with the free radical scavengers melatonin and N-tert-butyl-alpha-phenylnitrone, suggesting the involvement of free radicals. In the present study, effects of magnetic field exposure on brain cell DNA in the rat were further investigated. Exposure to a 60-Hz magnetic field at 0.01 mT for 24 hr caused a significant increase in DNA single- and double-strand breaks. Prolonging the exposure to 48 hr caused a larger increase. This indicates that the effect is cumulative. In addition, treatment with Trolox (a vitamin E analog) or 7-nitroindazole (a nitric oxide synthase inhibitor) blocked magnetic-field-induced DNA strand breaks. These data further support a role of free radicals on the effects of magnetic fields. Treatment with the iron chelator deferiprone also blocked the effects of magnetic fields on brain cell DNA, suggesting the involvement of iron. Acute magnetic field exposure increased apoptosis and necrosis of brain cells in the rat. We hypothesize that exposure to a 60-Hz magnetic field initiates an iron-mediated process (e.g., the Fenton reaction) that increases free radical formation in brain cells, leading to DNA strand breaks and cell death. This hypothesis could have an important implication for the possible health effects associated with exposure to extremely low-frequency magnetic fields in the public and occupational environments.

E)(VT, AE, AO) Lai HC, Chan HW, Singh NP. Effects of radiation from a radiofrequency identification (RFID) microchip on human cancer cells. Int J Radiat Biol. 2016;92(3):156-161, 2016.

PURPOSE: Radiofrequency identification (RFID) microchips are used to remotely identify objects, e.g. an animal in which a chip is implanted. A passive RFID microchip absorbs energy from an external source and emits a radiofrequency identification signal which is then decoded by a detector. In the present study, we investigated the effect of the radiofrequency energy emitted by a RFID microchip on human cancer cells. **MATERIALS AND METHODS:** Molt-4 leukemia, BT474 breast cancer, and HepG2 hepatic cancer cells were exposed in vitro to RFID microchip-emitted radiofrequency field for 1 h. Cells were counted before and after exposure. Effects of pretreatment with the spin-trap compound N-tert-butyl-alpha-phenylnitrone or the iron-chelator deferoxamine were also investigated. **RESULTS**: We found that the energy effectively killed/retarded the growth of the three different types of cancer cells, and the effect was blocked by the spin-trap compound or the iron-chelator, whereas an inactive microchip and energy from the external source had no significant effect on the cells. **CONCLUSION**: Data of the present study suggest that radiofrequency field from the microchip affects cancer cells via the Fenton Reaction. Implantation of RFID microchips in tumors may provide a new method for cancer treatment.

(E) (VT, AE, IFR) Lazzarini R, Eléxpuru-Zabaleta M, Piva F, Giulietti M, Fulgenzi G, Tartaglione MF, Laura Zingaretti L, Tagliabracci A, Valentino M, Santarelli L, Bracci M. Effects of extremely low-frequency magnetic fields on human MDA-MB-231 breast cancer cells: proteomic characterization. Ecotoxicol Environ Saf 253:114650, 2023.

Extremely low-frequency electromagnetic fields (ELF-MF) can modify the cell viability and regulatory processes of some cell types, including breast cancer cells. Breast cancer is a multifactorial disease where a role for ELF-MF cannot be excluded. ELF-MF may influence the biological properties of breast cells through molecular mechanisms and signaling pathways that are still unclear. This study analyzed the changes in the cell viability, cellular morphology, oxidative stress response and alteration of proteomic profile in breast cancer cells (MDA-MB-231) exposed to ELF-MF (50 Hz, 1 mT for 4 h). Non-tumorigenic human breast cells (MCF-10A) were used as control cells. Exposed MDA-MB-231 breast cancer cells increased their viability and live cell number and showed a higher density and length of filopodia compared with the unexposed cells. In addition, ELF-MF induced an increase of the mitochondrial ROS levels and an alteration of mitochondrial morphology. Proteomic data analysis showed that ELF-MF altered the expression of 328 proteins in MDA-MB-231 cells and of 242 proteins in MCF-10A cells. Gene Ontology term enrichment analysis demonstrated that in both cell lines ELF-MF exposure up-regulated the genes enriched in "focal adhesion" and "mitochondrion". The ELF-MF exposure decreased the adhesive properties of MDA-MB-231 cells and increased the migration and invasion cell abilities. At the same time, proteomic analysis, confirmed by Real Time PCR, revealed that transcription factors associated with cellular reprogramming were upregulated in MDA-MB-231 cells and downregulated in MCF-10A cells after ELF-MF exposure. MDA-MB-231 breast cancer cells exposed to 1 mT 50 Hz ELF-MF showed modifications in proteomic profile together with changes in cell viability, cellular morphology, oxidative stress response, adhesion, migration and invasion cell abilities. The main signaling pathways involved were relative to focal adhesion, mitochondrion and cellular reprogramming.

(E) (VO, AE, IOD, IAO) Lee BC, Johng HM, Lim JK, Jeong JH, Baik KY, Nam TJ, Lee JH, Kim J, Sohn UD, Yoon G, Shin S, Soh KS. Effects of extremely low frequency magnetic field on the antioxidant defense system in mouse brain: a chemiluminescence study. J Photochem Photobiol B. 73(1-2):43-48, 2004.

Among the putative mechanisms, by which extremely low frequency (ELF) magnetic field (MF) may affect biological systems is that of increasing free radical life span in organisms. To test this hypothesis, we investigated whether ELF (60 Hz) MF can modulate antioxidant system in mouse brain by detecting chemiluminescence and measuring superoxide dismutase (SOD) activity in homogenates of the organ. Compared to sham exposed control group, lucigenin-initiated chemiluminescence in exposed group was not significantly increased. However, lucigenin-amplified t-butyl hydroperoxide (TBHP)-initiated brain homogenates chemiluminescence, was significantly increased in mouse exposed to 60 Hz, MF, 12 G for 3 h compared to sham exposed group. We also measured SOD activity, that plays a critical role of the antioxidant defensive system in brain. In the group exposed to 60 Hz, MF, 12 G for 3 h, brain SOD activity was significantly increased. These results suggest that 60 Hz, MF could deteriorate antioxidant defensive system by reactive oxygen species (ROS), other than superoxide radicals. Further studies are needed to identify the kind of ROS generated by the exposure to 60 Hz, MF and elucidate how MF can affect biological system in connection with oxidative stress.

(NE) (VT, AE) Lee HJ, Jin YB, Lee JS, Choi JI, Lee JW, Myung SH, Lee YS. Combined effects of 60 Hz electromagnetic field exposure with various stress factors on cellular transformation in NIH3T3 cells. Bioelectromagnetics. 33(3):207-214, 2012.

Epidemiological studies have suggested that extremely low-frequency magnetic fields (ELF-MF) are associated with an increased incidence of cancer. Studies using in vitro systems have reported mixed results for the effects of ELF-MF alone, and the World Health Organization (WHO) Research Agenda published in 2007 suggested that high priority research should include an evaluation of the co-carcinogenic effects of ELF-MF exposure using in vitro models. Here, the carcinogenic potential of ELF-MF exposure alone and in combination with various stress factors was investigated in NIH3T3 mouse fibroblasts using an in vitro cellular transformation assay. NIH3T3 cells were exposed to a 60 Hz ELF-MF (1 mT) alone or in combination with ionizing radiation (IR), hydrogen peroxide (H_2O_2), or c-Myc overexpression, and the resulting number of anchorage-independent colonies was counted. A 4 h exposure of NIH3T3 cells to ELF-MF alone produced no cell transformation. Moreover, ELF exposure did not influence the transformation activity of IR, H_2O_2, or activated c-Myc in our in vitro assay system, suggesting that 1 mT ELF-MF did not affect any additive or synergistic transformation activities in combination with stress factors such as IR, H_2O_2, or activated c-Myc in NIH3T3 cells.

(E) (VT, AE, IRF) Lee HM, Kwon UH, Kim H, Kim HJ, Kim B, Park JO, Moon ES, Moon SH. Pulsed electromagnetic field stimulates cellular proliferation in human intervertebral disc cells. Yonsei Med J. 51(6):954-959, 2010.

PURPOSE: The purpose of this study is to investigate the mechanism of cellular proliferation of electromagnetic field (EMF) on human intervertebral disc (IVD) cells. MATERIALS AND METHODS: Human IVD cells were cultured three-dimensionally in alginate beads. EMF was exposed to IVD cells with 650 Ω, 1.8 millitesla magnetic flux density, 60 Hz sinusoidal wave. Cultures were divided into a control and EMF group. Cytotoxicity, DNA synthesis and proteoglycan synthesis were measured by MTT assay, [(3)H]-thymidine, and [(35)S]-sulfate incorporation. To detect phenotypical expression, reverse transcription-polymerase chain reactions (RT-PCR) were performed for aggrecan, collagen type I, and type II mRNA expression. To assess action mechanism of EMF, IVD cells were exposed to EMF with N(G)-Monomethyl-L-arginine (NMMA) and acetylsalicylic acid (ASA). RESULTS: There was no cytotoxicity in IVD cells with the EMF group in MTT assay. Cellular proliferation was observed in the EMF group ($p < 0.05$). There was no difference in newly synthesized proteoglycan normalized by DNA synthesis between the EMF group and the control. Cultures with EMF showed no significant change in the expression of aggrecan, type I, and type II collagen mRNA compared to the control group. Cultures with NMMA (blocker of nitric oxide) or ASA (blocker of prostaglandin E2) exposed to EMF demonstrated decreased DNA synthesis compared to control cultures without NMMA or ASA ($p < 0.05$). CONCLUSION: EMF stimulated DNA synthesis in human IVD cells while no significant effect on proteoglycan synthesis and chondrogenic phenotype expressions. DNA synthesis was partially mediated by nitric oxide and prostaglandin E2. EMF can be utilized to stimulate proliferation of IVD cells, which may provide efficient cell amplification in cell therapy to degenerative disc disease.

Lewczuk B, Redlarski G, Zak A, Ziółkowska N, Przybylska-Gornowicz B, Krawczuk M. Influence of electric, magnetic, and electromagnetic fields on the circadian system: current stage of knowledge. Biomed Res Int. 2014:169459, 2014. (review)

One of the side effects of each electrical device work is the electromagnetic field generated near its workplace. All organisms, including humans, are exposed daily to the influence of different types of this field, characterized by various physical parameters. Therefore, it is important to accurately determine the effects of an electromagnetic field on the physiological and pathological processes occurring in cells, tissues, and organs. Numerous epidemiological and experimental data suggest that the extremely low frequency magnetic field generated by electrical transmission lines and electrically powered devices and the high frequencies electromagnetic radiation emitted by electronic devices have a potentially negative impact on the circadian system. On the other hand, several studies have found no influence of these fields on chronobiological parameters. According to the current state of knowledge, some previously proposed hypotheses, including one concerning the key role of melatonin secretion disruption in pathogenesis of electromagnetic field induced diseases, need to be revised. This paper reviews the data on the effect of electric, magnetic, and electromagnetic fields on melatonin and cortisol rhythms-two major markers of the circadian system as well as on sleep. It also provides the basic information about the nature, classification, parameters, and sources of these fields.

(E) (VT, AE, IOD, IAO) Lewicka M, Henrykowska GA, Pacholski K, Szczęsny A, Dziedziczak-Buczyńska M, Buczyński A. The impact of electromagnetic radiation of different parameters on platelet oxygen metabolism - in vitro studies. Adv Clin Exp Med. 24(1):31-35, 2015.

BACKGROUND: Electromagnetic radiation emitted by a variety of devices, e.g. cell phones, computers and microwaves, interacts with the human body in many ways. Research studies carried out in the last few decades have not yet resolved the issue of the effect of this factor on the human body and many questions are left without an unequivocal answer. Various biological and health-related effects have not been fully recognized. Thus further studies in this area are justified. OBJECTIVES: A comparison of changes within catalase enzymatic activity and malondialdehyde concentration arising under the influence of the electromagnetic radiation emitted by car electronics, equipment used in physiotherapy and LCD monitors. MATERIAL AND METHODS: The suspension of human blood platelets at a concentration of 1 × 109/0.001 dm 3, obtained from whole blood by manual apheresis, was the study material. Blood platelets were exposed to an electromagnetic field for 30 min in a laboratory stand designed for the reconstruction of the electromagnetic radiation generated by car electronics, physiotherapy equipment and LCD monitors. The changes in catalase activity and malondialdehyde concentration were investigated after the exposure and compared to the control values (unexposed material). RESULTS: An increase in catalase activity and malondialdehyde concentration was observed after 30 min exposure of platelets to EMF regardless of the radiation source. The most significant changes determining the degree of oxidative stress were observed after exposure to the EMF generated by car electronics. CONCLUSIONS: The low frequency electromagnetic fields generated by car electronics, physiotherapy equipment and LCD monitors may be a cause of oxidative stress in the human body and may lead to free radical diseases.

(NE) (HU, CE) Li L, Xiong DF, Liu JW, Li ZX, Zeng GC, Li HL. A cross-sectional study on oxidative stress in workers exposed to extremely low frequency electromagnetic fields. Int J Radiat Biol. 91(5):420-425, 2015.

PURPOSE: To investigate whether extremely low frequency electromagnetic field (ELF-EMF) exposure could induce oxidative stress in workers performing tour-inspection near transformers and distribution power lines. MATERIALS AND METHODS: Occupational short-term 'spot' measurements were performed. In total, 310 inspection workers exposed to ELF-EMF were selected as the exposure group and 300 logistical staff as the control group. Plasma total antioxidant capacity (T-AOC) and glutathione peroxidase (GPx) activity were tested by the colorimetric method. Superoxide dismutase (SOD) activity was tested using the xanthine oxidase method. Plasma malondialdehyde (MDA) concentration was determined with a thiobarbituric acid assay. The micronucleus cell frequency (MCF) and Micronuclei frequency (MN) were also tested for genotoxic assessment. RESULTS: No significant changes of enzyme activities or MDA concentration were found. Neither the frequency of micronucleus lymphocytes nor micronuclei frequency changes

were statistically significant. CONCLUSION: Continual ELF-EMF exposure might not induce oxidative stress in workers from a power supply bureau.

(E) (VO, AE, CE, IAO) Li SS, Zhang ZY, Yang CJ, Lian HY, Cai P. Gene expression and reproductive abilities of male Drosophila melanogaster subjected to ELF-EMF exposure. Mutat Res. 758(1-2):95-103, 2013.

Extremely low frequency electromagnetic field (ELF-EMF) exposure is attracting increased attention as a possible disease-inducing factor. The in vivo effects of short-term and long-term ELF-EMF exposure on male Drosophila melanogaster were studied using transcriptomic analysis for preliminary screening and QRT-PCR for further verification. Transcriptomic analysis indicated that 439 genes were up-regulated and 874 genes were down-regulated following short-term exposures and that 514 genes were up-regulated and 1206 genes were down-regulated following long-term exposures (expression >2- or <0.5-fold, respectively). In addition, there are 238 up-regulated genes and 598 down-regulated genes in the intersection of short-term and long-term exposure (expression >2- or <0.5-fold). The DEGs (differentially expressed genes) in D. melanogaster following short-term exposures were involved in metabolic processes, cytoskeletal organization, mitotic spindle organization, cell death, protein modification and proteolysis. Long-term exposure let to changes in expression of genes involved in metabolic processes, response to stress, mitotic spindle organization, aging, cell death and cellular respiration. In the intersection of short-term and long-term exposure, a series of DEGs were related to apoptosis, aging, immunological stress and reproduction. To check the ELF-EMF effects on reproduction, some experiments on male reproduction ability were performed. Their results indicated that short-term ELF-EMF exposure may decrease the reproductive ability of males, but long-term exposures had no effect on reproductive ability. Down-regulation of ark gene in the exposed males suggests that the decrease in reproductive capacity may be induced by the effects of ELF-EMF exposure on spermatogenesis through the caspase pathway. QRT-PCR analysis confirmed that jra, ark and decay genes were down regulated in males exposed for 1 Generation (1G) and 72h, which suggests that apoptosis may be inhibited in vivo. ELF-EMF exposure may have accelerated cell senescence, as suggested by the down-regulation of both cat and jra genes and the up-regulation of hsp22 gene. Up-regulation of totA and hsp22 genes during exposure suggests that exposed flies might induce an in vivo immune response to counter the adverse effects encountered during ELF-EMF exposure. Down-regulation of cat genes suggests that the partial oxidative protection system might be restrained, especially during short-term exposures. This study demonstrates the bioeffects of ELF-EMF exposure and provides evidence for understanding the in vivo mechanisms of ELF-EMF exposure on male D. melanogaster.

(E) (VO, AE, IFR, IAO) Lian HY, Lin KW, Yang C, Cai P. Generation and propagation of yeast prion [URE3] are elevated under electromagnetic field. Cell Stress Chaperones. 23(4):581-594, 2018.

We studied the effect of 2.0 GHz radio frequency electromagnetic field (RF-EMF) and 50 Hz extremely low frequency electromagnetic field (ELF-EMF) exposure on prion generation and propagation using two budding yeast strains, NT64C and SB34, as model organisms. Under exposure to RF-EMF or ELF-EMF, the de novo generation and propagation of yeast prions [URE3] were elevated in both strains. The elevation increased over time, and the effects of ELF-EMF occurred in a dose-dependent manner. The transcription and expression levels of the molecular chaperones Hsp104, Hsp70-Ssa1/2, and Hsp40-Ydj1 were not statistically significantly changed after exposure. Furthermore, the levels of ROS, as well as the activities of superoxide dismutase (SOD) and catalase (CAT), were significantly elevated after short-term, but not long-term exposure. This work demonstrated for the first time that EMF exposure could elevate the de novo generation and propagation of yeast prions and supports the hypothesis that ROS may play a role in the effects of EMF on protein misfolding. The effects of EMF on protein folding and ROS levels may mediate the broad effects of EMF on cell function.

(E) (VT, AE, AO) Liu DD, Ren Z, Yang G, Zhao QR, Mei YA. Melatonin protects rat cerebellar granule cells against electromagnetic field-induced increases in Na+ currents through intracellular Ca2+ release. J Cell Mol Med. 18(6):1060-1070, 2014.

Although melatonin (MT) has been reported to protect cells against oxidative damage induced by electromagnetic radiation, few reports have addressed whether there are other protective mechanisms. Here, we investigated the effects of MT on extremely low-frequency electromagnetic field (ELF-EMF)-induced Na_v activity in rat cerebellar granule cells (GCs). Exposing cerebellar GCs to ELF-EMF for 60 min. significantly increased the Na_v current (I_{Na}) densities by 62.5%. MT (5 μM) inhibited the ELF-EMF-induced I_{Na} increase. This inhibitory effect of MT is mimicked by an MT_2 receptor agonist and was eliminated by an MT_2 receptor antagonist. The Na_v channel steady-state activation curve was significantly shifted towards hyperpolarization by ELF-EMF stimulation but remained unchanged by MT in cerebellar GC that were either exposed or not exposed to ELF-EMF. ELF-EMF exposure significantly increased the intracellular levels of phosphorylated PKA in cerebellar GCs, and both MT and IIK-7 did not reduce the ELF-EMF-induced increase in phosphorylated PKA. The inhibitory effects of MT on ELF-EMF-induced Na_v activity was greatly reduced by the calmodulin inhibitor KN93. Calcium imaging showed that MT did not increase the basal intracellular Ca^{2+} level, but it significantly elevated the intracellular Ca^{2+} level evoked by the high K^+ stimulation in cerebellar GC that were either exposed or not exposed to ELF-EMF. In the presence of ruthenium red, a ryanodine-sensitive receptor blocker, the MT-induced increase in intracellular calcium levels was reduced. Our data show for the first time that MT protects against neuronal I_{Na} that result from ELF-EMF exposure through Ca^{2+} influx-induced Ca^{2+} release.

(E) (VO, CE, IOD, DAO) Liu Y, Weng E, Zhang Y, Hong R. [Effects of extremely low frequency electromagnetic field and its combination with lead on the antioxidant system in mouse] Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 20(4):263-265, 2002. [Article in Chinese]

OBJECTIVE: To study the effects of extremely low frequency electromagnetic field(ELF EMF) and its combination with lead on the antioxidant system in mouse brain and liver tissues. METHOD: Mice were exposed to a 50 Hz sinusoidal 0.2 mT or 6.0 mT EMF for 2 weeks. At the same time, some groups were exposed to lead(50 mg/kg). After the exposure, the antioxidant system and cell membrane fluidity in brain and liver were measured. RESULTS: Malondiadehyde(MDA) content in brain and liver increased from the control levels of (1.33 +/- 0.12) and (3.95 +/- 0.21) nmol/mg pro to (1.35 +/- 0.09) and (6.15 +/- 0.28) nmol/mg pro respectively following 0.2 mT exposure, and to (3.98 +/- 0.10) and (6.50 +/- 0.79) nmol/mg pro respectively following 6.0 mT exposure. Total antioxidant capability(T-AOC) in brain and liver decreased from the control levels of (4.39 +/- 0.48) and (2.45 +/- 0.21) U/mg pro to (3.99 +/- 0.39) and (1.92 +/- 0.32) U/mg pro respectively following 0.2 mT, and to (3.12 +/- 0.37) and (1.57 +/- 0.14) U/mg pro respectively following 6.0 mT. GSH content decreased only in liver tissue from the control level of (194.60 +/- 20.93) mg/g pro to (189.24 +/- 5.61) mg/g pro(0.2 mT) and (153.04 +/- 1.18) mg/g pro(6.0 mT). Cellular membrane fluidity decreased from the control levels of (1.396 +/- 0.040) and (2.899 +/- 0.552) to (1.224 +/- 0.190) and (1.894 +/- 0.0761) (0.2 mT), (1.159 +/- 0.179) and (1.516 +/- 0.204)(6.0 mT) respectively. Compared with single EMF exposure(6.0 mT), EMF combined with lead exposure induced remarkable increase in MDA, GSH content and T-AOC and decrease in cell membrane fluidity both in the brain and liver, and increase in SOD activity only in liver. CONCLUSION: ELF EMF might alter the metabolism of free radicals, decrease anti-oxidant capability and enhance lipid peroxidation. The combination of EMF with lead showed synergic effects on lipid peroxidation.

(E) (VO, CE, IOD, DAO, AO) Luo X, Chen M, Duan Y, Duan W, Zhang H, He Y, Yin C, Sun G, Sun X. Chemoprotective action of lotus seedpod procyanidins on oxidative stress in mice induced by extremely low-frequency electromagnetic field exposure. Biomed Pharmacother. 82:640-648, 2016.

With the increasing use of electromagnetic technology, the effects of extremely low-frequency electromagnetic fields (ELF-EMF) on biological systems, central neurotransmitter systems, and human health have attracted extensive attention worldwide. In this study, lotus seedpod procyanidins (LSPCs) were evaluated for their protective effects on ELF-EMF induced oxidative stress injury in mice. Sixty male ICR mice were used for the experiment. The mice were randomly divided into five equal groups. The control group did not receive LSPCs or ELF-EMF but orally received normal saline. The ELF-EMF group received ELF-EMF exposure plus normal saline orally. The other three groups received ELF-EMF exposure plus LSPCs orally (60, 90, or 120mg kg(-1).bw, respectively). Each group exposed to ELF-EMF at 8 mT, 4h day(-1) for 28 consecutive days after administration daily of LSPCs or normal saline to mice for 15 consecutive days with the exception of the control group. Thereafter, blood and cerebral cortex of the mice were analyzed for antioxidant indices, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase

(GR), glutathione-S-transferase (GST) and malondialdehyde (MDA). LSPCs administration at different doses significantly inhibited oxidative stress damage of mice induced by ELF-EMF. LSPCs treatment augmented SOD, CAT, GSH-Px, GR and GST activity. Furthermore, administration significantly lowered MDA level in LSPCs treatment groups LSPCs. All results indicated LSPCs can effectively prevent oxidative stress injury induced by ELF-EMF exposure, which may be related to its ability of scavenging free radicals and stimulating antioxidant enzyme activity.

(E) (VO, AE, DAO) Luo K, Luo C, Li G, Yao X, Gao R, Hu Z, Zhang G, Zhao H. High-voltage electrostatic field-induced oxidative stress: Characterization of the physiological effects in Sitobion avenae (Hemiptera: Aphididae) across multiple generations. Bioelectromagnetics. 40(1):52-61, 2019.

In recent decades, man-made electric fields have greatly increased the intensity of electrostatic fields that are pervasively present in the environment. To better understand the physiological alterations exhibited by herbivorous insects in response to changing electric environments, we determined the activities of anti-oxidative enzymes and the metabolic rate of Sitobion avenae Fabricius (Hemiptera: Aphididae) over multiple generations in response to direct and host-seed exposure to a high-voltage electrostatic field (HVEF) of varying strength for different durations. Under controlled greenhouse conditions, 20-min direct exposure of S. avenae and wheat seeds to a 2- or 4-kV/cm HVEF resulted in significantly increased superoxide dismutase (SOD) activity in the sixth, 11th, 16th, and 21st generations relative to the control activities, whereas significantly decreased SOD activity was detected in the second generation. In addition, the activities of catalase (CAT) and peroxidase (POD) in S. avenae showed significant decreases over multiple generations. We also examined the suppressive effects of the duration of 4-kV/cm treatment on aphid physiology. The results showed that exposure to the 4-kV/cm HVEF for 20 min exerted adverse effects on CAT and POD activities and significantly decreased the metabolic rates of S. avenae, as demonstrated through evaluations of CO_2 production rate, and these parameters were not significantly affected by higher HVEF durations. Overall, these findings increase our understanding of plant-pest interactions under novel HVEF environments and provide information that can improve integrated management strategies for S. avenae.

(E) (VO, CE, IAO) Lupi, D., Tremolada, P., Colombo, M., Giacchini, R., Benocci, R., Parenti, P., Parolini, M., Zambon, G., Vighi, M. Effects of Pesticides and Electromagnetic Fields on Honeybees: A Field Study Using Biomarkers. *Int J Environ Res* 14: 107-122, 2020.

The effects of pesticide mixtures and electric and magnetic fields on honeybees were evaluated in three experimental sites located in northern Italy: a control site far from anthropogenic-stress sources, a semi-natural site close to a high-voltage electric line and an agricultural site with intensive pesticide use. From each experimental site, young workers and foraging bees were taken monthly from May to October and analyzed for four enzymatic biomarkers: acetylcholinesterase (AChE), catalase (CAT), glutathione S-transferase (GST) and alkaline phosphatase (ALP). The results revealed time- and site-specific effects in respect to control site, confirming the

role of biomarkers as diagnostic and early-warning tools for multi-stress sources on honeybees. In the electromagnetic-stress site, the effect of an over-activation of all analyzed biomarkers was observed at the end of the season. According to other literature findings, this event was related to a behavioral over-activation in a period in which bees should prepare themselves for overwintering. This finding poses potential problems for winter survival. In the pesticide-stress site, different pesticide-induced responses were identified. We demonstrated in the field that pesticide mixtures currently used in agriculture could greatly affect the biochemical parameters of bees (with both enzymatic under- and over-activations).

(E) (VO, CE, IAO, IX) Lupi D, Marco Palamara Mesiano , Agnese Adani, Roberto Benocci, Roberto Giacchini, Paolo Parenti, Giovanni Zambon, Antonio Lavazza, Maria Beatrice Boniotti, Stefano Bassi, Mario Colombo, Paolo Tremolada Combined Effects of Pesticides and Electromagnetic-Fields on Honeybees: Multi-Stress Exposure. Insects 2021;12(8):716.

Honeybee and general pollinator decline is extensively reported in many countries, adding new concern to the general biodiversity loss. Many studies were addressed to assess the causes of pollinator decline, concluding that in most cases multi-stress effects were the most probable ones. In this research, the combined effects of two possible stress sources for bees, pesticides and electromagnetic fields (multi-stress conditions), were analyzed in the field. Three experimental sites were chosen: a control one far from direct anthropogenic stress sources, a pesticide-stress site and multi-stress one, adding to the same exposure to pesticides the presence of an electromagnetic field, coming from a high-voltage electric line. Experimental apiaries were monitored weekly for one year (from April 2017 to April 2018) by means of colony survival, queen activity, storage and brood amount, parasites and pathogens, and several biomarkers in young workers and pupae. Both exposure and effect biomarkers were analysed: among the first, acetylcholinesterase (AChE), catalase (CAT), glutathione S-transferase (GST) and alkaline phosphatase (ALP) and Reactive Oxygen Species (ROS); and among the last, DNA fragmentation (DNAFRAGM) and lipid peroxidation (LPO). Results showed that bee health conditions were the worst in the multi-stress site with only one colony alive out of the four ones present at the beginning. In this site, a complex picture of adverse effects was observed, such as disease appearance (American foulbrood), higher mortality in the underbaskets (common to pesticide-stress site), behavioral alterations (queen changes, excess of honey storage) and biochemical anomalies (higher ALP activity at the end of the season). The overall results clearly indicate that the multi-stress conditions were able to induce biochemical, physiological and behavioral alterations which severely threatened bee colony survival.

(E) (VO, AC, IFR) Lupke M, Rollwitz J, Simkó M. Cell activating capacity of 50 Hz magnetic fields to release reactive oxygen intermediates in human umbilical cord blood-derived monocytes and in Mono Mac 6 cells. Free Radic Res. 38(9):985-993, 2004.

The aim of this study was to investigate the mechanism of cell activation induced by extremely low frequency magnetic fields (ELF-MF) (50 Hz) in human cells. We examined the production of free radicals in human umbilical cord blood-derived monocytes and in human Mono Mac 6 cells. The release of superoxide radical anions was analyzed using nitroblue tetrazolium chloride and the total of reactive oxygen species (ROS) was detected using dihydrorhodamine 123. Our results show a significant increase of superoxide radical anion production up-to 1.4 fold as well as an increase in ROS release up-to 1.2 fold upon exposure of monocytes to 1 mT ELF-MF (45 min). Mono Mac 6 cells exhibit higher superoxide radical anion and ROS production up-to 1.4 and 1.5 fold, respectively. These results indicate that Mono Mac 6 cells are more sensitive to ELF-MF than monocytes. Using diphenyleneiodonium chloride (DPI) a specific inhibitor for the NADPH oxidase, the MF-effect was not inhibited in Mono Mac 6 cells. Therefore, we suggest that ELF-MF exposure induces the activation of NADH oxidase in these cells. However, the MF-effect was inhibited by DPI in monocytes, indicating the activation of the NADPH oxidase after exposure to ELF-MF.

(E) (VT, AE, IFR) Luukkonen J, Liimatainen A, Juutilainen J, Naarala J. Induction of genomic instability, oxidative processes, and mitochondrial activity by 50Hz magnetic fields in human SH-SY5Y neuroblastoma cells. Mutat Res. 760:33-41, 2014.

Epidemiological studies have suggested that exposure to 50Hz magnetic fields (MF) increases the risk of childhood leukemia, but there is no mechanistic explanation for carcinogenic effects. In two previous studies we have observed that a 24-h pre-exposure to MF alters cellular responses to menadione-induced DNA damage. The aim of this study was to investigate the cellular changes that must occur already during the first 24h of exposure to MF, and to explore whether the MF-induced changes in DNA damage response can lead to genomic instability in the progeny of the exposed cells. In order to answer these questions, human SH-SY5Y neuroblastoma cells were exposed to a 50-Hz, 100-μT MF for 24h, followed by 3-h exposure to menadione. The main finding was that MF exposure was associated with increased level of micronuclei, used as an indicator of induced genomic instability, at 8 and 15d after the exposures. Other delayed effects in MF-exposed cells included increased mitochondrial activity at 8d, and increased reactive oxygen species (ROS) production and lipid peroxidation at 15d after the exposures. Oxidative processes (ROS production, reduced glutathione level, and mitochondrial superoxide level) were affected by MF immediately after the exposure. In conclusion, the present results suggest that MF exposure disturbs oxidative balance immediately after the exposure, which might explain our previous findings on MF altered cellular responses to menadione-induced DNA damage. Persistently elevated levels of micronuclei were found in the progeny of MF-exposed cells, indicating induction of genomic instability.

(E) (VT, AE, MC) Mahmoudinasab H, Sanie-Jahromi F, Saadat M. Effects of extremely low-frequency electromagnetic field on expression levels of some antioxidant genes in human MCF-7 cells. Mol Biol Res Commun. 5(2):77-85. 2016.

In the past three decades, study on the biological effects of extremely low-frequency electromagnetic fields (ELF-EMFs) has been of interest to scientists. Although the exact mechanism of its effect is not fully understood, free radical processes has been proposed as a possible mechanism. This study was designed to evaluate the effect of 50-Hz EMFs on the mRNA levels of seven antioxidant genes (*CAT*, *SOD1*, *SOD2*, *GSTO1*, *GSTM3*, *MSGT1*, and *MSGT3*) in human MCF-7 cells. The EMF exposure patterns were: 1) 5 min field-on/5 min filed-off, 2) 15 min field-on/15 min field-off, 3) 30 min field-on continuously. In all three exposure conditions we tried to have total exposure time of 30 minutes. Control cultures were located in the exposure apparatus when the power was off. The experiments were done at two field intensities; 0.25 mT and 0.50 mT. The RNA extraction was done at two times; immediately post exposure and two hours post exposure. The mRNA levels were determined using quantitative real-time polymerase chain reaction. MTT assay for three exposure conditions in the two field intensities represented no cytotoxic effect on MCF-7 cells. Statistical comparison showed a significant difference between 0.25 mT and 0.50 mT intensities for "the 15 min field-on/15 min field-off condition" (Fisher's exact test, P=0.041), indicating that at 0.50 mT intensity field, the number of down-regulated and/or up-regulated genes increased compared with the other ones. However, there is no statistical significant difference between the field intensities for the two others EMF exposure conditions.

(E) (VT, AE, IAO, IX) Mahmoudinasab H, Saadat M. Electromagnetic field could protect SH-SY5Y cells against cisplatin cytotoxicity, but not MCF-7 cells. DNA Cell Biol. 37(4):330-335, 2018a.

Cisplatin [cis-dichlorodiammine platinum (II), CDDP], morphine (Mor), and electromagnetic field (EMF) induced oxidative stress. In this study, we tried to increase the cytotoxicity of CDDP in combination with Mor and/or EMF in MCF-7 and SH-SY5Y cells. Furthermore, we evaluate the expression levels of 11 antioxidant genes in both cell lines. We designed four treatments: CDDP alone, "CDDP+Mor," "CDDP+EMF," and "CDDP+Mor+EMF." Serial dilutions of CDDP, Mor (5.0 μM), and EMF (50 Hz, 0.50 mT, "15 min field-on/15 min field-off") were used for estimation of relative IC_{50} values. The mRNA expression levels of antioxidant genes were determined by real-time PCR. The IC_{50} value of CDDP in "CDDP+Mor+EMF" treatment was significantly higher than CDDP alone and "CDDP+Mor" treatments in both cell lines. Whereas the expression levels of antioxidant genes in the four treatments showed similar patterns in MCF-7 cells, in SH-SY5Y cells, most of the antioxidant genes showed an upregulation with "CDDP+EMF" and "CDDP+Mor+EMF" treatments. Moreover, significant differences in the number of upregulated genes were observed between different treatments in SH-SY5Y cells. The molecular mechanism of CDDP-reduced cytotoxicity in our designed combinations is probably different in MCF-7 and SH-SY5Y cells. CDDP in combination with EMF could protect SH-SY5Y cells from the cytotoxicity, whereas it has no significant change in MCF-7 cells.

(E) (VT, AE, IX, MC) Mahmoudinasab H, Saadat M. Expressions of some antioxidant genes in SH-SY5Y cells treated with β-lapachone, morphine and electromagnetic field. Mol Biol Rep. 45(3):379-387, 2018b.

β-Lapachone (β-Lap), morphine (Mor), and electromagnetic field (EMF) generate reactive oxygen species. The goal of the present study was to examine the effects of Mor and EMF, in combination with β-Lap on the cell growth inhibition and expression of several antioxidant genes. The 0.50 mT intensity of 50 Hz EMF and two exposure conditions ("15 min field-on/15 min field-off" and "30 min field-on continuously") on SH-SY5Y cells were used. The effects of Mor and EMF, in combination with β-Lap on cell growth inhibition and the expression levels of several antioxidant genes (NQO1, NQO2, SOD1, SOD2, CAT, GSTO1, GSTM2, GSTM3, GSTP1, MGST1, MGST3) in SH-SY5Y cells were measured. The relative mRNA levels were calculated according to the [Formula: see text]. Whereas NQO1 mRNA level decreased in the "15 min field-on/15 min field-off" condition, the expression level of NQO2 was increased. Both NQO1 and NQO2 expressions increased in Mor treated cells. IC_{50} values of β-Lap in combination with Mor, EMF, and "Mor + EMF" were higher than cells treated only with β-Lap. The NQO1 expression level in the cells treated with β-Lap was higher than the other treatments, indicating that β-Lap induces the expression of NQO1. Moreover, multiple linear regression analysis indicated that NQO1 mRNA levels were associated positively with β-Lap and negatively with EMF. At least in part, the mRNA levels of NQO1 were associated with IC_{50} values of β-Lap in designed treatments. There is a negative association between mRNA levels of NQO1 and IC_{50} values of β-Lap but not NQO2.

(E) (VT, CE, DAO, IX) Maiullari S, Cicirelli A, Picerno A, Giannuzzi F, Gesualdo L, Notarnicola A, Sallustio F, Moretti B. Pulsed Electromagnetic Fields Induce Skeletal Muscle Cell Repair by Sustaining the Expression of Proteins Involved in the Response to Cellular Damage and Oxidative Stress. Int J Mol Sci 24(23):16631, 2023.

Pulsed electromagnetic fields (PEMF) are employed as a non-invasive medicinal therapy, especially in the orthopedic field to stimulate bone regeneration. However, the effect of PEMF on skeletal muscle cells (SkMC) has been understudied. Here, we studied the potentiality of 1.5 mT PEMF to stimulate early regeneration of human SkMC. We showed that human SkMC stimulated with 1.5 mT PEMF for four hours repeated for two days can stimulate cell proliferation without inducing cell apoptosis or significant impairment of the metabolic activity. Interestingly, when we simulated physical damage of the muscle tissue by a scratch, we found that the same PEMF treatment can speed up the regenerative process, inducing a more complete cell migration to close the scratch and wound healing. Moreover, we investigated the molecular pattern induced by PEMF among 26 stress-related cell proteins. We found that the expression of 10 proteins increased after two consecutive days of PEMF stimulation for 4 h, and most of them were involved in response processes to oxidative stress. Among these proteins, we found that heat shock protein 70 (HSP70), which can promote muscle recovery, inhibits apoptosis and decreases inflammation in skeletal muscle, together with thioredoxin, paraoxonase, and superoxide dismutase (SOD2), which can also promote skeletal muscle regeneration following injury. Altogether, these data support the possibility of using PEMF to increase SkMC regeneration and, for the first time, suggest a possible molecular mechanism, which

consists of sustaining the expression of antioxidant enzymes to control the important inflammatory and oxidative process occurring following muscle damage.

(E) (VO, CE, TOD, DAO) Maliszewska J, Marciniak P, Kletkiewicz H, Wyszkowska J, Nowakowska A, Rogalska J. Electromagnetic field exposure (50 Hz) impairs response to noxious heat in American cockroach. J Comp Physiol A Neuroethol Sens Neural Behav Physiol. 204:605-611, 2018.

Exposure to electromagnetic field (EMF) induces physiological changes in organism that are observed at different levels-from biochemical processes to behavior. In this study, we evaluated the effect of EMF exposure (50 Hz, 7 mT) on cockroach's response to noxious heat, measured as the latency to escape from high ambient temperature. We also measured the levels of lipid peroxidation and glutathione content as markers of oxidative balance in cockroaches exposed to EMF. Our results showed that exposure to EMF for 24, 72 h and 7 days significantly increases the latency to escape from noxious heat. Malondialdehyde (MDA) levels increased significantly after 24-h EMF exposure and remained elevated up to 7 days of exposure. Glutathione levels significantly declined in cockroaches exposed to EMF for 7 days. These results demonstrate that EMF exposure is a considerable stress factor that affects oxidative state and heat perception in American cockroach.

(E) (VO, CE, IFR, IOD) Manikonda PK, Rajendra P, Devendranath D, Gunasekaran B, Channakeshava, Aradhya SR, Sashidhar RB, Subramanyam C. Extremely low frequency magnetic fields induce oxidative stress in rat brain. Gen Physiol Biophys. 33(1):81-90, 2014.

The present investigation was conducted to understand the influence of long-term exposure of rats to extremely low frequency magnetic fields (ELF-MF), focusing on oxidative stress (OS) on different regions of rat's brain. Male Wistar rats (21-day-old) were exposed to ELF-MF (50 Hz; 50 and 100 μT) for 90 days continuously; hippocampal, cerebellar and cortical regions from rats were analyzed for (i) reactive oxygen species (ROS), (ii) metabolites indicative of OS and (iii) antioxidant enzymes. In comparison to control group rats, the rats that were continuously exposed to ELF-MF caused OS and altered glutathione (GSH/GSSG) levels in dose-dependent manner in all the regions of the brain. Accumulation of ROS, lipid peroxidation end products and activity of superoxide dismutase in different regions was in the descending order of cerebellum < hippocampus < cortex. Decrement in GSH/GSSG levels and increment in glutathione peroxidase activity were in the descending order of hippocampus < cerebellum < cortex. The continuous exposure to ELF-MF caused OS in all the examined regions of brain more significantly at 100 μT than at 50 μT. Varied influences observed in different regions of the brain, as documented in this study, may contribute to altered metabolic patterns in its related regions of the central nervous system, leading to aberrant neuronal functions.

(E) (VT AE, IFR, AO) Mannerling AC, Simkó M, Mild KH, Mattsson MO. Effects of 50-Hz magnetic field exposure on superoxide radical anion formation and HSP70 induction in human K562 cells. Radiat Environ Biophys. 49(4):731-741, 2010.

Epidemiological studies suggest a correlation between exposure to low-level extremely low-frequency (ELF) magnetic fields (MF) and certain cancers and neurodegenerative diseases. Experimental studies have not provided any mechanism for such effects, although at flux density levels significantly higher than the ones encountered in epidemiological studies, radical homoeostasis and levels of stress response proteins can be affected. Here, we report on the influence of MF exposure (50-Hz sine wave; 1 h; 0.025-0.10 mT; vertical or horizontal MF exposure direction) on different cellular parameters (proliferation, cell cycle distribution, superoxide radical anion, and HSP70 protein levels) in the human leukaemia cell line K562. The positive control heat treatment (42 degrees C, 1 h) did not affect either cell proliferation or superoxide radical anion production but caused accumulation of cells in the G2 phase and increased the stress protein HSP70. MF exposure (0.10 mT, 1 h) did not affect either cell cycle kinetics or proliferation. Both vertical and horizontal MF exposures for 1 h caused significantly and transiently increased HSP70 levels (>twofold), at several flux densities, compared to sham controls and also compared to heat treatment. This exposure also increased (30-40%) the levels of the superoxide radical anion, comparable to the positive control PMA. Addition of free radical scavengers (melatonin or 1,10-phenantroline) inhibited the MF-induced increase in HSP70. In conclusion, an early response to ELF MF in K562 cells seems to be an increased amount of oxygen radicals, leading to HSP70 induction. Furthermore, the results suggest that there is a flux density threshold where 50-Hz MF exerts its effects on K562 cells, at or below 0.025 mT, and also that it is the MF, and not the induced electric field, which is the active parameter.

(NE) (VT, AE) Markkanen A, Naarala J, Juutilainen J. A Study on the effects of 50 Hz magnetic fields on UV-induced radical reactions in murine fibroblasts. J Radiat Res (Tokyo). 51(5):609-613, 2010.

The aim of this study was to test the hypothesis that the "radical pair mechanism" (magnetic field effect on recombination rate of radical pairs) explains our previous findings indicating that 50 Hz magnetic fields (MF) of about 100 μT modify biological responses to ultraviolet (UV) radiation. In the present study, the effects of 50 Hz MF on cellular oxidative processes induced by UV radiation were investigated. Murine L929 fibroblast cells were exposed to 50 Hz MF of 100 or 300 μT during a 1-h UV exposure or for 24 h before it. The decay kinetics of oxidative reactions were analysed by measuring ultraweak chemiluminescence (photon emissions) of the exposed cells by scintillation counter in the out-of-coincidence mode. No significant MF effects were found. The results do not support the hypothesis that 100-300 μT MF modify biological responses to UV radiation by causing an overall change in oxidative reactions at cellular level.

(E) (VT, AE, AO) Martínez MA, Úbeda A, Moreno J, Trillo MÁ. Power frequency magnetic fields affect the p38 MAPK-mediated regulation of NB69 cell proliferation implication of free radicals. Int J Mol Sci. 17(4):510, 2016.

The proliferative response of the neuroblastoma line NB69 to a 100 μT, 50 Hz magnetic field (MF) has been shown mediated by activation of the MAPK-ERK1/2 pathway. This work investigates the MF effect on the cell cycle of NB69, the participation of p38 and c-Jun N-terminal (JNK) kinases in the field-induced proliferative response and the potential involvement of reactive oxygen species (ROS) in the activation of the MAPK-ERK1/2 and -p38 signaling pathways. NB69 cultures were exposed to the 100 μT MF, either intermittently for 24, 42 or 63 h, or continuously for periods of 15 to 120 min, in the presence or absence of p38 or JNK inhibitors: SB203580 and SP600125, respectively. Antioxidant N-acetylcysteine (NAC) was used as ROS scavenger. Field exposure induced transient activation of p38, JNK and ERK1/2. The MF proliferative effect, which was mediated by changes in the cell cycle, was blocked by the p38 inhibitor, but not by the JNK inhibitor. NAC blocked the field effects on cell proliferation and p38 activation, but not those on ERK1/2 activation. The MF-induced proliferative effects are exerted through sequential upregulation of MAPK-p38 and -ERK1/2 activation, and they are likely mediated by a ROS-dependent activation of p38.

(E) (VT, AE, IFR, MC) Martínez MA, Úbeda A, Trillo MA. Role of NADPH oxidase in MAPK signaling activation by a 50 Hz magnetic field in human neuroblastoma cells. Electromagn Biol Med 40(1):103-116, 2021.

Our previous studies have shown that intermittent exposure to a 50-Hz, 100-μT sine wave magnetic field (MF) promotes human NB69 cell proliferation, mediated by activation of the epidermal growth factor receptor (EGFR) and pathways MAPK-ERK1/2 and p38; being the effects on proliferation and p38 activation blocked by the chelator N-acetylcysteine. The present work investigates the MF effects on free radical (FR) production, and the potential involvement of NADPH oxidase, the main source of reactive oxygen species (ROS), in the MF-induced activation of MAPK pathways. To this end, the field effects on MAPK-ERK1/2, -p38 and -JNK activation in the presence or absence of the NADPH oxidase inhibitor, diphenyleneiodonium chloride (DPI), as well as the expression of the p67phox subunit, were analyzed. The results revealed that field exposure increases FR production and induces early, transient expression of the cytosolic component of the NADPH oxidase, p67phox. Also, the MF-induced activation of the MAPK-JNK pathway, but not that of -ERK1/2 or -p38 pathways, was prevented in the presence of the DPI, which has been shown to significantly reduce p67phox expression. These data, together with those from previous studies, identify various, FR-dependent or -independent mechanisms, involved in the MF-induced proliferative response mediated by MAPK signaling activation.

(E) (VO, AE, DAO) Martínez-Sámano J, Torres-Durán PV, Juárez-Oropeza MA, Elías-Viñas D, Verdugo-Díaz L. Effects of acute electromagnetic field exposure and movement restraint on antioxidant system in liver, heart, kidney and plasma of Wistar rats: a preliminary report. Int J Radiat Biol. 86(12):1088-1094, 2010.

PURPOSE: The aim of the present study was to evaluate the early effects of acute (2 h) exposure to extremely low frequency electromagnetic fields (ELF-EMF), as well as movement restraint (MR) and the combination of both on the antioxidant systems in the plasma, liver, kidney, and heart of rats. MATERIALS AND METHODS: Twenty-four adult male Wistar rats were divided in two groups, restrained and unrestrained. The restrained animals were confined into an acrylic tube for 120 min. Half of the animals of each group were exposed to ELF-EMF (60 Hz, 2.4 mT) during the period of restriction. Immediately after treatment, reduced glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and thiobarbituric acid reactive substances (TBARS) were measured in tissues. RESULTS: GSH concentration was significantly lower in the heart of all experimental animals when compared to the control group; furthermore, the decrease was higher in the liver of restrained animals. SOD activity was lower in the plasma of restrained and EMF exposed animals compared to unrestrained rats. There were no significant differences in CAT activity and TBARS levels among all the experimental groups vs. the control group. CONCLUSION: Two hours of 60 Hz EMF exposure might immediately alter the metabolism of free radicals, decreasing SOD activity in plasma and GSH content in heart and kidney, but does not induce immediate lipid peroxidation. Oxidative stress induced by movement restraint was stronger than that produced by EMF.

(E) (VO, AE, DAO) Martínez-Sámano J, Torres-Durán PV, Juárez-Oropeza MA, Verdugo-Díaz L. Effect of acute extremely low frequency electromagnetic field exposure on the antioxidant status and lipid levels in rat brain. Arch Med Res. 43(3):183-189, 2012.

BACKGROUND AND AIMS: It is generally accepted that electromagnetic fields (EMF) can exert biological effects; however, the mechanisms by which EMF elicits responses are still unknown. The present study was designed to assess the immediate effects of acute EMF exposure, movement restriction, and the combination of both on the antioxidant systems and lipid content in the whole brain of rat. METHODS: Thirty two male Wistar rats were arranged in four groups: control, EMF exposed, movement restrained (MR), and EMF + MR for 2 h. Rats were then sacrificed and their brains analyzed for superoxide dismutase and catalase activities, reduced glutathione, nitric oxide, total cholesterol, and triacylglycerol levels, as well as plasma corticosterone concentrations. RESULTS: Acute exposure to EMF induces reduction in catalase and superoxide dismutase activities, whereas the combination of EMF + MR also decreases both reduced glutathione and nitric oxide levels. Our results show that the acute exposure to EMF does not induce elevation of stress-hormone corticosterone but impairs the antioxidant status in rat brain. CONCLUSIONS: Plasma corticosterone concentration and antioxidant data indicate that the acute exposure to EMF appears to be a mild stressor that leads to some adaptive responses due to the activation of systems controlling the brain oxidative balance.

(E) (VO, CE, IOD) Martínez-Sámano J, Flores-Poblano A, Verdugo-Díaz L, Juárez-Oropeza MA, Torres-Durán PV. Extremely low frequency electromagnetic field exposure and restraint stress induce changes on the brain lipid profile of Wistar rats. BMC Neurosci. 19(1):31, 2018.

BACKGROUND: Exposure to electromagnetic fields can affect human health, damaging tissues and cell homeostasis. Stress modulates neuronal responses and composition of brain lipids. The aim of this study was to evaluate the effects of chronic extremely low frequency electromagnetic field (ELF-EMF) exposure, restraint stress (RS) or both (RS + ELF-EMF) on lipid profile and lipid peroxidation in Wistar rat brain. METHODS: Twenty-four young male Wistar rats were allocated into four groups: control, RS, ELF-EMF exposure, and RS + ELF-EMF for 21 days. After treatment, rats were euthanized, the blood was obtained for quantitate plasma corticosterone concentration and their brains were dissected in cortex, cerebellum and subcortical structures for cholesterol, triacylglycerols, total free fatty acids, and thiobarbituric acid reactive substances (TBARS) analysis. In addition, fatty acid methyl esters (FAMEs) were identified by gas chromatography. RESULTS: Increased values of plasma corticosterone were found in RS and ELF-EMF exposed groups ($p < 0.05$), this effect was higher in RS + ELF-EMF group ($p < 0.05$, vs. control group). Chronic ELF-EMF exposure increased total lipids in cerebellum, and total cholesterol in cortex, but decreased polar lipids in cortex. In subcortical structures, increased concentrations of non-esterified fatty acids were observed in RS + ELF-EMF group. FAMEs analysis revealed a decrease of polyunsaturated fatty acids of cerebellum and increases of subcortical structures in the ELF-EMF exposed rats. TBARS concentration in lipids was increased in all treated groups compared to control group, particularly in cortex and cerebellum regions. CONCLUSIONS: These findings suggest that chronic exposure to ELF-EMF is similar to physiological stress, and induce changes on brain lipid profile.

(E) (VT, AE, AO) Martino CF. Static magnetic field sensitivity of endothelial cells. Bioelectromagnetics. 32(6):506-508, 2011.

In this manuscript, data demonstrating the magnetic sensitivity of human umbilical vein endothelial cells (HUVECs) is presented. The effects of low level fields (LLF; 0.2-1 μT), 30 and 120 μT magnetic fields on the proliferation of endothelial cells were investigated. Primary HUVECs were cultured and exposed to the distinct magnetic conditions in the same incubator. Although cell numbers were slightly affected between 30 and 120 μT magnetic fields, reducing the magnetic field to low levels clearly inhibited proliferation. The rationale of introducing LLF is to elucidate a possible mechanism of interaction. Small differences of 30 μT reduce endothelial cell numbers significantly. The addition of free radical scavenger superoxide dismutase suppressed the enhanced proliferation caused by 120 μT static magnetic fields. It is proposed that the static magnetic field interacts with endothelial cells via a free radical mechanism.

(E) (VT, AE, IFR, LI) Martino CF, Castello PR. Modulation of hydrogen peroxide production in cellular systems by low level magnetic fields. PLoS One. 6(8):e22753, 2011.

Increased generation of reactive oxygen species (ROS) and an altered redox status have long been observed in cancer cells, suggesting that ROS might be involved in the development of these cells. However, recent studies suggest that inducing an excess of ROS in cancer cells can be exploited for therapeutic benefits. Cancer cells in advanced stage tumors frequently exhibit multiple genetic alterations and high oxidative stress, suggesting that it might be possible to preferentially modulate the development of these cells by controlling their ROS production. Low levels of ROS are also important for the development and survival of normal cells. In this manuscript, we present data on the influence of the suppression of the Earth's magnetic field (low level magnetic fields or LLF) which magnitudes range from 0.2 μT to 2 μT on the modulation of hydrogen peroxide (H(2)O(2)) in human fibrosarcoma cancer cell line HT1080, pancreatic AsPC-1 cancer cell line, and bovine pulmonary artery endothelial cells (PAEC) exposed to geomagnetic field (control; 45 μT-60 μT). Reduction of the Earth's magnetic field suppressed H(2)O(2) production in cancer cells and PAEC. The addition of catalase and superoxide dismutase (SOD) mimetic MnTBAP inhibited the magnetic field effect. Modulating ROS production by magnetic fields may open new venues of biomedical research and therapeutic strategies.

(E) (VO, CE, IAO, IX) Medina-Fernandez FJ, Escribano BM, Agüera E, Aguilar-Luque M, Feijoo M, Luque E, Garcia-Maceira FI, Pascual-Leone A, Drucker-Colin R, Tunez I. Effects of transcranial magnetic stimulation on oxidative stress in experimental autoimmune encephalomyelitis. Free Radic Res. 51(5):460-469, 2017.

Experimental autoimmune encephalomyelitis (EAE) reproduces a multiple sclerosis (MS)-like experimental model. The main objective was to evaluate the effect of extremely low-frequency electromagnetic fields (EL-EMF) application, like a paradigm of transcranial magnetic stimulation (TMS) in the development of EAE. Rats were injected with a single dose of 150 μg of myelin oligodendrocyte glycoprotein (MOG, fragment 35-55) to produce experimental MS. To assess the effect of TMS application in EAE, the rats were treated with TMS (60 Hz and 0.7 mT) for 2 h in the morning, once a day, 5 days a week, during 3 weeks. TMS was applied to the head. The effect of TMS on EAE was evaluated as motor symptoms and, oxidative and cell damage. The data showed that MOG induced motor symptoms as tail paralysis and limb paresis/paralysis, oxidative stress and cell death similar to MS when compared with control animals. Importantly, TMS application attenuated motor symptoms, oxidative and cell damage, whereas it increased antioxidant system. Our findings suggest that: (i) MOG reproduces an experimental model of MS characterised by oxidative and cell damage; and (ii) TMS application decreases oxidative stress and cell death induced by MOG.

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(E) (VO, CE, IAO, IX) Medina-Fernandez FJ, Escribano BM, Luque E, Caballero-Villarraso J, Gomez-Chaparro JL, Feijoo M, Garcia-Maceira FI, Pascual-Leone A, Drucker-Colin R, Tunez I. Comparative of transcranial magnetic stimulation and other treatments in experimental autoimmune encephalomyelitis. Brain Res Bull. 137:140-145, 2018

The effects of transcranial magnetic stimulation (TMS), natalizumab (nata), dimethyl fumarate (DMF) and dexamethasone (DEX) on clinical score and oxidative stress produced by a single dose of myelin oligodendrocyte glycoprotein (MOG) in tail of Dark Agouti rats was studied. TMS (60Hz and 0.7 mT), nata (5mg/kg), DMF (15mg/kg) and DEX (300μg/kg) was applied for 21 after the administration of MOG (150μg). We estimated clinical score, as well as lipid peroxides, carbonylated proteins and reduced glutathione (GSH)/oxidized glutathione (GSSG) ratio content in brain, spinal cord and blood. MOG triggered significant increase in clinical score and in the levels of lipid peroxides and carbonylated proteins levels, but reduced GSH/GSSG ratio in brain, spinal cord and blood. Both TMS and clinical treatments, although TMS more significantly, decreased the changes caused by MOG administration. These results support the antioxidant and neuroprotective action of TMS, as well as an activity higher than other clinical treatments.

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Medina-Fernández FJ, Escribano BM, Padilla-Del-Campo C, Drucker-Colín R, Pascual-Leone Á, Túnez I. Transcranial magnetic stimulation as an antioxidant. Free Radic Res. 52(4):381-389, 2018. (Review)

In the last decades, different transcranial magnetic stimulation protocols have been developed as a therapeutic tool against neurodegenerative and psychiatric diseases, although the biochemical, molecular and cellular mechanisms underlying these effects are not well known. Recent data show that those magnetic stimulation protocols showing beneficial effects could trigger an anti-oxidant action that would favour, at least partially, their therapeutic effect. We have aimed to review the molecular effects related to oxidative damage induced by this therapeutic strategy, as well as from them addressing a broader definition of the anti-oxidant concept.

(E) (VT, AE, DFR) Merighi S, Gessi S, Bencivenni S, Battistello E, Vincenzi F, Setti S, Cadossi M, Borea PA, Cadossi R, Varani K. Signaling pathways involved in anti-inflammatory effects of Pulsed Electromagnetic Field in microglial cells. Cytokine 2020;125:154777.

Literature studies suggest important protective effects of low-frequency, low-energy pulsed electromagnetic fields (PEMFs) on inflammatory pathways affecting joint and cerebral diseases. However, it is not clear on which bases they affect neuroprotection and

the mechanism responsible is yet unknown. Therefore the aim of this study was to identify the molecular targets of PEMFs anti-neuroinflammatory action. The effects of PEMF exposure in cytokine production by lipopolysaccharide (LPS)-activated N9 microglial cells as well as the pathways involved, including adenylyl cyclase (AC), phospholipase C (PLC), protein kinase C epsilon (PKC-ε) and delta (PKC-δ), p38, ERK1/2, JNK1/2 mitogen activated protein kinases (MAPK), Akt and caspase 1, were investigated. In addition, the ability of PEMFs to modulate ROS generation, cell invasion and phagocytosis, was addressed. PEMFs reduced the LPS-increased production of TNF-α and IL-1β in N9 cells, through a pathway involving JNK1/2. Furthermore, they decreased the LPS-induced release of IL-6, by a mechanism not dependent on AC, PLC, PKC-ε, PKC-δ, p38, ERK1/2, JNK1/2, Akt and caspase 1. Importantly, a significant effect of PEMFs in the reduction of crucial cell functions specific of microglia like ROS generation, cell invasion and phagocytosis was found. PEMFs inhibit neuroinflammation in N9 cells through a mechanism involving, at least in part, the activation of JNK MAPK signalling pathway and may be relevant to treat a variety of diseases characterized by neuroinflammation.

(E) (VT, AE, IFR, MC) Merla C, Liberti M, Consales C, Denzi A, Apollonio F, Marino C, Benassi B. Evidences of plasma membrane-mediated ROS generation upon ELF exposure in neuroblastoma cells supported by a computational multiscale approach. Biochim Biophys Acta Biomembr. 1861(8):1446-1457, 2019.

BACKGROUND: Molecular mechanisms of interaction between cells and extremely low frequency magnetic fields (ELF-MFs) still represent a matter of scientific debate. In this paper, to identify the possible primary source of oxidative stress induced by ELF-MF in SH-SY5Y human neuroblastoma cells, we estimated the induced electric field and current density at the cell level. METHODS: We followed a computational multiscale approach, estimating the local electric field and current density from the whole sample down to the single cell level. The procedure takes into account morphological modeling of SH-SY5Y cells, arranged in different topologies. Experimental validation has been carried out: neuroblastoma cells have been treated with Diphenyleneiodonium (DPI) -an inhibitor of the plasma membrane enzyme NADPH oxidase (Nox)- administered 24 h before exposure to 50 Hz (1 mT) MF. RESULTS: Macroscopic and microscopic dosimetric evaluations suggest that increased current densities are induced at the plasma membrane/extra-cellular medium interface; identifying the plasma membrane as the main site of the ELF-neuroblastoma cell interaction. The in vitro results provide an experimental proof that plasma membrane Nox exerts a key role in the redox imbalance elicited by ELF, as DPI treatment reverts the generation of reactive oxygen species induced by ELF exposure. GENERAL SIGNIFICANCE: Microscopic current densities induced at the plasma membrane are likely to play an active physical role in eliciting ELF effects related to redox imbalance. Multiscale computational dosimetry, supported by an in vitro approach for validation, is proposed as the innovative and rigorous paradigm to unveil mechanisms underlying the complex ELF-MF interactions.

(E) (VO, CE, DAO) Miao X, Wang Y, Lang H, Lin Y, Guo Q, Yang M, Guo J, Zhang Y, Zhang J, Liu J, Liu Y, Zeng L, Guo G. Preventing electromagnetic pulse irradiation damage on testis using selenium-rich Cordyceps fungi. A preclinical study in young male mice. OMICS. 21(2):81-89, 2017.

Networked 21st century society, globalization, and communications technologies are paralleled by the rise of electromagnetic energy intensity in our environments and the growing pressure of the environtome on human biology and health. The latter is the entire complement of environmental factors, including the electromagnetic energy and the technologies that generate them, enacting on the digital citizen in the new century. Electromagnetic pulse (EMP) irradiation might have serious damaging effects not only on electronic equipment but also in the whole organism and reproductive health, through nonthermal effects and oxidative stress. We sought to determine whether EMP exposure (1) induces biological damage on reproductive health and (2) the extent to which selenium-rich Cordyceps fungi (daily coadministration) offer protection on the testicles and spermatozoa. In a preclinical randomized study, 3-week-old male BALB/c mice were repeatedly exposed to EMP (peak intensity 200 kV/m, pulse edge 3.5 ns, pulse width 15 ns, 0.1 Hz, and 400 pulses/day) 5 days per week for four consecutive weeks, with or without coadministration of daily selenium-rich Cordyceps fungi (100 mg/kg). Testicular index and spermatozoa formation were measured at baseline and 1, 7, 14, 28, and 60 day time points after EMP exposure. The group without Cordyceps cotreatment displayed decreased spermatozoa formation, shrunk seminiferous tubule diameters, and diminished antioxidative capacity at 28 and 60 days after exposure ($p < 0.05$). The Cordyceps daily cotreatment alleviated the testicular damage by EMP exposure, increased spermatozoa formation, and reduced apoptotic spermatogenic cells. These observations warrant further preclinical and clinical studies as an innovative approach for potential protection against electromagnetic radiation in the current age of networked society and digital citizenship.

(E) (VO, AE, IAO) Migdał P, Murawska A, Strachecka A, Bieńkowski P, Roman A. Changes in the Honeybee Antioxidant System after 12 h of Exposure to Electromagnetic Field Frequency of 50 Hz and Variable Intensity. Insects. 2020 Oct 18;11(10):E713.

In recent years, on a global scale, more and more reports of a phenomenon called CCD (Colony Collapse Disorder) have been reported. In addition to pesticides, diseases, and other environmental stressors, electromagnetic fields are also mentioned as one of the possible causes of CCD. One of the body's first lines of defense against harmful factors is the antioxidant system. We hypothesized that electromagnetic field upregulate the activity of SOD (superoxide dismutase), CAT (catalases), and changed FRAP (total antioxidant potential) in honeybee hemolymph. In our research, 12 h bee's exposure to E-field was analyzed to determine changes in the antioxidant system. The frequency of 50 Hz and various intensities were used: 5.0 kV/m, 11.5 kV/m, 23.0 kV/m, and 34.5 kV/m. Superoxide dismutase was characterized by four times higher activity in the study groups as compared to the control group. Catalase

activity in all groups was characterized by statistically significantly different activity between the groups. The highest activity was recorded in the 34.5 kV/m group. The lowest activity was recorded in the 11.5 kV/m group. A relationship was found between different E-field intensities and changes in the antioxidant system.

(E) (VT, AE, IFR, IAO) Miliša M, Đikić D, Mandić T, Grozić D, Čolić I, Ostojić A. Response of aquatic protists to electric field exposure. Int J Radiat Biol. 93(8):818-830, 2017.

PURPOSE: To test the effects of short term exposure of aquatic organisms to electric field (EF) with negligible magnetic component. MATERIALS AND METHODS: We built a plate capacitor that served as a source of EF of strengths that can be found in nature near transmission lines. We exposed two cultured protist species Euglena viridis and Paramecium caudatum to EFs for 24 hours and monitored their abundance, morphology, intracellular superoxide anion (by DHE), hydrogen peroxide by (H_2DCF) and MDA contents, catalase (CAT) and superoxide dismutase (SOD) activity. RESULTS: We found that even short term exposure to low strength EF causes changes in population abundance, morphology and oxidative stress response in both species. As the EF strength increased, abundance of both species decreased. However, at weaker EFs fission rates were seemingly promoted. We noted decrease in size in both organisms in directions perpendicular to their fission planes correlated with EF strength. DHE and H_2DCF fluorescence intensity and SOD activity were higher in organisms exposed to the stronger EFs. CONCLUSIONS: We suggest that the electric component of the field, rather than the magnetic, is the main cause of all the noted effects. As a result, aquatic organisms should be given greater importance in studies assessing the effects of EMFs in spite of attenuating effects of water to EF strengths.

(E) (VO, AE, DAO) Mohamad EA, Elfky AA, El-Gebaly RH, Afify A. Study the change in the mosquito larvae (*Culex pipiens*) in water treated with short pulses electric filed. Electromagn Biol Med 41(1):80-92, 2022.

Electrical Pulsed Field (PEF), of pulse duration in 4 milliseconds, effect on mosquito larvae (*Culex pipiens*) as aquatic insects is assessed in this work. Mosquito larvae classes have been treated with electric field power values (66.66, 83.33, 100, 116.66 V/cm) with separate pulse number (60) and other classes of various pulse numbers have been treated (20, 40, 60, 80) with power of the electrical field 100 V/cm. The findings revealed that positively significant of increase of the applied electrical field strength or increase of the number of pulses. The rise in both cases leads to an increase in the mortality of 25%, 50%, and 75% of the mosquito larvae ($P < .05$). The impact was calculated with the bioassay system on mosque larvae, SDS-PAGE for whole body proteins, enzyme analysis and ultrastructural examination using TEM. The current study reveals that a low pulsed electric field can cause mosquito larvae genotoxic, changes in the insect's body proteins, which may affect the insect's ability to live. The increase in pulsed electric field parameters also activates oxidative stress in the insect cell by disrupting its secretion of enzymes that could affect the mosquito's capabilities in the future.

(E) (VO, VT, AE, IFR. IAO) Mohamed AF, Nasr M, Amer ME, Abuamara TMM, Abd-Elhay WM, Kaabo HF, Matar EER, El Moselhy LE, Gomah TA, El-Fatah Deban MA, Shebl RI. Anticancer and antibacterial potentials induced post short-term exposure to electromagnetic field and silver nanoparticles and related pathological and genetic alterations: in vitro study. Infect Agent Cancer 17(1):4, 2022.

Background: Resistance to antibiotics and anticancer therapy is a serious global health threat particularly in immunosuppressed cancer patients. Current study aimed to estimate the antibacterial and anticancer potentials of short-term exposure to extremely low frequency electromagnetic field (ELF-EMF) and silver nanoparticles (AgNPs) either in sole or combined form.
Methods: Antibacterial activity was evaluated via determination of the bacterial viable count reduction percentage following exposure, whereas their ability to induce apoptosis in breast cancer (MCF-7) cell line was detected using annexin V-fluorescein isothiocyanate and cell cycle analysis. Also, oxidative stress potential and molecular profile were investigated. **Results:** ELF-EMF and AgNPs significantly ($p < 0.01$) reduced K. pneumonia viable count of compared to that of S. aureus in a time dependent manner till reaching 100% inhibition when ELF-EMF was applied in combination to 10 μM/ml AgNPs for 2 h. Apoptosis induction was obvious following exposure to either ELF-EMF or AgNPs, however their apoptotic potential was intensified when applied in combination recording significantly ($p < 0.001$) induced apoptosis as indicated by elevated level of MCF-7 cells in the Pre G1 phase compared to control. S phase arrest and accumulation of cells in G2/M phase was observed following exposure to AgNPs and EMF, respectively. Up-regulation in the expression level of p53, iNOS and NF-kB genes as well as down-regulation of Bcl-2 and miRNA-125b genes were detected post treatment. **Conclusions:** The antibacterial and anticancer potentials of these agents might be related to their ability to induce oxidative stress, suggesting their potentials as novel candidates for controlling infections and triggering cancer cells towards self-destruction.

(E) (VT, AE, IFR) Mohammadi F, Ghanati F, Sharifi M, Chashmi NA. On the mechanism of the cell cycle control of suspension-cultured tobacco cells after exposure to static magnetic field. Plant Sci. 277:139-144. 2018.

One of the main sites of the magnetic fields influence on living cells is the cell cycle. The intensity of this influence however, varies depending on the cell type and the duration of the treatment. Suspension of cultured tobacco cells (Nicotiana tabacum cv. Barley 21) were synchronized via sucrose starvation at their stationary growth phase. The cells were then exposed to 0.2 m T SMF up to 24 h. The progression of different cell cycle phases was monitored through flow cytometry in a time course manner. Expression of cell cycle controlling genes and amounts of certain signaling molecules were measured as well. Exposure to SMF delayed G1.S transition which was accompanied by decrease of cyclin-dependent kinases A (CDK A) and D-type cyclin, but an increase in the adenylyl cyclase (AC), transcription factor E2F, retinoblastoma protein (Rbp), and CDK-inhibitor protein 21 (p21) transcript accumulation. Exposure

to SMF also increased the contents of nitric oxide (NO), hydrogen peroxide (H_2O_2), and salicylic acid (SA), compared to the control group. The results suggest a signaling pathway triggered by SMF starting from accumulation of NO and H_2O_2 followed by downstream events including the increase of cyclic nucleotides and subsequent decrease of both CDKA and CycD.

Montoya RD. Magnetic fields, radicals and cellular activity. Electromagn Biol Med. 36(1):102-113, 2017. (Review)

Some effects of low-intensity magnetic fields on the concentration of radicals and their influence on cellular functions are reviewed. These fields have been implicated as a potential modulator of radical recombination rates. Experimental evidence has revealed a tight coupling between cellular function and radical pair chemistry from signaling pathways to damaging oxidative processes. The effects of externally applied magnetic fields on biological systems have been extensively studied, and the observed effects lack sufficient mechanistic understanding. Radical pair chemistry offers a reasonable explanation for some of the molecular effects of low-intensity magnetic fields, and changes in radical concentrations have been observed to modulate specific cellular functions. Applied external magnetic fields have been shown to induce observable cellular changes such as both inhibiting and accelerating cell growth. These and other mechanisms, such as cell membrane potential modulation, are of great interest in cancer research due to the variations between healthy and deleterious cells. Radical concentrations demonstrate similar variations and are indicative of a possible causal relationship. Radicals, therefore, present a possible mechanism for the modulation of cellular functions such as growth or regression by means of applied external magnetic fields.

(E) (VT, AE, CE, IFR, IAO, DAO) Morabito C, Guarnieri S, Fanò G, Mariggiò MA. Effects of acute and chronic low frequency electromagnetic field exposure on PC12 cells during neuronal differentiation. Cell Physiol Biochem. 26(6):947-958, 2010a.

BACKGROUND/AIMS: The purpose of this study was to provide information about the in vitro neuritogenesis during cell exposure to extremely low frequency electromagnetic fields (ELF-EMFs) of different intensities and durations using pheochromocytoma-derived cell line (PC12 cells) as neuronal model. METHODS: Proliferative rates and neuritogenesis were tested by colorimetric assay and morphological analysis, respectively; reactive oxygen species (ROS) levels and intracellular Ca(2+) variations monitored using single cell videomicroscopy. RESULTS: The long-lasting ELF-EMF exposure (0.1-1.0 mT) did not appear to significantly affect the biological response (proliferation and neuritogenesis). However, during the acute ELF-EMF exposure (30 min), in undifferentiated

PC12 cells, there were increased ROS levels and decreased catalase activity, that, conversely, resulted increased after chronic exposure (7 days) at 1.0 mT. Acute exposure (0.1-1.0 mT) affected the spontaneous intracellular Ca(2+) variations in undifferentiated cells, in which basal intracellular Ca(2+) resulted increased after chronic exposure. In addition acute exposure affected cell response to a depolarizing agent, while basal membrane potential was not changed. CONCLUSION: Even if further studies remain necessary to identify the ROS/intracellular Ca(2+)cross-talking pathway activated by ELF-EMF exposure, we support the hypothesis that ROS and Ca(2+) could be the cellular "primum movens" of the ELF-EMF induced effects on biological systems.

(E) (VT, AE, IFR, IAO) Morabito C, Rovetta F, Bizzarri M, Mazzoleni G, Fanò G, Mariggiò MA. Modulation of redox status and calcium handling by extremely low frequency electromagnetic fields in C2C12 muscle cells: A real-time, single-cell approach. Free Radic Biol Med. 48(4):579-589, 2010b.

The biological effects of electric and magnetic fields, which are ubiquitous in modern society, remain poorly understood. Here, we applied a single-cell approach to study the effects of short-term exposure to extremely low frequency electromagnetic fields (ELF-EMFs) on muscle cell differentiation and function using C2C12 cells as an in vitro model of the skeletal muscle phenotype. Our focus was on markers of oxidative stress and calcium (Ca(2+)) handling, two interrelated cellular processes previously shown to be affected by such radiation in other cell models. Collectively, our data reveal that ELF-EMFs (1) induced reactive oxygen species production in myoblasts and myotubes with a concomitant decrease in mitochondrial membrane potential; (2) activated the cellular detoxification system, increasing catalase and glutathione peroxidase activities; and (3) altered intracellular Ca(2+)homeostasis, increasing the spontaneous activity of myotubes and enhancing cellular reactivity to a depolarizing agent (KCl) or an agonist (caffeine) of intracellular store Ca(2+)channels. In conclusion, our data support a possible link between exposure to ELF-EMFs and modification of the cellular redox state, which could, in turn, increase the level of intracellular Ca(2+)and thus modulate the metabolic activity of C2C12 cells.

(E) (VT, AE, IAO) Mshenskaya N, Sinitsyna Y, Kalyasova E, Valeria K, Zhirova A, Karpeeva I, Ilin N.
Influence of Schumann Range Electromagnetic Fields on Components of Plant Redox Metabolism in Wheat and Peas. Plants (Basel) 2022, 11(15):1955.

The Schumann Resonances (ScR) are Extremely Low Frequency (ELF) electromagnetic resonances in the Earth-ionosphere cavity excited by global lightning discharges. ScR are the part of electromagnetic field (EMF) of Earth. The influence of ScR on biological systems is still insufficiently understood. The purpose of the study is to characterize the possible role of the plant cell redox metabolism regulating system in the Schumann Resonances EMF perception. Activity of catalase and superoxide dismutase, their isoenzyme structure, content of malondialdehyde, composition of polar lipids in leaf extracts of wheat and pea plants treated with

short-time (30 min) and long-time (18 days) ELF EMF with a frequency of 7.8 Hz, 14.3 Hz, 20.8 Hz have been investigated. Short-time exposure ELF EMF caused more pronounced bio effects than long-time exposure. Wheat catalase turned out to be the most sensitive parameter to magnetic fields. It is assumed that the change in the activity of wheat catalase after a short-term ELF EMF may be associated with the ability of this enzyme to perceive the action of a weak EMF through calcium calmodulin and/or cryptochromic signaling systems.

(E) (VT, AE, IAO) Mustafa E, Makinistian L, Luukkonen J, Juutilainen J, Naarala J. Do 50/60 Hz magnetic fields influence oxidative or damage responses in human SH-SY5Y neuroblastoma cells? Int J Radiat Biol 98(10):1581-1591, 2022.

Purpose: We investigated possible effects of 50 Hz and 60 Hz magnetic fields (MFs) on reactive oxygen species (ROS) production, DNA damage, DNA damage repair rate, as well as gene expression related to oxidative stress and DNA damage signaling.***Materials and methods:*** Human SH-SY5Y neuroblastoma cells were sham-exposed or exposed to 100 μT_{RMS} MFs for 24 h, then assayed or further treated with 100 µM menadione for 1 h before the assay. The levels of ROS and cytosolic superoxide anion ($O_2^{\bullet-}$) were assayed fluorometrically. DNA damage and gene expression were assayed by comet assay and RT-qPCR, respectively. To examine whether MFs affected DNA damage repair rate, cells were allowed to repair their DNA for 1 or 2 h after menadione treatment and then assayed for DNA damage.***Results:*** There was suggestive evidence of a general low-magnitude increase in the expression of ROS-related genes (primarily genes with antioxidant activity) when quantified immediately after MF exposure, suggesting a response to a small increase in ROS level. The possible upregulation of ROS-related genes is supported by the finding that the level of menadione-induced ROS was consistently decreased by 50 Hz MFs (not significantly by 60 Hz MFs) in several measurements 30 - 60 min after MF exposure. MF exposures did not affect cytosolic $O_2^{\bullet-}$ levels, DNA damage, or its repair rate. Changes in the expression of DNA damage-signaling genes in the MF-exposed cells did not exceed the expected rate of false positive findings. No firm evidence was found for differential effects from 50 Hz vs. 60 Hz MFs.***Conclusions:*** While only weak effects were found on the endpoints measured, the results are consistent with MF effects on ROS signaling.

(E) (VT, AE, IFR)Muti ND, Salvio G, Ciarloni A, Perrone M, Tossetta G, Lazzarini R, Bracci M, Balercia G. Can extremely low frequency magnetic field affect human sperm parameters and male fertility? Tissue Cell 82:102045, 2023.

Exposure to extremely low frequency magnetic fields (ELF-MF) may have different effects on spermatozoa depending on the waveform, magnetic flux density, frequency of ELF-MF, and duration of exposure. In this study, we investigated the possible role of ELF-MF (50 Hz; 1 mT) exposure in altering sperm parameters. In this study we found that exposure to ELF-MF at the frequency of 50 Hz (1 mT) for two hours induces statistically significant alterations in progressive motility, morphology and reactive oxygen species (ROS) production of human spermatozoa, suggesting a role of ELF-MF in altering reproductive function of spermatozoa. Our results

represent an important discovery in the field since occupational exposure to the sine waveform 1 mT 50 Hz ELF-MF used in our study is possible in workplace. Moreover, these electromagnetic fields are product by many electronic devices and household appliances. Thus, alterations of progressive motility and morphology of spermatozoa would be important consequences of human exposures to ELF-MF.

(E) (VT, AE, IFR) Naarala J, Kesari KK, McClure I, Chavarriaga C, Juutilainen J, Martino CF. Direction-dependent effects of combined static and ELF magnetic fields on cell proliferation and superoxide radical production. Biomed Res Int. 2017:5675086, 2017.

Proliferation of human umbilical vein endothelial cells was stimulated by a nearly vertical 60 or 120 μT static magnetic field (MF) in comparison to cells that were shielded against MFs. When the static field was combined with an extremely low frequency (ELF) MF (18 Hz, 30 μT), proliferation was suppressed by a horizontal but not by a vertical ELF field. As these results suggested that the effects of an ELF MF depend on its direction in relation to the static MF, independent experiments were carried out to confirm such dependence using 50 Hz MFs and a different experimental model. Cytosolic superoxide level in rat glioma C6 cells exposed in the presence of a nearly vertical 33 μT static MF was increased by a horizontal 50 Hz, 30 μT MF, but not affected by a vertical 50 Hz MF. The results suggest that a weak ELF MF may interact with the static geomagnetic field in producing biological effects, but the effect depends on the relative directions of the static and ELF MFs.

(NE) (VT, AE) Nakayama M, Nakamura A, Hondou T, Miyata H. Evaluation of cell viability, DNA single-strand breaks, and nitric oxide production in LPS-stimulated macrophage RAW264 exposed to a 50-Hz magnetic field. Int J Radiat Biol. 92(10):583-589, 2016.

PURPOSE: Synergistic effects between cellular oxidative stress and magnetic fields may explain the adverse biological effects of 50/60 Hz magnetic fields. To determine whether this hypothesis holds in macrophage RAW264 cells, we measured DNA single-strand breaks (SSB), cell viability, and nitric oxide (NO) production in cells with or without exposure to 0.5-mT, 50-Hz magnetic fields for 24 h and with or without simultaneous stimulation via the bacterial endotoxin, lipopolysaccharide (LPS). MATERIALS AND METHODS: Macrophages stimulated with 10 ng/ml LPS for 1 h were exposed to or not exposed to a magnetic field and were then subjected to (1) the alkaline comet assay to measure SSBs, (2) trypan-blue exclusion assay for cell viability, and (3) measurements of NO for evaluation of oxidative stress. RESULTS: The 50-Hz magnetic field enhanced DNA SSB and decreased cell viability only in the LPS-stimulated macrophages in which NO production was greatly enhanced. The magnetic field alone did not alter NO production. CONCLUSION: Co-stimulation of the cell with LPS and a 50-Hz magnetic field promoted SSB and lowered cell viability, but these were not mediated by LPS-induced NO production.

(E) (VT, AE, IFR) Noda Y, Mori A, Liburdy RP, Packer L. Pulsed magnetic fields enhance nitric oxide synthase activity in rat cerebellum. Pathophysiology. 7(2):127-130, 2000.

The effect of pulsed magnetic fields on nitric oxide synthase (NOS) activity in the rat brain was investigated. Sprague-Dawley rats (male, 200-250 g body weight) brain were dissected regionally, and the crude enzyme solutions were treated with pulsed DC, AC or static DC magnetic fields at 0 degrees C for 1 h. After exposure, NOS activity was measured as nitrite and nitrate levels generated from incubation with arginine, CaCl(2) and beta-nicotinamide adenine dinucleotide phosphate. Under these experimental conditions, neither AC nor static DC field treatment showed any significant change in NOS activity. A significant increase in NOS activity was observed in the cerebellum (111.2+/-2.0%, $P<0.05$, five separate experiments) for a 1 Gauss (0.1 mT) pulsed DC field. Under the same experimental condition, only a slight change or no effect was observed in the hippocampus, cortex, medulla oblongata, hypothalamus, striatum and midbrain. These studies suggest that pulsed magnetic fields result in a different effect on NOS activity in the cerebellum of the rats.

Okano H. Effects of static magnetic fields in biology: role of free radicals. Front Biosci. 13:6106-6125, 2008. (Review)

Biological systems can respond to a wide range of static magnetic fields (SMF). Some of these responses seem to be mediated partly through free radical reactions. For example, in magnetic sense and navigation using the geomagnetic field, one of the most promising mechanisms for explaining magnetic compass is "a radical pair mechanism". Biological free radicals are most commonly oxygen or nitrogen based with an unpaired electron, leading to the terms "reactive oxygen species (ROS)" or "reactive nitrogen species (RNS)". When applying SMF to medical treatment, coupling SMF exposure with possible chemotherapy of cancers is a novel fascinating area that SMF could enhance agent-induced ROS production against tumors. In addition, one of the potent mechanisms of SMF effects on hemodynamics and blood pressure has sometimes been linked to nitric oxide pathway. However, health and environmental concerns have been raised because the SMF effects on oxidative stress leading to genetic mutation and apoptosis/necrosis have been found. It seems to take place from free radical generation.

(E) (VT, AE, IOD) Oliva M, De Marchi L, Cuccaro A, Fumagalli G, Freitas R, Fontana N, Raugi M, Barmada S, Pretti C. Introducing energy into marine environments: A lab-scale static magnetic field submarine cable simulation and its effects on sperm and larval development on a reef forming serpulid. Environ Pollut. 328:121625, 2023.

Non-chemical sources of anthropogenic environmental stress, such as artificial lights, noise and magnetic fields, are still an underestimate factor that may affect the wildlife. Marine environments are constantly subjected to these kinds of stress, especially nearby to urbanized coastal areas. In the present work, the effect of static magnetic fields, associated with submerged electric cables,

was evaluated in gametes and early life stages of a serpulid polychaete, namely Ficopomatus enigmaticus. Specifically, biochemical/physiological impairments of sperm, fertilization rate inhibition and incorrect larval development were assessed. We evaluated differences between two selected magnetic field induction values (0.5 and 1 mT) along a range of exposure times (30 min-48 h), for a sound evaluation on this species. We found that a magnetic induction of 1 mT, a typical value that can be found at distance of tens of cm from a submerged cable, may be considered a biologically and ecologically relevant for sessile organisms and for coastal environments more generally. This value exerted statistically significant effects on membranes, DNA integrity, kinetic parameters and mitochondrial activity of sperm cells. Moreover, a significant reduction in fertilization rate was observed in sperm exposed to the same magnetic induction level (1 mT) for 3 h, compared to controls. Regarding early larval stages, 48-h exposure did not affect the correct development. Our results represent a starting point for a future focus of research on magnetic field effects on early life stages of aquatic invertebrates, using model species as representative for reef-forming/encrusting organisms and ecological indicators of soft sediment quality.

(E) (VO, CE, DOD)

Orel VE, Krotevych M, Dasyukevich O, Rykhalskyi O, Syvak L, Tsvir H, Tsvir D, Garmanchuk L, Orel VB, Sheina I, Rybka V , Shults NV, Suzuki YJ, Gychka SG

Effects induced by a 50 HZ electromagnetic field and doxorubicin on Walker-256 carcinosarcoma growth and hepatic redox state in rats. Electromagn Biol Med 40 (4):75-487, 2021

We compare the effects of an extremely low-frequency electromagnetic field (EMF) with the chemotherapeutic agent doxorubicin (DOX) on tumor growth and the hepatic redox state in Walker-256 carcinosarcoma-bearing rats. Animals were divided into five groups with one control (no tumor) and four tumor-bearing groups: no treatment, DOX, DOX combined with EMF and EMF. While DOX and DOX + EMF provided greater inhibition of tumor growth, treatment with EMF alone resulted in some level of antitumor effect ($p < .05$). Superoxide dismutase, catalase activity and glutathione content were significantly decreased in the liver of tumor-bearing animals as compared with the control group ($p < .05$). The decreases in antioxidant defenses accompanied histological findings of suspected liver damage. However, hepatic levels of thiobarbituric acid reactive substances, an indicator of lipid peroxidation, were three times lower in EMF and DOX + EMF groups than in no treatment and DOX ($p < .05$). EMF and DOX + EMF showed significantly lower activity of serum ALT than DOX alone ($p < .05$). These results indicate that EMF treatment can inhibit tumor growth, causing less pronounced oxidative stress damage to the liver. Therefore, EMF can be used as a therapeutic strategy to influence the hepatic redox state and combat cancer with reduced side-effects.

(E) (VT, AE, IAO) Osera C, Fassina L, Amadio M, Venturini L, Buoso E, Magenes G, Govoni S, Ricevuti G, Pascale A. Cytoprotective response induced by electromagnetic stimulation on SH-SY5Y human neuroblastoma cell line. Tissue Eng Part A. 17(19-20):2573-2582, 2011.

It is well known that physiological functions and pathological conditions of cells and tissues can be influenced not only by chemical molecules, but also by physical stimuli such as electromagnetic waves. In particular, epidemiological studies suggest possible associations between exposure to electromagnetic fields and an increased risk of tumors and neurodegenerative disorders, such as Alzheimer's disease. However, depending on the dose and on the length of treatment, the electromagnetic stimuli can be harmful or induce a cytoprotective cellular response, suggesting a possible application in medical therapy. In this study, under a tissue engineering viewpoint, we investigated the effects of an electromagnetic wave (magnetic field intensity, 2 mT; frequency, 75 Hz) on a neuronal cellular model characterized by the overexpression of the amyloid precursor protein (APP). After a prolonged electromagnetic treatment, lower mitochondrial activity and proliferation rate, resulting in a higher cellular quiescence, were observed. Focusing on the stress and oxidative pathways, we detected an overall increase of two fundamental proteins, the chaperone heat shock protein HSP70 and the free radical scavenger superoxide dismutase-1 enzyme (SOD-1). Interestingly, we found that the electromagnetic stimulation promotes the nonamyloidogenic processing of APP through an increased expression of the α-secretase ADAM10 and an enhanced release of the soluble neurotrophic factor sAPPα (a product of the ADAM10-mediated cleavage of APP). In conclusion, these findings suggest that the electromagnetic stimulus, if properly administered in terms of dose and timing, is able to induce a cytoprotective response in the cell. Moreover, these results suggest a possible use of this particular physical stimulation to improve the functional capability of the cells to face noxae.

(E) (VT, AE, IAO, IX) Osera C, Amadio M, Falone S, Fassina L, Magenes G, Amicarelli F, Ricevuti G, Govoni S, Pascale A. Pre-exposure of neuroblastoma cell line to pulsed electromagnetic field prevents H2 O2 -induced ROS production by increasing MnSOD activity. Bioelectromagnetics. 36(3):219-232, 2015.

Electromagnetic fields (EMFs) have been linked to increased risk of cancers and neurodegenerative diseases; however, EMFs can also elicit positive effects on biological systems, and redox status seems crucially involved in EMF biological effects. This study aimed to assess whether a short and repeated pulsed EMF (PEMF) could trigger adaptive responses against an oxidative insult in a neuronal cellular model. We found that a 40 min overall (four times a week, 10 min each) pre-exposure to PEMF did not affect major physiological parameters and led to a significant increase of Mn-dependent superoxide dismutase activity in the human neuroblastoma SH-SY5Y cell line. In addition, we found PEMF-pre-exposed cells exhibited decreased reactive oxygen species production following a 30 min H2 O2 challenge, with respect to non pre-exposed cells. Our findings might provide new insights on the role played by short and repeated PEMF stimulations in the enhancement of cellular defenses against oxidative insults. Although studies in normal

neuronal cells would be useful to further confirm our hypothesis, we suggest that specific PEMF treatments may have potential biological repercussions in diseases where oxidative stress is implicated.

(E) (VT, AE, IFR) Pakhomova ON, Khorokhorina VA, Bowman AM, Rodaitė-Riševičienė R, Saulis G, Xiao S, Pakhomov AG. Oxidative effects of nanosecond pulsed electric field exposure in cells and cell-free media. Arch Biochem Biophys. 527(1):55-64, 2012.

Nanosecond pulsed electric field (nsPEF) is a novel modality for permeabilization of membranous structures and intracellular delivery of xenobiotics. We hypothesized that oxidative effects of nsPEF could be a separate primary mechanism responsible for bioeffects. ROS production in cultured cells and media exposed to 300-ns PEF (1-13 kV/cm) was assessed by oxidation of 2',7'-dichlorodihydrofluoresein (H(2)DCF), dihidroethidium (DHE), or Amplex Red. When a suspension of H(2)DCF-loaded cells was subjected to nsPEF, the yield of fluorescent 2',7'-dichlorofluorescein (DCF) increased proportionally to the pulse number and cell density. DCF emission increased with time after exposure in nsPEF-sensitive Jurkat cells, but remained stable in nsPEF-resistant U937 cells. In cell-free media, nsPEF facilitated the conversion of H(2)DCF into DCF. This effect was not related to heating and was reduced by catalase, but not by mannitol or superoxide dismutase. Formation of H(2)O(2) in nsPEF-treated media was confirmed by increased oxidation of Amplex Red. ROS increase within individual cells exposed to nsPEF was visualized by oxidation of DHE. We conclude that nsPEF can generate both extracellular (electrochemical) and intracellular ROS, including H(2)O(2) and possibly other species. Therefore, bioeffects of nsPEF are not limited to electropermeabilization; concurrent ROS formation may lead to cell stimulation and/or oxidative cell damage.

(E) (VO, AE, IOD, DAO) Pandir D, Sahingoz R. Magnetic field-induced oxidative stress and DNA damage in Mediterranean flour moth Ephestia kuehniella Zeller (Lepidoptera: Pyralidae) larvae. J Pest Sci 87(1): 79-87, 2014.

Ephestia kuehniella Zeller (Lepidoptera: Pyralidae) is cosmopolitan pest of stored products. The effect of strong magnetic fields (MFs) on DNA damage and oxidative stress on larvae stage of E. kuehniella was assessed. Antioxidant enzyme systems, which include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST), and malondialdehyde (MDA), the end product of lipid peroxidation as a result of strong MF intoxication that might occur in the larvae tissue, were evaluated. A simple technique of single-cell gel electrophoresis (DNA comet assay) enabled a quick detection of MF treatment on larvae. The larvae were exposed in a 1.4-Tesla (T) MF from a DC power supply at 50 Hz for different time periods (3, 6, 12, 24, 48,

and 72 h). MFs caused increasing DNA damage and demonstrated using the comet assay with its parameters including tail DNA%, tail length and tail moment. DNA damage at increasing exposure times were significantly larger than the control group ($p < 0.05$). These parameters were detected using BS 200 ProP with image analysis software. SOD, CAT, GPx, and GST activities decreased and MDA level increased in the MF-treated group in larvae tissue compared to control group for increasing exposure times at 1.4 T ($p < 0.05$). In our investigation, we showed that MFs caused oxidative stress and proved to be DNA damage as revealed by the comet assay. MFs may be used to determine potential toxic effects as a control agent against E. kuehniella larvae

(E) (VT, AE, IFR) Park JE, Seo YK, Yoon HH, Kim CW, Park JK, Jeon S. Electromagnetic fields induce neural differentiation of human bone marrow derived mesenchymal stem cells via ROS mediated EGFR activation. Neurochem Int. 62(4):418-424, 2013.

Even though the inducing effect of electromagnetic fields (EMF) on the neural differentiation of human bone marrow mesenchymal stem cells (hBM-MSCs) is a distinctive, the underlying mechanism of differentiation remains unclear. To find out the signaling pathways involved in the neural differentiation of BM-MSCs by EMF, we examined the CREB phosphorylation and Akt or ERK activation as an upstream of CREB. In hBM-MSCs treated with ELF-EMF (50 Hz, 1 mT), the expression of neural markers such as NF-L, MAP2, and NeuroD1 increased at 6 days and phosphorylation of Akt and CREB but not ERK increased at 90 min in BM-MSCs. Moreover, EMF increased phosphorylation of epidermal growth factor receptor (EGFR) as an upstream receptor tyrosine kinase of PI3K/Akt at 90 min. It has been well documented that ELF-MF exposure may alter cellular processes by increasing intracellular reactive oxygen species (ROS) concentrations. Thus, we examined EMF-induced ROS production in BM-MSCs. Moreover, pretreatment with a ROS scavenger, N-acetylcystein, and an EGFR inhibitor, AG-1478, prevented the phosphorylation of EGFR and downstream molecules. These results suggest that EMF induce neural differentiation through activation of EGFR signaling and mild generation of ROS.

(E) (VT, AE, IFR, DFR, IAO, DAO) Patruno A, Amerio P, Pesce M, Vianale G, Di Luzio S, Tulli A, Franceschelli S, Grilli A, Muraro R, Reale M. Extremely low frequency electromagnetic fields modulate expression of inducible nitric oxide synthase, endothelial nitric oxide synthase and cyclooxygenase-2 in the human keratinocyte cell line HaCat: potential therapeutic effects in wound healing. Br J Dermatol. 162(2):258-266, 2010.

BACKGROUND: Extremely low frequency (ELF) electromagnetic fields (EMF) are known to produce a variety of biological effects. Clinical studies are ongoing using EMF in healing of bone fractures and skin wounds. However, little is known about the mechanisms of action of ELF-EMF. Several studies have demonstrated that expression and regulation of nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) are vital for wound healing; however, no reports have demonstrated a direct action of ELF-EMF in the modulation of these inflammatory molecules in human keratinocytes. OBJECTIVES: The present study analysed the effect of ELF-EMF on the human keratinocyte cell line HaCaT in order to assess the mechanisms of action of ELF-EMF and to provide further support for their therapeutic use in wound healing. METHODS: Exposed HaCaT cells were compared with unexposed control cells. At different exposure times, expression of inducible NOS (iNOS), endothelial NOS (eNOS) and COX-2 was evaluated by Western blot analysis. Modulation of iNOS and eNOS was monitored by evaluation of NOS activities, production of nitric oxide (NO) and O(2)(-) and expression of activator protein 1 (AP-1). In addition, catalase activity and prostaglandin (PG) E(2) production were determined. Effects of ELF-EMF on cell growth and viability were monitored. RESULTS: The exposure of HaCaT cells to ELF-EMF increased iNOS and eNOS expression levels. These ELF-EMF-dependent increased expression levels were paralled by increased NOS activities, and increased NO production. In addition, higher levels of AP-1 expression as well as a higher cell proliferation rate were associated with ELF-EMF exposure. In contrast, ELF-EMF decreased COX-2 expression, PGE(2) production, catalase activity and O(2)(-) production. CONCLUSIONS: Mediators of inflammation, such as reactive nitrogen and PGE(2), and keratinocyte proliferation are critical for the tissue regenerative processes. The ability of ELF-EMF to upmodulate NOS activities, thus nitrogen intermediates, as well as cell proliferation, and to downregulate COX-2 expression and the downstream intermediate PGE(2), highlights the potential therapeutic role of ELF-EMF in wound healing processes.

(E) (VT, AE, IAO, IFR) Patruno A, Tabrez S, Amerio P, Pesce M, Vianale G, Franceschelli S, Grilli A, Kamal MA, Reale M. Kinetic study on the effects of extremely low frequency electromagnetic field on catalase, cytochrome P450 and inducible nitric oxide synthase in human HaCaT and THP-1 cell lines. CNS Neurol Disord Drug Targets. 10(8):936-944, 2011.

Extremely low frequency electromagnetic fields (ELF-EMF) have been found to produce a variety of biological effects. These effects of ELF-EMF depend upon frequency, amplitude, and length of exposure, and are also related to intrinsic susceptibility and responsiveness of different cell types. Although the mechanism of this interaction is still obscure, ELF-EMF can influence cell proliferation, differentiation, cell cycle, apoptosis, DNA replication and protein expression. The aim of this study was to estimate various kinetic constants of catalase, cytochrome P450 and inducible nitric oxide synthase in response to ELF-EMF exposure in human HaCaT and THP-1 cell lines. In order to evaluate the effect of ELF-EMF on the modulation of cellular responses to an inflammatory stimulus, both cell lines were treated with lipopolysaccharide. To the best of our knowledge there is no available report on such type of kinetic study of selected enzymes in response to ELF-EMF in these cell lines. Therefore, the current study may reveal novel mechanism of ELFEMF biological interaction with the enzymological and hormonal systems of living organisms. These new

insights may be important for ELF-EMF application particularly for wound healing, tissue regeneration, Parkinson's and Alzheimer's diseases.

(E) (VT, AE, IFR, DAO) Patruno A, Pesce M, Marrone A, Speranza L, Grilli A, De Lutiis MA, Felaco M, Reale M. Activity of matrix metallo proteinases (MMPs) and the tissue inhibitor of MMP (TIMP)-1 in electromagnetic field-exposed THP-1 cells. J Cell Physiol. 227(6):2767-2774, 2012.

Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) are the main determinants of tissue remodeling in both physiological and pathological processes. Metabolic processes, which generate oxidants and antioxidants can be influenced by environmental factors such as electromagnetic fields (EMF). We analyzed the effects of EMF on the activity and expression of MMPs in THP-1 cells. Cells were exposed to a 50 Hz, 1 mT EMF for 24 h and incubated with or without LPS. Our data indicate that THP-1 cells exposed to EMF causes a reduction of anti-oxidant enzyme activity and an enhancement of nitrogen intermediates involving the iNOS pathway. We then analyzed the role of nitration of TIMP-1 in increasing the activity of MMPs in EMF exposed cells. Molecular modeling tools were employed to identify the most plausible sites in the active conformation of TIMP-1; at least two protein sites, Y120 and Y38 and/or Y72 were identified. Reactive nitrogen species (RNS) may affect protein targets, such as TIMP-1, which are crucial for the regulation of MMP activities by oxidation of sulfydryl groups, or by nitration of tyrosine residues. These results may suggest a pathway connecting an imbalance of MMPs and their cognate inhibitor TIMP-1.

(E) (VT, AE, IAO) Patruno A, Tabrez S, Pesce M, Shakil S, Kamal MA, Reale M. Effects of extremely low frequency electromagnetic field (ELF-EMF) on catalase, cytochrome P450 and nitric oxide synthase in erythro-leukemic cells. Life Sci. 121:117-123, 2015.

AIMS: Extremely low frequency electromagnetic fields (ELF-EMFs) are widely employed in electrical appliances and different equipment such as television sets, mobile phones, computers and microwaves. The molecular mechanism through which ELF-EMFs can influence cellular behavior is still unclear. A hypothesis is that ELF-EMFs could interfere with chemical reactions involving free radical production. Under physiologic conditions, cells maintain redox balance through production of ROS/RNS and antioxidant molecules. The altered balance between ROS generation and elimination plays a critical role in a variety of pathologic conditions including neurodegenerative diseases, aging and cancer. Actually, there is a disagreement as to whether there is a causal or coincidental relationship between ELF-EMF exposure and leukemia development. Increased ROS levels have been observed in several hematopoietic malignancies including acute and chronic myeloid leukemias. MAIN METHODS: In our study, the effect of ELF-EMF exposure on catalase, cytochrome P450 and inducible nitric oxide synthase activity and expression by Western blot analysis in myelogenous leukemia cell line K562 was evaluated. KEY FINDINGS: A significant modulation of iNOS, CAT and Cyt P450 protein expression was recorded as a result of ELF-EMF exposure in both phorbol 12-myristate 13-acetate (PMA)-stimulated and non-

stimulated cell lines. Modulation in kinetic parameters of CAT, CYP-450 and iNOS enzymes in response to ELF-EMF indicates an interaction between the ELF-EMF and the enzymological system. SIGNIFICANCE: These new insights might be important in establishing a mechanistic framework at the molecular level within which the possible effects of ELF-EMF on health can be understood.

(E) (VO, CE, IAO. DAO, DOD) Payez A, Ghanati F, Behmanesh M, Abdolmaleki P, Hajnorouzi A, Rajabbeigi E. Increase of seed germination, growth and membrane integrity of wheat seedlings by exposure to static and a 10-KHz electromagnetic field. Electromagn Biol Med. 32(4):417-429, 2013.

There is a large body of experimental data demonstrating various effects of magnetic field (MF) on plants growth and development. Although the mechanism(s) of perception of MF by plants is not yet elucidated, there is a possibility that like other stimuli, MF exerts its effects on plants by changing membrane integrity and conductance of its water channels, thereby influencing growth characteristics. In this study, the seeds of wheat (Triticum aestivum L. cv. Kavir) were imbibed in water overnight and then treated with or without a 30-mT static magnetic field (SMF) and a 10-kHz electromagnetic field (EMF) for 4 days, each 5 h. Water uptake of seeds reduced 5 h of the treatment with EMF but did not show changes in SMF treatment. Exposure to both magnetic fields did not affect germination percent of the seeds but increased the speed of germination, compared to the control group. Treatment with EMF significantly reduced seedling length and subsequently vigor index I, while SMF had no effects on these parameters. Both treatments significantly increased vigor index II, compared to the control group. These treatments also remarkably increased catalase activity and proline contents of seedlings but reduced the activity of peroxidase, the rate of lipid peroxidation and electrolyte leakages of membranes. The results suggest promotional effects of EMFs on membrane integrity and growth characteristics of wheat seedlings.

(E) (IV, AE, IFR) Pilla AA.Electromagnetic fields instantaneously modulate nitric oxide signaling in challenged biological systems. Biochem Biophys Res Commun. 426(3):330-333, 2012.

This study shows that a non-thermal pulse-modulated RF signal (PRF), configured to modulate calmodulin (CaM) activation via acceleration of Ca(2+) binding kinetics, produced an immediate nearly 3-fold increase in nitric oxide (NO) from dopaminergic MN9D cultures ($P < 0.001$). NO was measured electrochemically in real-time using a NO selective membrane electrode, which showed the PRF effect occurred within the first seconds after lipopolysaccharide (LPS) challenge. Further support that the site of action of PRF involves CaM is provided in human fibroblast cultures challenged with low serum and exposed for 15 min to the identical PRF signal. In this case a CaM antagonist W-7 could be added to the culture 3 h prior to PRF exposure. Those results showed the PRF signal produced nearly a two-fold increase in NO, which could be blocked by W-7 ($P < 0.001$). To the authors' knowledge this is the first report of a real-time effect of non-thermal electromagnetic fields (EMF) on NO release from challenged cells. The results provide mechanistic support for

the many reported bioeffects of EMF in which NO plays a role. Thus, in a typical clinical application for acute post operative pain, or chronic pain from, e.g., osteoarthritis, EMF therapy could be employed to modulate the dynamics of NO via Ca/CaM-dependent constitutive nitric oxide synthase (cNOS) in the target tissue. This, in turn, would modulate the dynamics of the signaling pathways the body uses in response to the various phases of healing after physical or chemical insult or injury.

(E) (VO, CE, IFR) Piszczek P, Wojcik-Piotrowicz K, Nowak B, Guzdek P, Novak P, Pytko-Polonczyk J, Gil K, Kaszuba-Zwoinska J. Phagocytosis of latex beads by a human monocytic Mono Mac 6 cell line and effects of low-frequency electromagnetic field interaction. J Physiol Pharmacol 2023 Apr;74(2). doi: 10.26402/jpp.2023.2.10.

Some studies have shown that electromagnetic fields (EMFs) may impact immune response cells and their functions. The first stage of the defense from pathogens is innate immunity encompassing phagocytosis and phagocytosis-related intracellular effects. Our work aimed to determine the influence of a low-frequency electromagnetic field (7 Hz, 30 mTrms) on the phagocytosis process of latex beads (LBs), the production of reactive oxygen species (ROS), and viability changes in a human monocytic Mono Mac 6 (MM6) cell line as an experimental model of the phagocytosing cells in in vitro cell culture conditions. For these purposes, cells were firstly activated with infectious agents such as lipopolysaccharide (LPS), Staphylococcal enterotoxin B (SEB), or the proliferatory agent phytohaemagglutinin (PHA), and then a phagocytosis test was performed. Cell viability and range of phagocytosis of latex beads by MM6 cells were measured by flow cytometry, and the level of ROS was evaluated with the use of a cytochrome C reduction test. The obtained results revealed that applied EMF exposure mainly increased the necrosis parameter of cell death when they were pre-stimulated with SEB as an infectious factor and subsequently phagocytosed LBs (P=0.001). Prestimulation with other agents like LPS or PHA preceding phagocytosis resulted in no statistically significant changes in cell death parameters. The level of ROS depended on the used stimulatory agent, phagocytosis, and/or EMF exposure. The obtained effects for EMF exposure indicated only a slight decrease in the ROS level for cells phagocytosing latex beads and being treated with SEB or PHA, while the opposite effect was observed for LPS pre-stimulated cells (data not statistically significant). The results concerning the viability of phagocytosing cells, the effectiveness of the phagocytosis process, and the level of radical forms might result from applied EMF parameters like signal waveform, frequency, flux density, and especially single EMF exposure.

(E) (VO, CE, IAO, IX) Politański P, Rajkowska E, Pawlaczyk-Łuszczyńska M, Dudarewicz A, Wiktorek-Smagur A, Sliwińska-Kowalska M, Zmyślony M. Static magnetic field affects oxidative stress in mouse cochlea. Int J Occup Med Environ Health. 23(4):377-384, 2010.

OBJECTIVE: It has been shown that oxidative stress plays an important role in development of noise induced hearing loss. Since static magnetic fields (SMF) exposure may alter dynamics of oxidative processes in the tissue, the aim of the study was to assess the influence of SMF on noise-induced alteration in the cochlear level of reactive oxygen species (ROS) and hearing thresholds. MATERIALS AND METHODS: Auditory brainstem response (ABR), lipid peroxidation (LPO) levels, super-oxide dismutase (SOD) activity and catalase activity were assessed in the cochlea prior to, and at five time-points over two weeks following exposure of C57BL/6 mice to 8h, 119 dB SPL, 4 kHz octave band noise. RESULTS: The ABR indicated no permanent functional damage due to noise exposure either for the 4 kHz and 8 kHz SMF-exposed group or for animals not exposed to SMF. However, significant differences in LPO level, catalase and SOD activity between animals exposed to noise and SMF and those exposed to noise only were observed. CONCLUSIONS: The results suggest that SMF causes an increase in ROS level in the cochlea after noise exposure and, at the same time, it speeds up activation of antioxidative enzymes.

(E) (VT, AE, DFR, IFR) Poniedzialek B, Rzymski P, Nawrocka-Bogusz H, Jaroszyk F, Wiktorowicz K. The effect of electromagnetic field on reactive oxygen species production in human neutrophils in vitro. Electromagn Biol Med. 32(3):333-341, 2013a.

The present study was undertaken in order to determine the effect of low frequency electromagnetic field (EMF) on reactive oxygen species (ROS) production in human neutrophils in peripheral blood in vitro. We investigated how differently generated EMF and several levels of magnetic induction affect ROS production. To evaluate the level of ROS production, two fluorescent dyes were used: 2'7'-dichlorofluorscein-diacetate and dihydrorhodamine. Phorbol 12-myristate 13-acetate (PMA), known as strong stimulator of the respiratory burst, was also used. Alternating magnetic field was generated by means of Viofor JPS apparatus. Three different levels of magnetic induction have been analyzed (10, 40 and 60 μT). Fluorescence of dichlorofluorescein and 123 rhodamine was measured by flow cytometry. The experiments demonstrated that only EMF tuned to the calcium ion cyclotron resonance frequency was able to affect ROS production in neutrophils. Statistical analysis showed that this effect depended on magnetic induction value of applied EMF. Incubation in EMF inhibited cell activity slightly in unstimulated neutrophils, whereas the activity of PMA-stimulated neutrophils has increased after incubation in EMF.

(E) (VT, AE, DFR, IFR) Poniedziałek B, Rzymski P, Karczewski J, Jaroszyk F, Wiktorowicz K. Reactive oxygen species (ROS) production in human peripheral blood neutrophils exposed in vitro to static magnetic field. Electromagn Biol Med. 32(4):560-568, 2013b.

The aim of this study was to determine the effect of gradient static magnetic field (SMF) on reactive oxygen species (ROS) production in human neutrophils in peripheral blood in vitro. Blood samples collected from healthy individuals were incubated in an

inhomogeneous SMF (in a south or north pole of the field) for 15, 30 or 45 minutes. The maximum value of induction (B_{max}) amounted to ≈ 60 mT. To determine the strength of the ROS production, dihydrorhodamine (123DHR) as fluorophore and phorbol 12-myristate 13-acetate (PMA) as respiratory burst stimulator were used. 123DHR oxidation by ROS was measured by flow cytometry. The exposure of blood samples to SMF induced statistically significant changes in ROS production in unstimulated and PMA-stimulated neutrophils. The observed effects were highly correlated with the exposure time and depended on the orientation of the field. Although intracellular mechanisms underlying such interactions are not thoroughly understood, it could be presumed that SMF affects ROS metabolic oscillations and their formation and inactivation. This study emphasizes the importance of proper adjustment of exposure time to SMF for any potential therapeutic applications.

(E) (VT, AE, IFR) Pooam M, Nakayama M, Nishigaki C, Miyata H. Effect of 50-Hz sinusoidal magnetic field on the production of superoxide anion and the expression of heat-shock protein 70 in RAW264 cells. Int J Chem 9:23-36, 2017.

There is a growing concern if the power-line frequency (50/60 Hz) magnetic field (termed in this paper ELF-MF) increases cancer risks. Since one of the major causes of cancer is cellular oxidative stress, whether the ELF-MF increases the oxidative stress is a central problem in the studies on the biological effect of the ELF-MF. Here, we have investigated the effect of 50-Hz sinusoidal magnetic field on the production of O_2^-, the expression of heat shock protein (HSP) 70 and the mitochondrial membrane potential in cell line macrophage RAW264 cells. Macrophages were exposed to or not exposed to 0.1-mT or 0.5-mT, 50-Hz sinusoidal magnetic field and were subjected to (1) assay for O_2^- (2) analysis of the expression of HSP70, and (3) measurement of the mitochondrial membrane potential with a fluorescent indicator. The 50-Hz magnetic field enhanced production of O_2^- and the expression of HSP70, both of which are consistent with previous studies. The exposure to 50-Hz magnetic field decreased mitochondrial membrane potential indicating the diminished activity of mitochondria. The uncoupler of mitochondrial function, carbonyl cyanide p-trifluoromethoxyphenylhydrazone diminished the membrane potential, as expected. On the other hand, it increased the production of O_2^-. The results collectively suggest that the 50-Hz magnetic field diminished the mitochondrial membrane potential, which led to the increase in the production of O_2^- and the expression of HSP70 protein.

(E) (VT AE, IFR) Potenza L, Martinelli C, Polidori E, Zeppa S, Calcabrini C, Stocchi L, Sestili P, Stocchi V. Effects of a 300 mT static magnetic field on human umbilical vein endothelial cells. Bioelectromagnetics. 31(8):630-639, 2010.

This study describes the effects of a static magnetic field (SMF) on cell growth and DNA integrity of human umbilical vein endothelial cells (HUVECs). Fast halo assay was used to investigate nuclear damage; quantitative polymerase chain reaction (QPCR), standard PCR, and real-time PCR were used to evaluate mitochondrial DNA integrity, content, and gene expression. HUVECs were continually exposed to a 300 mT SMF for 4, 24, 48, and 72 h. Compared to control samples (unexposed cultures) the SMF-exposed

cells did not show a statistically significant change in their viability. Conversely, the static field was shown to be significant after 4 h of exposure, inducing damage on both the nuclear and mitochondrial levels, reducing mitochondrial content and increasing reactive oxygen species. Twenty-four hours of exposure increased mitochondrial DNA content as well as expression of one of the main genes related to mitochondrial biogenesis. No significant differences between exposed and sham cultures were found after 48 and 72 h of exposure. The results suggest that a 300 mT SMF does not cause permanent DNA damage in HUVECs and stimulates a transient mitochondrial biogenesis.

(E) (VO, CE, IOD, IAO) Rageh MM, El-Gebaly RH, El-Bialy NS. Assessment of genotoxic and cytotoxic hazards in brain and bone marrow cells of newborn rats exposed to extremely low-frequency magnetic field. J Biomed Biotechnol. 2012:716023, 2012.

The present study aimed to evaluate the association between whole body exposure to extremely low frequency magnetic field (ELF-MF) and genotoxic , cytotoxic hazards in brain and bone marrow cells of newborn rats. Newborn rats (10 days after delivery) were exposed continuously to 50 Hz, 0.5 mT for 30 days. The control group was treated as the exposed one with the sole difference that the rats were not exposed to magnetic field. Comet assay was used to quantify the level of DNA damage in isolated brain cells. Also bone marrow cells were flushed out to assess micronucleus induction and mitotic index. Spectrophotometric methods were used to measure the level of malondialdehyde (MDA) and the activity of glutathione (GSH) and superoxide dismutase (SOD). The results showed a significant increase in the mean tail moment indicating DNA damage in exposed group ($P < 0.01$, 0.001, 0.0001). Moreover ELF-MF exposure induced a significant ($P < 0.01$, 0.001) four folds increase in the induction of micronucleus and about three folds increase in mitotic index ($P < 0.0001$). Additionally newborn rats exposed to ELF-MF showed significant higher levels of MDA and SOD ($P < 0.05$). Meanwhile ELF-MF failed to alter the activity of GSH. In conclusion, the present study suggests an association between DNA damage and ELF-MF exposure in newborn rats.

(E) (HU, AE, DOD) Raggi F, Vallesi G, Rufini S, Gizzi S, Ercolani E, Rossi R. ELF magnetic therapy and oxidative balance. Electromagn Biol Med. 27(4):325-339, 2008.

Knowledge about the relationship between exposure to extremely low-frequency (ELF) EMF and formation (or neutralization) of free radicals in the living cells is limited. Studies performed on animals and plants have shown conflicting effects on the relation between EMF and oxidative stress. Very few experiments have been performed on humans. The present study reports on the effects of an ELF magnetic therapy device (Seqex) on oxidative scale in humans. This device supplies complex magnetic signals with specific choices of frequency, intensity, and shape that are based on Liboff's ion cyclotron resonance hypothesis. Thirty-two healthy volunteers were treated using the Seqex cycle. A quantitative determination of oxidative stress was obtained at three time points by measuring malondialdehyde (MDA) concentrations in peripheral blood before and after the cycle and one month following completion of the

cycle. A highly significant reduction in mean MDA (53.8%, p = 0.0002) was found at the end of the treatment. One month later the mean MDA had again risen, but there was still a significant overall reduction of 15.6% (p = 0.010) compared to original values.

(E) (VO, AE, IAO) Rajabbeigi E, Ghanati F, Abdolmaleki P, Payez A. Antioxidant capacity of parsley cells (Petroselinum crispum L.) in relation to iron-induced ferritin levels and static magnetic field. Electromagn Biol Med. 32(4):430-441, 2013.

This study was aimed to evaluate antioxidant response of parsley cells to 21 ppm iron and static magnetic field (SMF; 30 mT). The activity of catalase (CAT) and ascorbate peroxidase (APX) and the contents of malonyldialdehyde, iron and ferritin were measured at 6 and 12 h after treatments. Exposure to SMF increased the activity of CAT in treated cells, while combination of iron and SMF treatments as well as iron supply alone decreased CAT activity, compared to that of control cells. Combination of SMF with iron treatment reduced iron content of the cells and ameliorated mal effect of iron on CAT activity. All treatments reduced APX activity; however, the content of total ascorbate increased in response to iron and SMF+iron. The results showed that among the components of antioxidant system of parsley cells, enhanced activity of CAT in SMF-treated cells and increase of ascorbate in SMF+Fe-treated ones were responsible for the maintenance of membranes integrity. Ferritin contents of SMF- and SMF+Fe-treated cells also decreased significantly 12 h after treatments, compared to those of the control cells. These results cast doubt on the proposed functions of ferritin as a putative reactive oxygen species detoxifying molecule.

(E)(VT, AE, IFR, IX)Ramazi S, Salimian M, Allahverdi A, Kianamiri S, Abdolmaleki P. Synergistic cytotoxic effects of an extremely low-frequency electromagnetic field with doxorubicin on MCF-7 cell line. Sci Rep 13(1):8844, 2023.

Breast cancer is one of the leading causes of cancer deaths in women worldwide. Magnetic fields have shown anti-tumor effects in vitro and in vivo as a non-invasive therapy method that can affect cellular metabolism remotely. Doxorubicin (DOX) is one of the most commonly used drugs for treating breast cancer patients. It can be assumed that combining chemotherapy and magnetotherapy is one of the most effective treatments for breast cancer. This study aimed to investigate the potential cytotoxic effect of DOX at low concentrations in combination with extremely low-frequency electromagnetic fields (ELF-EMF; 50 Hz; 20 mT). The breast cancer cell line MCF-7 was examined for oxidative stress, cell cycle, and apoptosis. MCF-7 cells were treated with various concentrations of DOX as an apoptosis-inducing agent and ELF-EMF. Cytotoxicity was examined using the MTT colorimetric assay at 12, 24, and 48 h. Consequently, concentration- and time-dependent cytotoxicity was observed in MCF-7 cells for DOX within 24 h. The MTT assay results used showed that a 2 μM concentration of DOX reduced cell viability to 50% compared with control, and as well, the combination of ELF-EMF and DOX reduced cell viability to 50% compared with control at > 0.25 μM doses for 24 h. In MCF-7 cells, combining 0.25 μM DOX with ELF-EMF resulted in increased ROS levels and DOX-induced apoptosis. Flow cytometry analysis, on the other hand, revealed enhanced arrest of MCF-7 cells in the G0-G1 phase of the cell cycle, as well as inducing apoptotic cell death

in MCF-7 cells, implying that the synergistic effects of 0.25 μM DOX and ELF-EMF may represent a novel and effective agent against **breast cancer.**

(NE) (VO, CE, free radicals and enzymes) Rasaeifar K, Zavareh S, Hajighasem-Kashani M, Nasiri M. Effects of pulsed electromagnetic fields and N-acetylcysteine on transplantation of vitrified mouse ovarian tissue. Electromagn Biol Med 42(2):67-80, 2023.

In this experimental study, adult female NMRI mice were randomly assigned to five groups: control; (fresh ovarian transplantation, OT); sham ;(vitrified OT); NAC ;(vitrified OT treated with N-acetyl cysteine, NAC); EMF ;(vitrified OT treated with pulsed electromagnetic fields, PEMF); and NAC+EMF ;(vitrified OT combined with NAC and PEMF). We conducted histological assessments to evaluate follicle reservation and vascularization. Furthermore, we examined the relative expression of *Fgf-2, Vegf, Tnf-α, Il-6, Il-1*, and *Cd31* genes on days 2 and 7 after OT. Additionally, we measured total antioxidant capacity (TAC), malondialdehyde (MDA) levels, as well as the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPX). Our results demonstrated that NAC, PEMF, and NAC+PEMF treatments significantly increased the number of follicles. Moreover, we observed a more pronounced development of vascularization in the NAC, PEMF, and PEMF+NAC groups. The relative expression levels of *Fgf-2, Vegf, Tnf-α, Il-1β*, and *Il-6* were significantly elevated in the NAC, PEMF, and NAC+PEMF groups. Notably, TAC levels decreased significantly in the NAC group compared to the control group. Additionally, the MDA level showed a significant decrease in the PEMF+NAC group when compared to the other groups. Overall, the combination of NAC and PEMF exhibited a synergistic effect in promoting angiogenesis and protecting against oxidative stress and inflammation during OT.

(E) (VO, CE, IX) Rauš Balind S, Selaković V, Radenović L, Prolić Z, Janać B. Extremely low frequency magnetic field (50 Hz, 0.5 mT) reduces oxidative stress in the brain of gerbils submitted to global cerebral ischemia. PLoS One. 9(2):e88921, 2014.

Magnetic field as ecological factor has influence on all living beings. The aim of this study was to determine if extremely low frequency magnetic field (ELF-MF, 50 Hz, 0.5 mT) affects oxidative stress in the brain of gerbils submitted to 10-min global cerebral ischemia. After occlusion of both carotid arteries, 3-month-old gerbils were continuously exposed to ELF-MF for 7 days. Nitric oxide and superoxide anion production, superoxide dismutase activity and index of lipid peroxidation were examined in the forebrain cortex, striatum and hippocampus on the 7(th) (immediate effect of ELF-MF) and 14(th) day after reperfusion (delayed effect of ELF-MF). Ischemia per se increased oxidative stress in the brain on the 7(th) and 14(th) day after reperfusion. ELF-MF also increased oxidative stress, but to a greater extent than ischemia, only immediately after cessation of exposure. Ischemic gerbils exposed to ELF-MF had increased oxidative stress parameters on the 7(th) day after reperfusion, but to a lesser extent than ischemic or ELF-MF-exposed

animals. On the 14(th) day after reperfusion, oxidative stress parameters in the brain of these gerbils were mostly at the control levels. Applied ELF-MF decreases oxidative stress induced by global cerebral ischemia and thereby reduces possible negative consequences which free radical species could have in the brain. The results presented here indicate a beneficial effect of ELF-MF (50 Hz, 0.5 mT) in the model of global cerebral ischemia.

(E) (VT, AE, IAO) Reale M, De Lutiis MA, Patruno A, Speranza L, Felaco M, Grilli A, Macrì MA, Comani S, Conti P, Di Luzio S. Modulation of MCP-1 and iNOS by 50-Hz sinusoidal electromagnetic field. Nitric Oxide. 15(1):50-57, 2006.

The purpose of this study was to investigate whether overnight exposure to 1 mT-50 Hz extremely low-frequency sinusoidal electromagnetic field (EMF) affects the expression and production of inducible nitric oxide synthase (iNOS) and monocyte chemotactic protein-1 (MCP-1) in human monocytes. RT-PCR and Western blot analysis demonstrate that EMF exposure affects the expression of iNOS and MCP-1 in cultured human mononuclear cells at the mRNA level and protein synthesis. Interestingly, the effects of EMF exposure clearly differed with respect to the potentiation and inhibition of iNOS and MCP-1 expression. Whereas iNOS was down-regulated both at the mRNA level and at the protein level, MCP-1 was up-regulated. These results provide helpful information regarding the EMF-mediated modulation of the inflammatory response in vivo. However, additional studies are necessary to demonstrate that EMF acts as a nonpharmacological inhibitor of NO and inducer of MCP-1 in some diseases where the balance of MCP-1 and NO may be important.

(E) (VT, AE, IFR) Reale M, Kamal MA, Patruno A, Costantini E, D'Angelo C, Pesce M, Greig NH. Neuronal cellular responses to extremely low frequency electromagnetic field exposure: implications regarding oxidative stress and neurodegeneration. PLoS One. 9(8):e104973, 2014.

Neurodegenerative diseases comprise both hereditary and sporadic conditions characterized by an identifying progressive nervous system dysfunction and distinctive neuopathophysiology. The majority are of non-familial etiology and hence environmental factors and lifestyle play key roles in their pathogenesis. The extensive use of and ever increasing worldwide demand for electricity has stimulated societal and scientific interest on the environmental exposure to low frequency electromagnetic fields (EMFs) on human health. Epidemiological studies suggest a positive association between 50/60-Hz power transmission fields and leukemia or lymphoma development. Consequent to the association between EMFs and induction of oxidative stress, concerns relating to development of neurodegenerative diseases, such as Alzheimer disease (AD), have been voiced as the brain consumes the greatest fraction of oxygen and is particularly vulnerable to oxidative stress. Exposure to extremely low frequency (ELF)-EMFs are reported to alter animal behavior and modulate biological variables, including gene expression, regulation of cell survival, promotion of cellular differentiation, and changes in cerebral blood flow in aged AD transgenic mice. Alterations in inflammatory responses have also been

reported, but how these actions impact human health remains unknown. We hence evaluated the effects of an electromagnetic wave (magnetic field intensity 1mT; frequency, 50-Hz) on a well-characterized immortalized neuronal cell model, human SH-SY5Y cells. ELF-EMF exposure elevated the expession of NOS and O2-, which were countered by compensatory changes in antioxidant catylase (CAT) activity and enzymatic kinetic parameters related to CYP-450 and CAT activity. Actions of ELF-EMFs on cytokine gene expression were additionally evaluated and found rapidly modified. Confronted with co-exposure to H2O2-induced oxidative stress, ELF-EMF proved not as well counteracted and resulted in a decline in CAT activity and a rise in O2- levels. Together these studies support the further evaluation of ELF-EMF exposure in cellular and in vivo preclinical models to define mechanisms potentially impacted in humans.

(E) (VO, CE, LI, IAO, DAO) Regoli F, Gorbi S, Machella N, Tedesco S, Benedetti M, Bocchetti R, Notti A, Fattorini D, Piva F, Principato G. Pro-oxidant effects of extremely low frequency electromagnetic fields in the land snail Helix aspersa. Free Radic Biol Med. 39(12):1620-1628, 2005.

Pro-oxidant effects of extremely low frequency (ELF) 50-Hz magnetic fields were investigated in the land snail Helix aspersa exposed both in short-term laboratory treatments and under field conditions by maintaining the organisms in the proximity of a power line for up to 2 months. Oxidative perturbations were investigated as individual antioxidants (catalase, glutathione reductase, glutathione S-transferases, and total glutathione) and total scavenging capacity toward peroxyl radicals and hydroxyl radicals. Accumulation of lipid peroxidation products, destabilization of lysosomal membranes, and loss of DNA integrity were also evaluated as markers of cell damage. The overall results indicated an oxidative challenge caused by ELF magnetic fields with particularly prompt and sensitive responses for catalase, glutathione reductase, and the overall capability to neutralize peroxyl radicals. Cell injuries occurred to different extents according to duration and intensity of electromagnetic exposure and confirmed complex cause-effect relationships between pro-oxidant factors, efficiency of antioxidant defenses, and the onset of oxidative toxicity. This study highlights the importance of a multimarker approach for detecting a wide panel of biological responses, the necessity of investigating the long-term effects of early oxidative responses, and the role of ELF in enhancing susceptibility to other forms of pathologies or diseases.

(E) (VT, AE, IFR) Rollwitz J, Lupke M, Simkó M. Fifty-hertz magnetic fields induce free radical formation in mouse bone marrow-derived promonocytes and macrophages. Biochim Biophys Acta. 1674(3):231-238, 2004.

Our findings show a significant increase of free radical production after exposure to 50 Hz electromagnetic fields at a flux density of 1 mT to mouse bone marrow-derived (MBM) promonocytes and macrophages, indicating the cell-activating capacity of extremely low frequency magnetic fields (ELF-MF). We demonstrate that after exposure to ELF-MF mainly superoxide anion radicals were produced, both in MBM macrophages (33%) and also in their precursor cells (24%). To elucidate whether NADPH- or NADH-oxidase functions are target proteins for MF interaction, the flavoprotein inhibitor diphenyleneiodonium chloride (DPI) was used. MF-

induced free radical production was not inhibited by DPI, whereas tetradecanoylphorbolacetate (TPA)-induced free radical production was diminished by about 70%. TPA is known to induce a direct activation of NADPH-oxidase through the PKC pathway. Since DPI lacks an inhibitory effect in MF-exposed MBM cells, we suggest that 50 Hz MF stimulates the NADH-oxidase pathway to produce superoxide anion radicals, but not the NADPH pathway. Furthermore, we showed an oscillation (1-10 days) in superoxide anion radical release in mouse macrophages, indicating a cyclic pattern of NADH-oxidase activity.

(NE) (IV, CE) Romeo S, Sannino A, Scarfì MR, Massa R, d'Angelo R, Zeni O. Lack of effects on key cellular parameters of MRC-5 human lung fibroblasts exposed to 370 mT static magnetic field. Sci Rep 6:19398, 2016.

The last decades have seen increased interest toward possible adverse effects arising from exposure to intense static magnetic fields. This concern is mainly due to the wider and wider applications of such fields in industry and clinical practice; among them, Magnetic Resonance Imaging (MRI) facilities are the main sources of exposure to static magnetic fields for both general public (patients) and workers. In recent investigations, exposures to static magnetic fields have been demonstrated to elicit, in different cell models, both permanent and transient modifications in cellular endpoints critical for the carcinogenesis process. The World Health Organization has therefore recommended in vitro investigations as important research need, to be carried out under strictly controlled exposure conditions. Here we report on the absence of effects on cell viability, reactive oxygen species levels and DNA integrity in MRC-5 human foetal lung fibroblasts exposed to 370 mT magnetic induction level, under different exposure regimens. Exposures have been performed by using an experimental apparatus designed and realized for operating with the static magnetic field generated by permanent magnets, and confined in a magnetic circuit, to allow cell cultures exposure in absence of confounding factors like heating or electric field components.

(E) (VT, AE, IFR) Roy S, Noda Y, Eckert V, Traber MG, Mori A, Liburdy R, Packer L. The phorbol 12-myristate 13-acetate (PMA)-induced oxidative burst in rat peritoneal neutrophils is increased by a 0.1 mT (60 Hz) magnetic field. FEBS Lett. 376(3):164-166, 1995.

Magnetic fields (MF) may affect biological systems by increasing free radical concentrations. To test this, we have investigated whether low frequency (60 Hz) low intensity (0.1 mT) MF can modulate the phorbol 12-myristate 13- acetate (PMA) induced respiratory burst in primed rat peritoneal neutrophils, followed in real time using the dye 2',7'-dichlorofluorescin (DCFH), which reacts with free radical-derived oxidants such as H2O2 (which is formed from the dismutation of superoxide) to become 2',7'-dichlorofluorecein (DCF), a highly fluorescent compound. In the presence of the MF, a 12.4% increase in the fluorescence signal was observed in PMA-stimulated neutrophils ($n = 5$, $P < 0.02$, 18 pairs of measurements). We believe this represents the first experimental observation of MF influencing events involving free radical species generated during signal transduction in living cells.

(E) (VT, AE, IFR) Sadeghipour R, Ahmadian S, Bolouri B, Pazhang Y, Shafiezadeh M. Effects of extremely low-frequency pulsed electromagnetic fields on morphological and biochemical properties of human breast carcinoma cells (T47D). Electromagn Biol Med. 31(4):425-435, 2012.

This study was carried out to investigate the effects of 100 and 217 Hz extremely low-frequency pulsed electromagnetic fields (ELF-PEMF) on cell proliferation, actin reorganization, and ROS generation in a human breast carcinoma cells (T47D). Cells were exposed for 24-72 h, at 100 and 217 Hz, 0.1 mT. The treatment induced a time dependent decrease in cell growth after 72 h and revealed an increase in fluorescence intensity in cytoplasm and actin aggregations around the nucleus as detected by fluorescence microscopy. The amount of actin in T47D cells increased after 48 h exposure to 100 Hz and 24 h to 217 Hz while no changes in nuclear morphology were detected. Exposing the cells to 217 Hz for 72 h caused a dramatically increase of intracellular ROS generation while with exposure to 100 Hz it remained nearly unchanged. These results suggest that exposure to ELF-PEMF (100, 217 Hz, 0.1 mT) are able inducing an increase of actin level, its migration toward nucleus but despite of these changes and dramatically increase in ROS generation the symptoms of apoptosis were not observed. Our results support the hypothesis that cell response to EMF may only be observed at certain window effects; such as frequency and intensity of EMF parameters.

(E) (VT, CE, IOD, IAO, DAO) Sahebjamei H, Abdolmaleki P, Ghanati F. Effects of magnetic field on the antioxidant enzyme activities of suspension-cultured tobacco cells. Bioelectromagnetics. 28(1):42-47, 2007.

Effects of magnetic fields (MFs) on the activities of antioxidant enzymes of suspension-cultured tobacco cells were investigated. Compared with the control cells, exposure of the cells to static MF with the magnitudes of 10 and 30 mT for 5 days, 5 h each day, increased the activity of superoxide dismutase (SOD). In contrast, the activity of the catalase (CAT) and ascorbate peroxidase (APX) was decreased by MF, compared with those of the control cells. Level of lipid peroxidation was also increased by MF. It suggests that MF could deteriorate antioxidant defense system of plant cells.

(E) (VT, CE, IFR, DAO IX) Salek F, Baharara J, Shahrokhabadi KN, Amini E. The guardians of germ cells; Sertoli-derived exosomes against electromagnetic field-induced oxidative stress in mouse spermatogonial stem cells. Theriogenology 2021;173:112-122.

Nowadays, prolonged exposure to electromagnetic fields (EMF) has raised public concern about the detrimental potential of EMF on spermatogonial stem cells (SSCs) and spermatogenesis. Recent studies introduced the fundamental role of Sertoli cell paracrine signaling in the regulation of SSCs maintenance and differentiation in fertility preservation. Thus we investigated the therapeutic effect of Sertoli-derived exosomes (Sertoli-EXOs) as powerful paracrine mediators in SSCs subjected to EMF and its underlying mechanisms. SSCs and Sertoli cells were isolated from neonate mice testis, and identified by their specific markers. Then SSCs were

exposed to 50 Hz EMF with intensity of 2.5 mT (1 h for 5 days) and supplemented with exosomes that were isolated from pre-pubertal Sertoli cells. Sertoli-EXOs were characterized and the uptake was observed by PKH26 labeling. The cell viability, colonization efficiency, reactive oxygen species (ROS) balance, cell cycle arrest and apoptosis induction were then analysed. SSCs were confirmed by immunocytochemistry (Oct4, Plzf) and Sertoli cells were identified through Sox9 and vimentin expression by immunocytochemistry and Real-time PCR (qRT-PCR), respectively. Our results demonstrated the detrimental effect of EMF via ROS accumulation that reduced the expression of catalase antioxidant, cell viability and colonization of SSCs. Also, AO/PI and flow cytometry analysis demonstrated the elevation of apoptosis in SSCs exposed to EMF in comparison with control. qRT-PCR data confirmed the up-regulation of apoptotic gene (Caspase-3) and down-regulation of SSCs specific gene (GFRα1). Consequently, the administration of Sertoli-EXOs exerted ameliorative effect on SSCs and significantly improved these changes through the regulation of oxidative stress. These findings suggest that Sertoli-EXOs have positive impact on SSCs exposed to EMF and can be useful in further investigation of Sertoli-EXOs as a novel therapeutic agent which may recover the deregulated SSCs microenvironment and spermatogenesis after exposure to EMF.

(E) (VO, CE, IFR) Salunke BP, Umathe SN, Chavan JG. Experimental evidence for involvement of nitric oxide in low frequency magnetic field induced obsessive compulsive disorder-like behavior. Pharmacol Biochem Behav. 122:273-278, 2014.

It is well documented that extremely low frequency magnetic field (ELF MF) produced effects on the function of nervous system in humans and laboratory animals. Dopaminergic and serotonergic pathways have been implicated in obsessive compulsive disorder (OCD). Recently involvement of nitric oxide (NO) in OCD-like behavior is suggested. Hence, the present study was carried out to understand the involvement of dopamine, serotonin and NO in ELF MF induced OCD-like behavior. Swiss albino mice were exposed to ELF MF (50Hz, 10G) for 8h/day for 7, 30, 60, 90 and 120days by subjecting them to Helmholtz coils. OCD-like behavior was assessed in terms of marble burying behavior (MBB) test. Results revealed that ELF MF induced time dependant MBB, on 7th, 30th, 60th, 90th, and 120th exposure day. Further, levels of dopamine, serotonin and NO after 120days of ELF MF exposure were determined in regions of the brain. The neurohumoral studies revealed that exposure to ELF MF increased NO levels in cortex, hippocampus and hypothalamus, and levels of dopamine and serotonin remain unaffected. As OCD-like behavior after ELF MF exposure was associated with higher levels of NO with no significant change in serotonin and dopamine, the effect of such exposure was studied in groups concurrently treated with NO modulators, NO precursor, L-ARG (400mg/kg) or NOS inhibitor, L-NAME (15.0mg/kg) or 7-NI (10.0mg/kg). These treatments revealed that NO precursor exacerbated and NOS inhibitors attenuated ELF MF induced OCD-like behavior with corresponding changes in the levels of NO.

Santini SJ, Cordone V, Falone S, Mijit M, Tatone C, Amicarelli F, Di Emidio G. Role of Mitochondria in the Oxidative Stress Induced by Electromagnetic Fields: Focus on Reproductive Systems. Oxid Med Cell Longev. 2018:5076271, 2018. (Review)

Modern technologies relying on wireless communication systems have brought increasing levels of electromagnetic field (EMF) exposure. This increased research interest in the effects of these radiations on human health. There is compelling evidence that EMFs affect cell physiology by altering redox-related processes. Considering the importance of redox *milieu* in the biological competence of oocyte and sperm, we reviewed the existing literature regarding the effects of EMFs on reproductive systems. Given the role of mitochondria as the main source of reactive oxygen species (ROS), we focused on the hypothesis of a mitochondrial basis of EMF-induced reproductive toxicity. MEDLINE, Web of Science, and Scopus database were examined for peer-reviewed original articles by searching for the following keywords: "extremely low frequency electromagnetic fields (ELF-EMFs)," "radiofrequency (RF)," "microwaves," "Wi-Fi," "mobile phone," "oxidative stress," "mitochondria," "fertility," "sperm," "testis," "oocyte," "ovarian follicle," and "embryo." These keywords were combined with other search phrases relevant to the topic. Although we reported contradictory data due to lack of uniformity in the experimental designs, a growing body of evidence suggests that EMF exposure during spermatogenesis induces increased ROS production associated with decreased ROS scavenging activity. Numerous studies revealed the detrimental effects of EMFs from mobile phones, laptops, and other electric devices on sperm quality and provide evidence for extensive electron leakage from the mitochondrial electron transport chain as the main cause of EMF damage. In female reproductive systems, the contribution of oxidative stress to EMF-induced damages and the evidence of mitochondrial origin of ROS overproduction are reported, as well. In conclusion, mitochondria seem to play an important role as source of ROS in both male and female reproductive systems under EMF exposure. Future and more standardized studies are required for a better understanding of molecular mechanisms underlying EMF potential challenge to our reproductive system in order to improve preventive strategies.

Schuermann D, Mevissen M Manmade Electromagnetic Fields and Oxidative Stress-Biological Effects and Consequences for Health. Int J Mol Sci 2021 Apr 6;22(7):3772.(Review)

Concomitant with the ever-expanding use of electrical appliances and mobile communication systems, public and occupational exposure to electromagnetic fields (EMF) in the extremely-low-frequency and radiofrequency range has become a widely debated environmental risk factor for health. Radiofrequency (RF) EMF and extremely-low-frequency (ELF) MF have been classified as possibly carcinogenic to humans (Group 2B) by the International Agency for Research on Cancer (IARC). The production of reactive oxygen species (ROS), potentially leading to cellular or systemic oxidative stress, was frequently found to be influenced by EMF exposure in animals and cells. In this review, we summarize key experimental findings on oxidative stress related to EMF exposure from animal and cell studies of the last decade. The observations are discussed in the context of molecular mechanisms and functionalities relevant to health such as neurological function, genome stability, immune response, and reproduction. Most animal and many cell studies showed increased oxidative stress caused by RF-EMF and ELF-MF. In order to estimate the risk for human health by manmade exposure, experimental studies in humans and epidemiological studies need to be considered as well.

(E) (VO. CE. IOD, DAO) Seif F, Bayatiani MR, Ansarihadipour H, Habibi G, Sadelaji S. Protective properties of Myrtus communis extract against oxidative effects of extremely low-frequency magnetic fields on rat plasma and hemoglobin. Int J Radiat Biol. 95:215-224, 2019.

PURPOSE: This study investigates the protective properties of Myrtus communis extract against oxidative effects of Extremely Low Frequency Magnetic Fields (ELFMF). Also this study is aimed to analyze the conformational changes of hemoglobin, oxidative damages to plasma proteins and antioxidant power of plasma following exposure to ELFMF. MATERIALS AND METHODS: Adult male rats were divided into 3 groups: (1) control, (2) ELFMF exposure, and (3) ELFMF exposure after Myrtus communis extract administration. The magnetic field (0.7 mT, 50 Hz) was produced by a Helmholtz coil for one month, 2 hours a day. The Myrtus communis extract was injected intraperitoneally at a dose of 0.5 mg/kg before exposure to ELFMF. The oxidative effects of ELFMF were studied by evaluating the hemoglobin, methemoglobin (metHb) and hemichrome levels, absorption spectrum of hemoglobin (200 to 700 nm), oxidative damage to plasma proteins by measuring protein carbonyl (PCO) levels and plasma antioxidant power according to ferric reducing ability of plasma (FRAP). The mean and standard errors of mean were determined for each group. One-way ANOVA analysis was used to compare the means of groups. The significance level was considered to be $P < 0.05$. Moreover, artificial neural network (ANN) analysis was used to identify the predictive parameters for estimating the oxyhemoglobin (oxyHb) concentration. RESULTS: Exposure to ELFMF decreased the FRAP which was in concomitant with a significant increase in plasma PCO, metHb and hemichrome concentrations ($p < 0.001$). Oxidative modifications of Hb were shown by reduction in optical density at 340nm (globin-heme interaction) and 420 nm (heme-heme interaction). Administration of Myrtus communis extract increased FRAP values and decreased plasma POC, metHb and hemichrome concentrations. Also a significant increase in Hb absorbance at 340, 420, 542 and 577 nm showed the protective properties of Myrtus communis extract against ELFMF-induced oxidative stress in erythrocytes. ANN analysis showed that optical absorption of hemoglobin at 520, 577, 542, and 630 nm and concentration of metHb and hemichrome were the most important parameters in predicting the oxyHb concentration. CONCLUSIONS: Myrtus communis extract enhances the ability of erythrocytes and plasma to deal with oxidative conditions during exposure to ELFMF. Also ANN analysis can predict the most important parameters in relation to Hb structure during oxidative stress.

(E) (VO, IOD, IAO, DAO) Seifirad S, Farzampour S, Nourbakhsh M, Amoli MM, Razzaghy-Azar M, Larijani B Effects of extremely low frequency electromagnetic fields on paraoxonase serum activity and lipid peroxidation metabolites in rat. J Diabetes Metab Disord. 13(1):85, 2014.

BACKGROUND: Atherogenic effects of ELF-MF exposure have not been studied well so far. Therefore we have hypothesized that ELF-MF exposure might have atherogenic effect by impairing antioxidant function and increasing lipid peroxidation. This study was therefore undertaken to examine the effects of ELF-MF on paraoxonase (PON) activity, antioxidant capacity and lipid peroxidation metabolites. Effects of time on remodeling of antioxidant system were also investigated in this study. METHODS: Seventy five Wistar rats were randomly allocated into five groups as follows: 1) Sham exposure, 2) Single exposure to 60 Hz, sacrificed immediately after exposure, 3) Single exposure to 60 Hz, sacrificed 72 hours after exposure, 4) Fourteen days of exposure to 60 Hz, sacrificed immediately after exposure, and 5) Fourteen days of exposure to 60 Hz, sacrificed 72 hours after exposure. Blood samples were collected and analyzed. The results were compared using ANOVA and post hoc Tukey HSD for multiple caparisons. RESULTS: Single ELF-MF exposure significantly increased lipid peroxidation (CD and MDA) and increased antioxidant serum activity (HDL, paraoxonase activity, and serum total antioxidant capacity). Chronic ELF-MF exposure increased lipid peroxidation and affected antioxidant system. Free fatty acids levels were significantly increased after both single and two weeks exposure. Chronic exposure led to irreversible changes while acute exposure tended to reversible alterations on above mentioned parameters. CONCLUSIONS: According to the results of this study, ELF-MF exposure could impair oxidant-antioxidant function and might increase oxidative stress and lipid peroxidation. Antioxidant capability was dependent on the duration and continuity of ELF-MF exposure.

(E) (VO, CE, IFR, IOD, IAO) Selaković V, Rauš Balind S, Radenović L, Prolić Z, Janać B. Age-dependent effects of ELF-MF on oxidative stress in the brain of mongolian gerbils. Cell Biochem Biophys. 66(3):513-521, 2013.

The aim of study was to investigate the effects of extremely low frequency magnetic field (ELF-MF; 50 Hz; 0.1, 0.25 and 0.5 mT) on oxidative stress in the brain of 3- (adult) and 10-month-old (middle-aged) gerbils. Nitric oxide (NO) level, superoxide (O(2) (-)) production, superoxide dismutase (SOD) activity, and index of lipid peroxidation (ILP) were measured in the forebrain cortex, striatum, hippocampus, and cerebellum immediately and 3 days after cessation of 7-day exposure. In all gerbils, ELF-MF significantly increased oxidative stress in all tested brain regions. This effect was correlated with the value of magnetic induction and was higher in middle-aged gerbils. Three days after cessation of exposure, the values of examined parameters were closer to control levels. In adult gerbils, the effect of ELF-MF of 0.1 mT on NO level, O(2) (-) production and SOD activity was almost fully disappeared, and ILP was at the control level regardless of the value of magnetic induction. In middle-aged gerbils, the effect of ELF-MF was still present but to a lesser degree than those observed immediately after cessation of exposure. These findings pointed out the ability of ELF-MF to induce age- and magnetic induction-dependent modification of oxidative stress in the brain.

(E) (VO, CE, IAO) Şenol N, Kaya E, Coşkun Ö, Aslankoç R, Çömlekçi S. Evaluation of the Effects of a 50 Hz Electric Field on Brain Tissue by Immunohistochemical Method, and on Blood Tissue by Biochemical, Physiological and Comet Method. Applied Sciences 13(5):3276, 2023.

The aim of this study was to evaluate the possible effects of a 50 Hz electric field on brain tissue and the positive effects of juglone (5-hydroxy-1,4-naphthoquinone) antioxidant activity, using the immunohistochemical technique on male Wistar-Albino rats. The effects on blood tissue were also examined using biochemical, physiological and comet methods. Animals were randomly divided into three groups (eight in each group): group I: control, group II: electric field, group III: 50 Hz electric field + juglone (5-hydroxy-1,4-naphthoquinone)/300 ppm. Juglone was applied per day by gavage over 30 days. At the end of the experimental procedure, animals were sacrificed and brain tissue was subjected to routine histologic and immunohistochemical processes. As a result of histopathological examination, the brain tissue of rats with 50 Hz electric field exposure showed severe histopathological changes. The differences between groups were statistically significant according to total comet score ($p = 0.001$). For the antioxidant parameters on the blood, SOD activity in the electric field group was significantly higher among the other groups, although we did not find significant differences in MDA, CAT activity level.

Seyhan N, Güler G. Review of in vivo static and ELF electric fields studies performed at Gazi Biophysics Department. Electromagn Biol Med. 25(4):307-323, 2006. (review)

In vivo effects of Static Electric and ELF Magnetic and Electric fields have been carried out for more than 20 years in the Bioelectromagnetic Laboratory at the Biophysics Department of the Medical Faculty of Gazi University. In this article, the results of in vivo ELF Electric field studies are presented as a review. Static and 50 Hz ELF (Extremely Low Frequency) Electric (E) fields effects on free radical synthesis, antioxidant enzyme level, and collagen synthesis were analyzed on tissues of guinea pigs, such as brain, liver, lung, kidney, spleen, testis, and plasma. Animals were exposed to static and ELF electric fields with intensities ranging from 0.3 kV/m to 1.9 kV/m in vertical and horizontal directions. Exposure periods were 1, 3, 5, 7, and 10 days. Electric fields were generated from a specially designed parallel plate capacitor system. The results indicate that the effects of electric fields on the tissues studied depend significantly on the type and magnitude of electric field and exposure period.

(E) (AS, CE, MC, OX, MA, ND) Shabani Z, Nejad DM, Ghadiri T, Karimipour M. Evaluation of the neuroprotective effects of Vitamin E on the rat substantia nigra neural cells exposed to electromagnetic field: An ultrastructural study. Electromagn Biol Med 40(3):428-437, 2021.

Electromagnetic fields (EMFs) could induce oxidative stress (OS) in human tissues. Lipid peroxidation (LPO) is the main hallmark of OS that harms neural cell components, primarily lipids in the myelin sheaths and membranes. Vitamin E is a lipophilic antioxidant that protects cells from OS-related damages and inhibits the LPO process. In this study, male rats were assigned into three groups of Control, EMF, and EMF+ Vitamin E. The EMF producer equipment produced an alternate current of 50 Hz, 3 Mili Tesla (mT). At the end of the experiment, half of the substantia nigra in every sample was used for measurement of the malondialdehyde (MDA) level as the end-product of the LPO and activity of superoxide dismutase (SOD) enzyme. The next half of the tissue was prepared for

transmission electron microscopy (TEM). In the EMF group, MDA level was enhanced and SOD value decreased significantly compared to the control group, but Vitamin E could restore these changes. In rats undergone EMF, heterochromatic nucleus and destruction in some portions of the nuclear membrane were detected. The segmental separation or destruction of myelin sheath lamellae was observed in nerve fibers. In treated animals, the nucleus was round, less heterochromatic, with a regular membrane. Separation of myelin sheath lamellae in some nerve fibers was slighter than the radiation group. Considering the results, EMF exposure induces LPO and triggers ultrastructural changes in the cell membranes, nucleus, and myelin sheath of substantia nigra cells, but Vitamin E consumption weakens these neuropathological alterations.

(E) (VO, CE, DAO) Sharifian A, Gharavi M, Pasalar P, Aminian O. Effect of extremely low frequency magnetic field on antioxidant activity in plasma and red blood cells in spot welders. Int Arch Occup Environ Health. 82(2):259-266, 2009.

OBJECTIVE: The purpose of this study was to determine a possible relation between exposure to extremely low frequency magnetic field (ELF-MF) and the human antioxidant activity. METHODS: The total serum antioxidant status (TAS), red blood cells (RBCs) glutathione peroxidase (GPX) and superoxide dismutase (SOD) were measured in 46 spot welders who were occupationally exposed to ELF-MF (magnetic field strength = 8.8-84 microTesla (microT), frequency = 50 Hertz (Hz) and electric field strength = 20-133 V/m). The results were compared with a nonexposed ELF-MF control group. The correlation between magnetic field strength and antioxidant activity in RBCs and plasma was then assessed. RESULTS: No significant differences in TAS levels were observed (P value = 0.065). However, in RBCs of exposed group, a significant decrease in SOD and GPX activities was observed (P value = 0.001 and 0.003, respectively). This decrease was measured as 22 and 12.3%, respectively. Furthermore, a significant negative correlation between SOD/GPX activities and magnetic field intensity was observed (coefficients of SOD: -0.625, significance: 0.0001 and coefficients of GPX: -0.348, significance: 0.018). CONCLUSION: The results of this study indicate that ELF-MF could influence the RBC antioxidant activity and might act as an oxidative stressor. Intracellular antioxidant enzymes such as SOD and GPX were found to be the most important markers involving in this process. The influence of magnetic field on the antioxidant activity of RBCs might occur even at the recommended levels of exposure.

(E) (VT, AE, IFR) Sherrard RM, Morellini N, Jourdan N, El-Esawi M, Arthaut LD, Niessner C, Rouyer F, Klarsfeld A, Doulazmi M, Witczak J, d'Harlingue A, Mariani J, Mclure I, Martino CF, Ahmad M. Low-intensity electromagnetic fields induce human cryptochrome to modulate intracellular reactive oxygen species. PLoS Biol. 16(10):e2006229, 2018.

Exposure to man-made electromagnetic fields (EMFs), which increasingly pollute our environment, have consequences for human health about which there is continuing ignorance and debate. Whereas there is considerable ongoing concern about their harmful effects, magnetic fields are at the same time being applied as therapeutic tools in regenerative

medicine, oncology, orthopedics, and neurology. This paradox cannot be resolved until the cellular mechanisms underlying such effects are identified. Here, we show by biochemical and imaging experiments that exposure of mammalian cells to weak pulsed electromagnetic fields (PEMFs) stimulates rapid accumulation of reactive oxygen species (ROS), a potentially toxic metabolite with multiple roles in stress response and cellular ageing. Following exposure to PEMF, cell growth is slowed, and ROS-responsive genes are induced. These effects require the presence of cryptochrome, a putative magnetosensor that synthesizes ROS. We conclude that modulation of intracellular ROS via cryptochromes represents a general response to weak EMFs, which can account for either therapeutic or pathological effects depending on exposure. Clinically, our findings provide a rationale to optimize low field magnetic stimulation for novel therapeutic applications while warning against the possibility of harmful synergistic effects with environmental agents that further increase intracellular ROS.

(E) (VO, AE, IFR, IAO, DAO) Shine MB, Guruprasad KN, Anand A. Effect of stationary magnetic field strengths of 150 and 200 mT on reactive oxygen species production in soybean. Bioelectromagnetics. 33(5):428-437, 2012.

Our previous investigation reported the beneficial effect of pre-sowing magnetic treatment for improving germination parameters and biomass accumulation in soybean. In this study, soybean seeds treated with static magnetic fields of 150 and 200 mT for 1 h were evaluated for reactive oxygen species (ROS) and activity of antioxidant enzymes. Superoxide and hydroxyl radicals were measured in embryos and hypocotyls of germinating seeds by electron paramagnetic resonance spectroscopy and kinetics of superoxide production; hydrogen peroxide and antioxidant activities were estimated spectrophotometrically. Magnetic field treatment resulted in enhanced production of ROS mediated by cell wall peroxidase while ascorbic acid content, superoxide dismutase and ascorbate peroxidase activity decreased in the hypocotyl of germinating seeds. An increase in the cytosolic peroxidase activity indicated that this antioxidant enzyme had a vital role in scavenging the increased H(2)O(2) produced in seedlings from the magnetically treated seeds. Hence, these studies contribute to our first report on the biochemical basis of enhanced germination and seedling growth in magnetically treated seeds of soybean in relation to increased production of ROS.

(E) (VO, CE, IFR, DFR, IAO, DAO) Shokrollahi S, Ghanati F, Sajedi RH, Sharifi M. Possible role of iron containing proteins in physiological responses of soybean to static magnetic field. J Plant Physiol. 226:163-171, 2018.

Iron is a component of many proteins that have crucial roles in plant growth and development, such as ferritin and catalase. Iron also, as a ferromagnetic element, is assumed to be influenced by a static magnetic field (SMF). In the present study, we examined the relationship between ferrous content and gene expression and activity of ferritin

and catalase in soybean plants under the influence of 0, 20, and 30 mT SMF for 5 day, 5 h each. Exposure to 20 mT decreased gene expression of Fe transporter, ferrous and H_2O_2 contents and gene expression, content and activity of ferritin and catalase. Opposite responses were observed under 30 mT treatments. The results suggest that SMF triggered a signaling pathway that is mediated by iron. The structure and activity of purified ferritin and apoferritin from horse spleen, and catalase from bovine liver proteins under SMF were evaluated as well. Secondary structure of proteins were not influenced by SMF (evidenced by far-UV circular dichroism), whereas their tertiary structure, size, and activity were altered (shown by fluorescence spectroscopy and dynamic light-scattering). From these results, it is likely that the number of iron atoms is involved in the nature of influence of SMF on protein structure.

(E) (VO, CE, IAO) Sieroń K, Knapik K, Onik G, Romuk E, Birkner E, Kwiatek S, Sieroń A. Electromagnetic Fields Modify Redox Balance in the Rat Gastrointestinal Tract. Front Public Health 9:710484, 2021.

Objective: The aim of the study was to assess the influence of electromagnetic fields with divergent physical properties on the prooxidative and antioxidative balances in homogenates of the tongue, salivary glands, esophagus, stomach, and small and large intestines of rats. **Material and Methods:** Forty rats were randomly divided into four equal groups, namely, a control group, a group exposed to low-frequency electromagnetic fields (LF-EMFs; frequency: 50 Hz; intensity: 10 kV/m; magnetic induction: 4.3 pT), a group exposed to radiofrequency electromagnetic fields (RF-EMFs) emitted by mobile phones (frequency: 900 MHz), and a group exposed simultaneously to LF-EMFs and RF-EMFs emitted by mobile phones. After 28 consecutive days of the experiment, the following pro- and antioxidative markers were assessed in the gastrointestinal tract homogenates: superoxide dismutase (SOD) and its two isoenzymes (Mn-SOD, Cu,Zn-SOD) catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), total antioxidative capacity (TAC), total oxidative status (TOS), and malondialdehyde (MDA). **Results:** In rats exposed to LF-EMFs, higher concentrations of the markers of prooxidant processes, MDA or TOS, were observed in the salivary glands, esophagus, and small intestine homogenates in comparison with the control group. Additionally, in the group of rats opposite to the control, antioxidant activity was observed. The main differences included a higher activity of Cu,Zn-SOD in homogenates of the tongue, salivary glands, and esophagus as well as decreased activity of CAT in homogenates of the tongue, esophagus, and small intestine. In animals exposed to RF-EMFs, the concentration of TOS was higher in the large intestine than in control rats. The main difference of antioxidant activity was presented by decreased Cu,Zn-SOD in homogenates of the salivary glands, stomach, small and large intestine as well as CAT in homogenates of the tongue, esophagus, stomach, and small and large intestine. Moreover, in rats exposed simultaneously to LF-EMFs and RF-EMFs, a lower concentration of TOS was observed. Antioxidant activity was presented by a decreased activity of CAT in homogenates of the tongue, esophagus, stomach, and small and large intestine in comparison to the control group. **Conclusion:** Among those applied in the study, electromagnetic fields of a low-frequency caused the most significant disturbances of oxidative stress in the rat gastrointestinal tract.

(E) (VT, AE, IFR) Simkó M, Droste S, Kriehuber R, Weiss DG. Stimulation of phagocytosis and free radical production in murine macrophages by 50 Hz electromagnetic fields. Eur J Cell Biol. 80(8):562-566, 2001.

Effects of 50 Hz electromagnetic fields on phagocytosis and free radical production were examined in mouse bone marrow-derived macrophages. Macrophages were in vitro exposed to electromagnetic fields using different magnetic field densities (0.5-1.5 mT). Short-time exposure (45 min) to electromagnetic fields resulted in significantly increased phagocytic uptake (36.3% +/- 15.1%) as quantified by measuring the internalization rate of latex beads. Stimulation with 1 nM 12-0-tetradecanoylphorbol-13-acetate (TPA) showed the same increased phagocytic activity as 1 mT electromagnetic fields. However, co-exposure to electromagnetic fields and TPA showed no further increase of bead uptake, and therefore we concluded that because of the absence of additive effects, the electromagnetic fields-induced stimulation of mouse bone marrow-derived macrophages does not involve the protein kinase C signal transduction pathway. Furthermore, a significant increased superoxide production after exposure to electromagnetic fields was detected.

Simkó M. Cell type specific redox status is responsible for diverse electromagnetic field effects. Curr Med Chem. 14(10):1141-1152, 2007. (review)

Epidemiologic and experimental research on the potential carcinogenic effects of extremely low frequency electromagnetic fields (ELF-EMF) has been performed for a long time. Epidemiologic studies regarding ELF-EMF-exposure have focused primarily on leukaemia development due to residential sources in children and adults, and from occupational exposure in adults, but also on other kinds of cancer. Genotoxic investigations of EMF have shown contradictory results, a biological mechanism is still lacking that can explain the link between cancer development and ELF-EMF-exposure. Recent laboratory research has attempted to show general biological effects, and such that could be related to cancer development and/or promotion. Metabolic processes which generate oxidants and antioxidants can be influenced by environmental factors, such as ELF-EMF. Increased ELF-EMF exposure can modify the activity of the organism by reactive oxygen species leading to oxidative stress. It is well established that free radicals can interact with DNA resulting in single strand breaks. DNA damage could become a site of mutation, a key step to carcinogenesis. Furthermore, different cell types react differently to the same stimulus, because of their cell type specific redox status. The modulation of cellular redox balance by the enhancement of oxidative intermediates, or the inhibition or reduction of antioxidants, is discussed in this review. An additional aspect of free radicals is their function to influence other illnesses such as Parkinson's and Alzheimer's diseases. On the other hand, modulation of antioxidants by ELF-EMF can lower the intracellular defence activity promoting the development of DNA damage. It has also been demonstrated that low levels of reactive oxygen species trigger intracellular signals that involve the transcription of genes and leading to responses including cell proliferation and apoptosis. In this review, a general overview is given about oxidative stress, as well as experimental studies are reviewed as they are related to changes in oxidant and antioxidant content

after ELF-EMF exposure inducing different biological effects. Finally, we conclude from our review that modulations on the oxidant and antioxidant level through ELF-EMF exposure can play a causal role in cancer development.

Simkó M, Mattsson MO. Extremely low frequency electromagnetic fields as effectors of cellular responses in vitro: possible immune cell activation. J Cell Biochem. 93(1):83-92, 2004. (review)

There is presently an intense discussion if electromagnetic field (EMF) exposure has consequences for human health. This include exposure to structures and appliances that emit in the extremely low frequency (ELF) range of the electromagnetic spectrum, as well as emission coming from communication devices using the radiofrequency part of the spectrum. Biological effects of such exposures have been noted frequently, although the implication for specific health effects is not that clear. The basic interaction mechanism(s) between such fields and living matter is unknown. Numerous hypotheses have been suggested, although none is convincingly supported by experimental data. Various cellular components, processes, and systems can be affected by EMF exposure. Since it is unlikely that EMF can induce DNA damage directly, most studies have examined EMF effects on the cell membrane level, general and specific gene expression, and signal transduction pathways. In addition, a large number of studies have been performed regarding cell proliferation, cell cycle regulation, cell differentiation, metabolism, and various physiological characteristics of cells. Although 50/60 Hz EMF do not directly lead to genotoxic effects, it is possible that certain cellular processes altered by exposure to EMF indirectly affect the structure of DNA causing strand breaks and other chromosomal aberrations. The aim of this article is to present a hypothesis of a possible initial cellular event affected by exposure to ELF EMF, an event which is compatible with the multitude of effects observed after exposure. Based on an extensive literature review, we suggest that ELF EMF exposure is able to perform such activation by means of increasing levels of free radicals. Such a general activation is compatible with the diverse nature of observed effects. Free radicals are intermediates in natural processes like mitochondrial metabolism and are also a key feature of phagocytosis. Free radical release is inducible by ionizing radiation or phorbol ester treatment, both leading to genomic instability. EMF might be a stimulus to induce an "activated state" of the cell such as phagocytosis, which then enhances the release of free radicals, in turn leading to genotoxic events. We envisage that EMF exposure can cause both acute and chronic effects that are mediated by increased free radical levels: (1) Direct activation of, for example macrophages (or other cells) by short-term exposure to EMF leads to phagocytosis (or other cell specific responses) and consequently, free radical production. This pathway may be utilized to positively influence certain aspects of the immune response, and could be useful for specific therapeutic applications. (2) EMF-induced macrophage (cell) activation includes direct stimulation of free radical production. (3) An increase in the lifetime of free radicals by EMF leads to persistently elevated free radical concentrations. In general, reactions in which radicals are involved become more frequent, increasing the possibility of DNA damage. (4) Long-term EMF exposure leads to a chronically increased level of free radicals, subsequently causing an inhibition of the effects of the pineal gland hormone melatonin. Taken together, these EMF induced reactions could lead to a higher incidence of DNA damage and therefore, to an increased risk of tumour development. While the effects on melatonin and the extension of the lifetime of radicals can explain the link between EMF exposure and the incidence of for

example leukaemia, the two additional mechanisms described here specifically for mouse macrophages, can explain the possible correlation between immune cell system stimulation and EMF exposure.

(E) (HU, AE, IAO, DFR) Sirmatel O, Sert C, Sirmatel F, Selek S, Yokus B. Total antioxidant capacity, total oxidant status and oxidative stress index in the men exposed to 1.5 T static magnetic field. Gen Physiol Biophys. 26(2):86-90, 2007a.

The aim of this study was to investigate the effects of a high-strength magnetic field produced by a magnetic resonance imaging (MRI) apparatus on oxidative stress. The effects of a 1.5 T static magnetic field on the total antioxidant capacity (TAC), total oxidant status (TOS) and oxidative stress index (OSI) in male subjects were investigated. In this study, 33 male volunteers were exposed to a 1.5 T static magnetic field for a short time and the TAC, TOS and OSI of each subject were determined. Magnetic field exposure was provided using a magnetic resonance apparatus; radiofrequency was not applied. Blood samples were taken from subjects and TAC, TOS and OSI values were measured using the methods of Erel. TAC showed a significant increase in post-exposures compared to pre-exposures to the magnetic field ($p < 0.05$). OSI and TOS showed a significant decrease in post-exposures compared to pre-exposures to a 1.5 T magnetic field (for each of two, $p < 0.01$). The 1.5 T static magnetic field used in the MRI apparatus did not yield a negative effect; on the contrary, it produced the positive effect of decreasing oxidative stress in men following short-term exposure.

(E) (HU, AE, IFR) Sirmatel O, Sert C, Tümer C, Oztürk A, Bilgin M, Ziylan Z. Change of nitric oxide concentration in men exposed to a 1.5 T constant magnetic field. Bioelectromagnetics. 28(2):152-154, 2007b.

This study was carried out in order to determine nitric oxide (NO) production immediately after a 1.5 T magnetic field 30 min exposure to an experimental group, comprising 33 healthy young male volunteers aged 18-26 years old. In addition, a control group, comprising 30 healthy male volunteers aged 19-26 years old, was not exposed to the magnetic field and their NO levels were also measured. The experimental group was exposed using a magnetic resonance imaging (MRI) apparatus. Nitrite and nitrate concentrations were determined by UV-VIS spectrophotometer. The results, related to the parameters measured in this study, were analyzed by one-way ANOVA. Total nitrite concentration in post-magnetic field samples was found to be higher than in pre-magnetic field samples ($P < .05$).

(E) (VT, AE, IFR) Solek P, Majchrowicz L, Bloniarz D, Krotoszynska E, Koziorowski M. Pulsed or continuous electromagnetic field induce p53/p21-mediated apoptotic signaling pathway in mouse spermatogenic cells in vitro and thus may affect male fertility. Toxicology. 382:84-92, 2017.

The impact of electromagnetic field (EMF) on the human health and surrounding environment is a common topic investigated over the years. A significant increase in the electromagnetic field concentration arouses public concern about the long-term effects of EMF on living organisms associated with many aspects. In the present study, we investigated the effects of pulsed and continuous electromagnetic field (PEMF/CEMF) on mouse spermatogenic cell lines (GC-1 spg and GC-2 spd) in terms of cellular and biochemical features in vitro. We evaluated the effect of EMF on mitochondrial metabolism, morphology, proliferation rate, viability, cell cycle progression, oxidative stress balance and regulatory proteins. Our results strongly suggest that EMF induces oxidative and nitrosative stress-mediated DNA damage, resulting in p53/p21-dependent cell cycle arrest and apoptosis. Therefore, spermatogenic cells due to the lack of antioxidant enzymes undergo oxidative and nitrosative stress-mediated cytotoxic and genotoxic events, which contribute to infertility by reduction in healthy sperm cells pool. In conclusion, electromagnetic field present in surrounding environment impairs male fertility by inducing p53/p21-mediated cell cycle arrest and apoptosis.

(E) (VT, AE, IFR) Solek P, Majchrowicz L, Koziorowski M. Aloe arborescens juice prevents EMF-induced oxidative stress and thus protects from pathophysiology in the male reproductive system in vitro. Environ Res. 166:141-149, 2018.

More and more studies suggest that prolonged exposure to EMF may cause adverse biological effects and point directly to a significantly negative correlation between EMF and human health, especially men fertility. In our previous study, we reported that this could be related to the EMF-induced reactive oxygen species formation, followed by DNA damage, cell cycle arrest and apoptosis induction. In this study, we decided to expand our research by the search for substances which would prevent EMF-induced damage in spermatogenic cells. Such an agent seems to be Aloe arborescens Mill. juice, which was shown to possess a wide range of protective properties. The administration of aloe extract helps among others to prevent the formation of free radicals by various biochemical pathways. Therefore, the main aim of our study was to provide a significant knowledge concerning the mechanism involved in the multi-pathway cytoprotective response of aloe juice against EMF. The study was carried out in an in vitro mouse spermatogenesis pathway cell lines (GC-1 spg and GC-2 spd). Our results suggest that the aloe juice has many positive effects, especially for the cellular antioxidant systems by reducing the intracellular reactive oxygen species pool induced by EMF. In consequence, aloe juice prevents DNA damage, cell cycle arrest and therefore the viability and metabolic activity of both cell line tested are preserved. In conclusion, our study provides new insight into the underlying mechanisms through which aloe juice prevents spermatogenic cells from cytotoxic and genotoxic events.

(E) (IV, AE, DFR) Song K, Im SH, Yoon YJ, Kim HM, Lee HJ, Park GS. A 60 Hz uniform electromagnetic field promotes human cell proliferation by decreasing intracellular reactive oxygen species levels. PLoS One. 13(7):e0199753, 2018.

Previously, we showed that exposure of human normal and cancer cells to a 6 mT, 60 Hz gradient electromagnetic field (EMF) induced genotoxicity. Here, we investigated the cellular effects of a uniform EMF. Single or repetitive exposure to a 6 mT, 60 Hz uniform EMF neither induced DNA damage nor affected cell viability in HeLa and primary IMR-90 fibroblasts. However, continuous exposure of these cells to an EMF promoted cell proliferation. Cell viability increased 24.4% for HeLa and 15.2% for IMR-90 cells after a total 168 h exposure by subculture. This increase in cell proliferation was directly correlated with EMF strength and exposure time. When further incubated without EMF, cell proliferation slowed down to that of unexposed cells, suggesting that the proliferative effect is reversible. The expression of cell cycle markers increased in cells continuously exposed to an EMF as expected, but the distribution of cells in each stage of the cell cycle did not change. Notably, intracellular reactive oxygen species levels decreased and phosphorylation of Akt and Erk1/2 increased in cells exposed to an EMF, suggesting that reduced levels of intracellular reactive oxygen species play a role in increased proliferation. These results demonstrate that EMF uniformity at an extremely low frequency (ELF) is an important factor in the cellular effects of ELF-EMF.

(E) (VT, AE, IFR) Sullivan K, Balin AK, Allen RG. Effects of static magnetic fields on the growth of various types of human cells. Bioelectromagnetics. 32(2):140-147, 2011.

The effects of a static magnetic field (SMF) on the proliferation of various types of human cells were determined. All cultures were maintained at 37 °C throughout the experiment. SMF was generated by placing two magnets oppositely oriented on either side of a T25 flask. The flux density in the flask ranged from 35 to 120 mT. Growth curves were constructed by plotting cell number at 18 h and 4, 7, 11, and 14 days after seeding, with the 18-h point being a measure of attachment efficiency. Exposure to SMF significantly decreased initial attachment of fibroblasts and decreased subsequent growth compared to sham-exposed control. Significant effects were observed in both fetal lung (WI-38) and adult skin fibroblasts, but they were generally larger in the fetal lung fibroblast line. SMF did not affect attachment of human melanoma cells, but inhibited their growth by 20% on day 7. SMF produced no effects in a human adult stem cell line. Oxidant production increased 37% in WI-38 cells exposed to SMF (230-250 mT) during the first 18 h after seeding, when cell attachment occurs. Conversely, no elevation in oxidant levels was observed after a prolonged 5-day exposure. These results indicate that exposure to SMF has significant biological effects in some, but not all types of human cells.

(E) (IV, AE, IFR, AO) Sun L, Chen L, Bai L, Xia Y, Yang X, Jiang W, Sun W. Reactive oxygen species mediates 50-Hz magnetic field-induced EGF receptor clustering via acid sphingomyelinase activation. Int J Radiat Biol. 94(7):678-684, 2018.

PURPOSE: Exposure to extremely low frequency electromagnetic fields (ELF-EMFs) could elicit biological effects including carcinogenesis. However, the detailed mechanisms by which these ELF-EMFs interact with biological system are currently unclear. Previously, we found that a 50-Hz magnetic field (MF) exposure could induce epidermal growth factor receptor (EGFR) clustering and phosphorylation on cell membranes. In the present experiment, the possible roles of reactive oxygen species (ROS) in MF-

induced EGFR clustering were investigated. MATERIALS AND METHODS: Human amnion epithelial (FL) cells were exposed to a 50-Hz MF with or without N-acetyl-l-cysteine (NAC) or pyrrolidine dithiocarbamate (PDTC). EGFR clustering on cellular membrane surface was analyzed using confocal microscopy after indirect immunofluorescence staining. The intracellular ROS level and acid sphingomyelinase (ASMase) activity were detected using an ROS assay kit and an Amplex® Red Sphingomyelinase Assay Kit, respectively. RESULTS: Results showed that exposure of FL cells to a 50-Hz MF at 0.4 mT for 15 min significantly enhanced the ROS level, induced EGFR clustering and increased ASMase activity. However, pretreatment with NAC or PDTC, the scavenger of ROS, not only counteracted the effects of a 50-Hz MF on ROS level and AMS activity, but also inhibited the EGFR clustering induced by MF exposure. CONCLUSIONS: The present and previous data suggest that ROS mediates the MF-induced EGFR clustering via ASMase activation.

(E) (VT, AE, DFR) Sun YL, Chen ZH, Chen XH, Yin C, Li DJ, Ma XL, Zhao F, Zhang G, Shang P, Qian AR. Diamagnetic levitation promotes osteoclast differentiation from RAW264.7 cells. IEEE Trans Biomed Eng. 62(3):900-908, 2015.

The superconducting magnet with a high magnetic force field can levitate diamagnetic materials. In this study, a specially designed superconducting magnet with large gradient high magnetic field (LGHMF), which provides three apparent gravity levels (μg, 1 g, and 2 g), was used to study its influence on receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclast differentiation from preosteoclast cell line RAW264.7. The effects of LGHMF on the viability, nitric oxide (NO) production, morphology in RAW264.7 cells were detected by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method, the Griess method, and the immunofluorescence staining, respectively. The changes induced by LGHMF in osteoclast formation, mRNA expression, and bone resorption were determined by tartrate-resistant acid phosphatase staining, semiquantity PCR, and bone resorption test, respectively. The results showed that: 1) LGHMF had no lethal effect on osteoclast precursors but attenuated NO release in RAW264.7 cells. 2) Diamagnetic levitation (μg) enhanced both the formation and bone resorption capacity of osteoclast. Moreover, diamagnetic levitation up-regulated mRNA expression of RANK, Cathepsin K, MMP-9, and NFATc1, while down-regulated RunX2 in comparison with controls. Furthermore, diamagnetic levitation induced obvious morphological alterations in osteoclast, including active cytoplasmic peripheral pseudopodial expansion, formation of pedosome belt, and aggregation of actin ring. 3) Magnetic field produced by LGHMF attenuated osteoclast resorption activity. Collectively, LGHMF with combined effects has multiple effects on osteoclast, which attenuated osteoclast resorption with magnetic field, whereas promoted osteoclast differentiation with diamagnetic levitation. Therefore, these findings indicate that diamagnetic levitation could be used as a novel ground-based microgravity simulator, which facilitates bone cell research of weightlessness condition.

(E) (VO, CE, IFR, IAO) Sun Y, Shi Z, Wang Y, Tang C, Liao Y, Yang C, Cai P. Coupling of oxidative stress responses to tricarboxylic acid cycle and prostaglandin E_2 alterations in Caenorhabditis elegans under extremely low-frequency electromagnetic field. Int J Radiat Biol. 2018 Oct 11:1-8. doi: 10.1080/09553002.2019.1524943. [Epub ahead of print]

PURPOSE: With all-pervasive presence of extremely low-frequency electromagnetic field (ELF-EMF) in modern life, ELF-EMF has been regarded as an essential factor which may induce changes in many organisms. The objective of the present study was to investigate the physiological responses of Caenorhabditis elegans (C. elegans) to 50 Hz, 3 mT ELF-EMF exposure. MATERIALS AND METHODS: Worms were exposed to ELF-EMF from the egg stage until reaching the fourth larva (L4) stage. After exposure, expressions of the tricarboxylic acid (TCA) cycle enzymes were examined by qRT-PCR and western blot analysis. Two lipid metabolites were detected by GC-MS. Reactive oxygen species (ROS) level was detected by dichlorofluorescein staining and worm antioxidant system was investigated by enzymatic activity analysis, including detection of the superoxide dismutase and catalase (CAT) activity and the total antioxidant capacity (T-AOC). RESULTS: The TCA cycle enzyme, fumarase was found with decreased expression under ELF-EMF exposure. And arachidonic acid (ArA) and prostaglandin E_2(PGE_2) showed elevated concentrations, with increased expression of prostaglandin E_2 synthase (PGES-2) in ELF-EMF exposed worms. Significant elevation of ROS level was identified accompanied with the significant depression of T-AOC in response to ELF-EMF. CONCLUSIONS: Our results suggested that exposure to 50 Hz, 3 mT ELF-EMF in C. elegans can elicit disruptions of the TCA cycle metabolism and PGE_2 formation, coupling ELF-EMF-induced oxidative stress responses. Our study probably will attract increasing attentions to the controllable application of ELF-EMF associated with health and disease.

(E) (VO, CE, IFR, IOD) Sun YY, Wang YH, Li ZH, Shi ZH, Liao YY, Tang C, Cai P. [Extremely low frequency electromagnetic radiation enhanced energy metabolism and induced oxidative stress in Caenorhabditis elegans]. Sheng Li Xue Bao. (3):388-394, 2019.

[Article in Chinese]

The aim of this study was to determine the effects of extremely low frequency electromagnetic field (ELF-EMF) on energy metabolism and oxidative stress in Caenorhabditis elegans (C. elegans). Worms in three adult stages (young adult stage, egg-laying stage and peak egg-laying stage) were investigated under 50 Hz, 3 mT ELF-EMF exposure. ATP levels, ATP synthase activity in vivo, reactive oxygen species (ROS) content, and changes of total antioxidant capacity (TAC) were detected, and worms' oxidative stress responses were also evaluated under ELF-EMF exposure. The results showed that ATP levels were significantly increased under this ELF-EMF exposure, and mitochondrial ATP synthase activity was upregulated simultaneously. In young adult stage, worms' ROS

level was significantly elevated, together with upregulated TAC but with a decreased ROS-TAC score indicated by principal component analysis. ROS level and TAC of worms had no significant changes in egg-laying and peak egg-laying stages. Based on these results, we concluded that ELF-EMF can enhance worm energy metabolism and elicit oxidative stress, mainly manifesting as ATP and ROS level elevation together with ATP synthase upregulation and ROS-TAC score decrease in young adult C. elegans.

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(E) (VT, AE, IFR, AO) Tang R, Xu Y, Ma F, Ren J, Shen S, Du Y, Hou Y, Wang T. Extremely low frequency magnetic fields regulate differentiation of regulatory T cells: Potential role for ROS-mediated inhibition on AKT. Bioelectromagnetics. 37(2):89-98, 2016.

Our previous studies showed that extremely low frequency magnetic fields (ELF-MFs) inhibited tumor growth and change proportion of splenic regulatory T cells (Treg cells). Here, we focus on the effect of ELF-MFs on lung metastatic melanoma mouse model and the regulatory mechanism of ELF-MFs on the differentiation of Treg cells. Tumor-bearing mice were exposed to sham ELF-MFs and ELF-MFs (0.4 T, 7.5 Hz) 2 h/day for 27 days. Metastatic tumor burden of lung was significantly decreased after ELF-MF treatment. Compared to the control group, expressions of matrix metalloproteinase (MMP2, MMP9) and forkhead box P3 (Foxp3) in lung nodules significantly decreased in the ELF-MF group. Moreover, in vitro, after stimulated with anti-CD3, anti-CD28 antibodies and transforming growth factor-β (TGF-β) and treated with ELF-MFs for 2 h, expression of Foxp3 in total T cells was significantly decreased. Differentiation rate of Treg cells was inhibited from 32.0% to 22.1% by ELF-MFs. Furthermore, reactive oxygen species (ROS) was increased and phospho-serine/threonine protein kinase (p-AKT) was inhibited in both T cells and Jurkat cells. ROS scavenger N-acetyl-l-cysteine reversed inhibition of AKT pathway and expression of Foxp3 from 18.6% to 26.6% in T cells. Taken together, our data show that ELF-MF exposure promoted the inhibitory effect of ROS on AKT pathway and decreased Foxp3 expression, which provides an explanation for why ELF-MF exposure can inhibit differentiation of Treg cells and enhance antitumor effect in metastatic melanoma mouse model.

(E) (VO, CE, IX)Tasset I, Medina FJ, Jimena I, Agüera E, Gascón F, Feijóo M, Sánchez-López F, Luque E, Peña J, Drucker-Colín R, Túnez I. Neuroprotective effects of extremely low-frequency electromagnetic fields on a Huntington's disease rat model: effects on neurotrophic factors and neuronal density. Neuroscience. 209:54-63, 2012.

There is evidence to suggest that the neuroprotective effect of exposure of extremely low-frequency electromagnetic fields (ELF-EMF) may be due, at least in part, to the effect of these fields on neurotrophic factors levels and cell survival, leading to an improvement in behavior. This study was undertaken to investigate the neuroprotective effects of ELFEF in a rat model of 3-nitropropionic acid (3NP)-induced Huntington's disease. Behavior patterns were evaluated, and changes in neurotrophic factor, cell damage, and oxidative stress biomarker levels were monitored in Wistar rats. Rats were given 3NP over four consecutive days (20 mg/kg body weight), whereas ELFEF (60 Hz and 0.7 mT) was applied over 21 days, starting after the last injection of 3NP. Rats

treated with 3NP exhibited significantly different behavior in the open field test (OFT) and the forced swim test (FST), and displayed significant differences in neurotrophic factor levels and oxidative stress biomarkers levels, together with a neuronal damage and diminished neuronal density, with respect neuronal controls. ELFEF improved neurological scores, enhanced neurotrophic factor levels, and reduced both oxidative damage and neuronal loss in 3NP-treated rats. ELFEF alleviates 3NP-induced brain injury and prevents loss of neurons in rat striatum, thus showing considerable potential as a therapeutic tool.

(E) (VO, CE, IOD, DAO) Tayefi H, Kiray A, Kiray M, Ergur BU, Bagriyanik HA, Pekcetin C, Fidan M, Ozogul C. The effects of prenatal and neonatal exposure to electromagnetic fields on infant rat myocardium. Arch Med Sci. 6(6):837-842, 2010.

INTRODUCTION: Electromagnetic fields (EMF) have adverse effects as a result of widespread use of electromagnetic energy on biological systems. The aim of this study was to investigate the effects of prenatal exposure to EMF on rat myocardium by biochemical and histopathological evaluations. **MATERIAL AND METHODS:** In this study, 10 pregnant Wistar rats were used. Half of the pregnant rats were exposed to EMF of 3 mT, and the other half to sham conditions during gestation. After parturition, rat pups in the 5 EMF-exposed litters from birth until postnatal day 20 were exposed to EMF of 3 mT for 4 h/day (EMF-exposed group, n = 30). Rat pups in sham litters from birth until postnatal day 20 were exposed to sham conditions (sham group, n= 20). **RESULTS:** In the EMF-exposed group, lipid peroxidation levels significantly increased compared to sham. Superoxide dismutase activities decreased significantly in the EMF-exposed group compared to sham. TUNEL staining showed that the number of TUNEL-positive cells increased significantly in EMF-exposed rats compared with sham. Under electron microscopy, there were mitochondrial degeneration, reduction in myofibrils, dilated sarcoplasmic reticulum and perinuclear vacuolization in EMF-exposed rats. **CONCLUSIONS:** In conclusion, the results show that prenatal exposure to EMF causes oxidative stress, apoptosis and morphological pathology in myocardium of rat pups. The results of our study indicate a probable role of free radicals in the adverse effects of prenatal exposure to EMF. Further studies are needed to demonstrate whether the EMF exposure can induce adverse effects on the myocardium.

(E) (VO, AE, IFR)Tekutskaya EE, Ryabova IS, Kozin SV, Popov KA, Malyshko VV. Changes in Free Radical Processes under the Influence of Low-Frequency Electromagnetic Field in Rats. Bull Exp Biol Med 2022;172(5):566-569.

We studied the effect of a low-frequency (LF) electromagnetic field (EMF) on the state of the antioxidant system of Wistar rats in vivo. It was found that changes in activity of antioxidant enzymes and H_2O_2 content in the blood plasma of rats exposed to LF EMF depended on the frequency of EMF. We propose a mechanism of the protective effects of low doses of ROS the generation of which is stimulated by LF EMF.

(E) (VO, CE, IFR) Tian L, Y. Luo, A. Zhan, J. Ren, H. Qin, and Y. Pan. Hypomagnetic Field Induces the Production of Reactive Oxygen Species and Cognitive Deficits in Mice Hippocampus. *Int. J. Mol. Sci* 23:3622, 2022.

Previous studies have found that hypomagnetic field (HMF) exposure impairs cognition behaviors in animals; however, the underlying neural mechanisms of cognitive dysfunction are unclear. The hippocampus plays important roles in magnetoreception, memory, and spatial navigation in mammals. Therefore, the hippocampus may be the key region in the brain to reveal its neural mechanisms. We recently reported that long-term HMF exposure impairs adult hippocampal neurogenesis and cognition through reducing endogenous reactive oxygen species (ROS) levels in adult neural stem cells that are confined in the subgranular zone (SGZ) of the hippocampus. In addition to adult neural stem cells, the redox state of other cells in the hippocampus is also an important factor affecting the functions of the hippocampus. However, it is unclear whether and how long-term HMF exposure affects ROS levels in the entire hippocampus (i.e., the dentate gyrus (DG) and ammonia horn (CA) regions). Here, we demonstrate that male C57BL/6J mice exposed to 8-week HMF exhibit cognitive impairments. We then found that the ROS levels of the hippocampus were significantly higher in these HMF-exposed mice than in the geomagnetic field (GMF) group. PCR array analysis revealed that the elevated ROS levels were due to HMF-regulating genes that maintain the redox balance in vivo, such as *Nox4*, *Gpx3*. Since high levels of ROS may cause hippocampal oxidative stress, we suggest that this is another reason why HMF exposure induces cognitive impairment, besides the hippocampal neurogenesis impairments. Our study further demonstrates that GMF plays an important role in maintaining hippocampal function by regulating the appropriate endogenous ROS levels.

(E) (HU, CE, IFR, IOD, DAO) Tiwari R, Bhargava SC, Ahuja YR. The Potential Bioeffects of Extremely Low Frequency Electromagnetic Fields on Melatonin Levels & Related Oxidative Stress in Electric Utility Workers Exposed to 132 kV Substation. J Electromag Analy Appl 5: 393-403, 2013.

Electricity substations take electricity from power lines and transformer lines to transform it from high to low voltage and distribute to the consumers. These substations generate low frequency electromagnetic fields similar to those emitted from over head power lines and electrical appliances at home. The present study is focused on assessing the potential bioeffects of Extremely Low Frequency Electromagnetic Fields (ELF-EMFs) on melatonin level and oxidative stress biomarkers, in subjects occupationally exposed to 132 kV high voltage substation in Hyderabad, India. These subjects are involved in maintenance and installation of power line distribution at electricity transmission network. The ELFEMFs exposed subjects (n = 142) included the electric utility workers, who were compared with age, and socioeconomic status matched controls (n = 151). The subjects were professionally categorized based on their job titles, with different exposure levels, as administrative workers (low exposure), maintenance workers (medium exposure) and liveline workers (high exposure). The plasma melatonin levels were significantly suppressed in the high exposed subjects *i.e.*, hotline workers ($p < 0.05$). The oxidant status levels of plasma Malondialdehyde (MDA) and Nitric Oxide (NO) showed significantly increased levels

in all the exposed subjects ($p < 0.05$). The activity levels of erythrocyte antioxidative enzyme when compared to control subjects were significantly reduced in the exposed subjects of all the categories ($p < 0.05$).

(E) (HU, LE, GE, OX) Tiwari R, Lakshmi NK, Bhargava SC, Ahuja YR. Epinephrine, DNA integrity and oxidative stress in workers exposed to extremely low-frequency electromagnetic fields (ELF-EMFs) at 132 kV substations. Electromagn Biol Med. 2015;34(1):56-62.

There is apprehension about widespread use of electrical and electromagnetic gadgets which are supposed to emit electromagnetic radiations. Reports are controversy. These electromagnetic fields (EMFs) have considerable effect on endocrine system of exposed subjects. This study was focused to assess the possible bioeffects of extremely low-frequency (ELF)-EMFs on epinephrine level, DNA damage and oxidative stress in subjects occupationally exposed to 132 kV high-voltage substations. The blood sample of 142 exposed subjects and 151 non-exposed individuals was analyzed. Plasma epinephrine was measured by enzyme-linked immunosorbent assay, DNA damage was studied by alkaline comet assay along with oxidative stress. Epinephrine levels of sub-groups showed mean concentration of 75.22 ± 1.46, 64.43 ± 8.26 and 48.47 ± 4.97 for high, medium and low exposed groups, respectively. DNA damage ranged between 1.69 μm and 9.91 μm. The oxidative stress levels showed significant increase. The individuals employed in the live-line procedures were found to be vulnerable for EM stress with altered epinephrine concentrations, DNA damage and increased oxidative stress.

(E) (VO, CE, IAO)Todorović D, Mirčić D, Ilijin L, Mrdaković M, Vlahović M, Prolić Z, Mataruga VP. Effect of magnetic fields on antioxidative defense and fitness-related traits of Baculum extradentatum (insecta, phasmatodea). Bioelectromagnetics. 33(3):265-273, 2012.

This study aimed to determine the effect of magnetic fields on the antioxidative defense and fitness-related traits of Baculum extradentatum. Following exposure to magnetic fields, antioxidative defense (superoxide dismutase (SOD), catalase (CAT) activities, and total glutathione (GSH) content) and fitness-related traits (egg mortality, development dynamics, and mass of nymphs) were monitored in nymphs. The experimental groups were: control (kept out of influence of the magnets), a group exposed to a constant magnetic field (CMF) of 50 mT, and a group exposed to an alternating magnetic field (AMF) of 50 Hz, 6 mT. We found increased SOD and CAT activities in animals exposed to constant and AMFs, whereas GSH activity was not influenced by experimental magnetic fields. No differences were found in egg mortality between control and experimental groups. Significant differences in the time of development between the control and the CMF group were observed, as well as between the CMF and the AMF group. No

differences were found in the mass of the nymphs between the three experimental groups. In conclusion, CMF and AMF have the possibility to modulate the antioxidative defense and some of the fitness-related traits in B. extradentatum.

(E) (VO, CE, IAO) Todorović D, Ilijin L, Mrdaković M, Vlahović M, Filipović A, Grčić A, Perić-Mataruga V. Long - term exposure of cockroach Blaptica dubia (Insecta: Blaberidae) nymphs to magnetic fields of different characteristics: Effects on antioxidant biomarkers and nymphal gut mass. Int J Radiat Biol. 2019 Mar 1:1-26. doi: 10.1080/09553002.2019.1589017. [Epub ahead of print]

PURPOSE: The main goal of this study was to analyze the long - term effects of static (SMF) and extremely low frequency magnetic field (ELF MF) on nymphal gut mass and antioxidant biomarkers in this tissue of cockroach Blaptica dubia. MATERIALS AND METHODS: One month old nymphs were exposed to magnetic field (MF) for 5 months in three experimental groups: control, exposure to a SMF (110 mT) and exposure to ELF MF (50 Hz, 10 mT). RESULTS: The gut masses of the MF groups were significantly lower when compared to control. Superoksid dismutase (SOD) and catalase (CAT) activities were markedly higher than for the control and the differences between the MF groups were statistically significant only for SOD. The applied MF had no effect on total glutathione (GSH) content. Glutathione reductase (GR) and glutathione S-transferase (GST) activities were significantly lower in both MF groups in comparison to the control. There was a significant difference between MF groups for GR activity. Principal Component Analysis (PCA) showed that CAT and GST were the main factors contributing to differentiation of the control group from the treated experimental groups along PCA 1, and SOD and GR along PCA 2. PCA revealed clear separation between experimental groups depend on antioxidant biomarker response. CONCLUSION: The applied magnetic fields could be considered a potential stressor influencing gut mass, as well as examined antioxidative biomarkers.

(E) (VO, CE, IOD, DAO, IX) Tony SK, Ismail HA, Hatour FS, Mahmoud ME. Hazardous effects of high voltage electromagnetic field on albino rats and protective role of Rosmarinus officinalis. Environ Sci Pollut Res Int 29(12):17932-17942, 2022.

Electromagnetic fields (EMFs) are common in our everyday lives. They have many origins and severe effects on individuals and environments where they inflict a great deal of health and psychological harm. The current study investigated the impact of high voltage (H.V.) EMF 5.4 kV/m for 2 and 4 h per day with a frequency equal to 50 Hz alternating current (AC) on body weight (b.wt), blood indices, and certain liver enzymes of albino rats after 25 days of exposure to the electromagnetic field. This work focuses on the therapeutic action of methanol extract of Rosmarinus officinalis (R. officinalis) leaves at a dose (5 mg/kg b. wt) against harmful EMF-induced effects. The findings showed that electromagnetic field exposure induced a substantial decrease in red blood cells (RBC), haemoglobin concentration (Hb), and catalase activity (CAT). Although white blood cells (WBCs), aspartate aminotransferase (AST),

alanine aminotransferase (ALT), total bilirubin, urea, creatinine, uric acid, and malondialdehyde (MDA) levels have increased significantly under EMF treatment. Treatment with R. officinalis showed attenuation in these parameters that were induced in rats exposed to H.V. These findings were followed by the histopathological analysis of the liver in the observations. Finally, we conclude that R. officinalis leaves extract offered substantial protection against H.V-induced liver damage and can be applied in drug production.

(NE) (VO, CE, IX) Túnez I, Drucker-Colín R, Jimena I, Medina FJ, Muñoz Mdel C, Peña J, Montilla P. Transcranial magnetic stimulation attenuates cell loss and oxidative damage in the striatum induced in the 3-nitropropionic model of Huntington's disease. J Neurochem. 97(3):619-630, 2006.

An investigation was conducted on the effect of transcranial magnetic field stimulation (TMS) on the free radical production and neuronal cell loss produced by 3-nitropropionic acid in rats. The effects of 3-nitropropionic acid were evaluated by examining the following changes in: the quantity of hydroperoxides and total radical-trapping antioxidant potential (TRAP), lipid peroxidation products, protein carbonyl groups, reduced glutathione (GSH) content, glutathione peroxidase (GSH-Px), catalase and succinate dehydrogenase (SDH) activities; total nitrite and cell death [morphological changes, quantification of neuronal loss and lactate dehydrogenase (LDH) levels]. Our results reveal that 3-nitropropionic acid induces oxidative and nitrosative stress in the striatum, prompts cell loss and also shows that TMS prevents the harmful effects induced by the acid. In conclusion, the results show the ability of TMS to modify neuronal response to 3-nitropropionic acid.

(NE) (VO, CE) Türközer Z, Güler G, Seyhan N. Effects of exposure to 50 Hz electric field at different strengths on oxidative stress and antioxidant enzyme activities in the brain tissue of guinea pigs. Int J Radiat Biol. 84(7):581-590, 2008.

PURPOSE: The aim of this study was to evaluate the possible effects of varied exposure to 50 Hz extremely low frequency (ELF) electric field (EF) on the lipid peroxidation levels and antioxidant enzyme activities in the brain homogenates of guinea pigs. Subjects were exposed to 2 kV/m, 2.5 kV/m, 3 kV/m, 3.5 kV/m, 4 kV/m, 4.5 kV/m and 5 kV/m electric fields for three days, 8 h a day in both vertical and horizontal directions. MATERIALS AND METHODS: Malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were measured in order to identify possible alterations in lipid peroxidation levels and antioxidant status due to electric field exposure. Xanthine oxidase (XO), myeloperoxidase (MPO) and adenosine deaminase (ADA) activities were also evaluated in the same samples. RESULTS: Although the study showed several positive but non-significant findings ($p > 0.05$), we did not find significant differences among all of the exposed groups and sham groups in lipid peroxidation levels and enzyme activities ($p > 0.05$) at all strengths and in both directions. Furthermore, the result was the same when the comparison was made between the groups in vertical directions and horizontal directions ($p > 0.05$). CONCLUSION: The present study observed effects of 50 Hz EF exposure on lipid peroxidation levels and antioxidant defense mechanisms but these were not

statistically significant at the 95% confidence level. Further research on the effects ELF-EF exposure on lipid peroxidation levels and antioxidant defence mechanisms are warranted.

(E) (VO, AE, TFR, DFR) Van Huizen AV, Morton JM, Kinsey LJ, Von Kannon DG, Saad MA, Birkholz TR, Czajka JM, Cyrus J, Barnes FS, Beane WS. Weak magnetic fields alter stem cell-mediated growth. Sci Adv. 5(1):eaau7201, 2019.

Biological systems are constantly exposed to electromagnetic fields (EMFs) in the form of natural geomagnetic fields and EMFs emitted from technology. While strong magnetic fields are known to change chemical reaction rates and free radical concentrations, the debate remains about whether static weak magnetic fields (WMFs; <1 mT) also produce biological effects. Using the planarian regeneration model, we show that WMFs altered stem cell proliferation and subsequent differentiation via changes in reactive oxygen species (ROS) accumulation and downstream heat shock protein 70 (Hsp70) expression. These data reveal that on the basis of field strength, WMF exposure can increase or decrease new tissue formation in vivo, suggesting WMFs as a potential therapeutic tool to manipulate mitotic activity.

(NE) (VT, AE) Vannoni D, Albanese A, Battisti E, Aceto E, Giglioni S, Corallo C, Carta S, Ferrata P, Fioravanti A, Giordano N. In vitro exposure of human osteoarthritic chondrocytes to ELF fields and new therapeutic application of musically modulated electromagnetic fields: biological evidence. J Biol Regul Homeost Agents. 26(1):39-49, 2012.

Osteoarthritis (OA) is the most frequently occurring rheumatic disease, caused by metabolic changes in chondrocytes, the cells that maintain cartilage. Treatment with electromagnetic fields (MF) produces benefits in patients affected by this pathology. Isolated human osteoarthritic (OA) chondrocytes were cultured in vitro under standard conditions or stimulated with IL-1beta or IGF-1, to mimic the imbalance between chondroformation and chondroresorption processes observed in OA cartilage in vivo. The cells were exposed for a specific time to extremely low frequency (ELF; 100-Hz) electromagnetic fields and to the Therapeutic Application of Musically Modulated Electromagnetic Fields (TAMMEF), which are characterized by variable frequencies, intensities, and waveforms. Using flow cytometry, we tested the effects of the different types of exposure on chondrocyte metabolism. The exposure of the cells to both systems enhances cell proliferation, does not generate reactive oxygen species, does not cause glutathione depletion or changes in mitochondrial transmembrane potential and does not induce apoptosis. This study presents scientific support to the fact that MF could influence OA chondrocytes from different points of view (viability, ROS production and apoptosis). We can conclude that both ELF and TAMMEF systems could be recommended for OA therapy and represent a valid non-pharmacological approach to the treatment of this pathology.

(E) (VT, AE, IFR, IOD) Vergallo C, Panzarini E, Tenuzzo BA, Mariano S, Tata AM, Dini L. Moderate Static Magnetic Field (6 mT)-Induced Lipid Rafts Rearrangement Increases Silver NPs Uptake in Human Lymphocytes. Molecules. 25(6):1398, 2020.

One of the most relevant drawbacks in medicine is the ability of drugs and/or imaging agents to reach cells. Nanotechnology opened new horizons in drug delivery, and silver nanoparticles (AgNPs) represent a promising delivery vehicle for their adjustable size and shape, high-density surface ligand attachment, etc. AgNPs cellular uptake involves different endocytosis mechanisms, including lipid raft-mediated endocytosis. Since static magnetic fields (SMFs) exposure induces plasma membrane perturbation, including the rearrangement of lipid rafts, we investigated whether SMF could increase the amount of AgNPs able to pass the peripheral blood lymphocytes (PBLs) plasma membrane. To this purpose, the effect of 6-mT SMF exposure on the redistribution of two main lipid raft components (i.e., disialoganglioside GD3, cholesterol) and on AgNPs uptake efficiency was investigated. Results showed that 6 mT SMF: (i) induces a time-dependent GD3 and cholesterol redistribution in plasma membrane lipid rafts and modulates gene expression of ATP-binding cassette transporter A1 (ABCA1), (ii) increases reactive oxygen species (ROS) production and lipid peroxidation, (iii) does not induce cell death and (iv) induces lipid rafts rearrangement, that, in turn, favors the uptake of AgNPs. Thus, it derives that SMF exposure could be exploited to enhance the internalization of NPs-loaded therapeutic or diagnostic molecules.

(E) (VO, CE, DFR, DAO) Vignola MB, Dávila S, Cremonezzi D, Simes JC, Palma JA, Campana VR. Evaluation of inflammatory biomarkers associated with oxidative stress and histological assessment of magnetic therapy on experimental myopathy in rats. Electromagn Biol Med. 31(4):320-332. 2012.

The effect of pulsed electromagnetic field (PEMF) therapy, also called magnetic therapy, upon inflammatory biomarkers associated with oxidative stress plasma fibrinogen, nitric oxide (NO), L-citrulline, carbonyl groups, and superoxide dismutase (SOD) was evaluated through histological assessment, in rats with experimental myopathy. The groups studied were: (A) control (intact rats that received PEMF sham exposures); (B) rats with myopathy and sacrificed 24 h later; (C) rats with myopathy; (D) rats with myopathy and treated with PEMF; and (E) intact rats treated with PEMF. Groups A, C, D, and E were sacrificed 8 days later. Myopathy was induced by injecting 50 μl of 1% carrageenan λ (type IV) once sub-plantar. Treatment was carried out with PEMF emitting equipment with two flat solenoid disks for 8 consecutive days in groups D and E, at 20 mT and 50 Hz for 30 min/day/rat. The biomarkers were determined by spectrophotometry. The muscles (5/8) were stained with Hematoxylin-Eosin and examined by optic microscopy. Quantitative variables were statistically analyzed by the Fisher test, and categorical applying Pearson's Chi Squared test at $p < 0.05$ for

all cases. In Groups B and C, the biomarkers were significantly increased compared to A, D, and E groups: fibrinogen ($p < 0.001$); NO, L-citrulline and carbonyl groups ($p < 0.05$); SOD ($p < 0.01$) as well as the percentage of area with inflammatory infiltration ($p < 0.001$). PEMF caused decreased levels of fibrinogen, L-citrulline, NO, SOD, and carbonyl groups and significant muscle recovery in rats with experimental myopathies.

(E) (VT, AE, IAO) Villarini M, Moretti M, Scassellati-Sforzolini G, Boccioli B, Pasquini R. Effects of co-exposure to extremely low frequency (50 Hz) magnetic fields and xenobiotics determined in vitro by the alkaline comet assay. Sci Total Environ. 361(1-3):208-219, 2006.

In the present study, we used human peripheral blood leukocytes from 4 different donors, to investigate in vitro the possible genotoxic and/or co-genotoxic activity of extremely low frequency magnetic fields (ELF-MF) at 3 mT intensity. Two model mutagens were used to study the possible interaction between ELF-MF and xenobiotics: N-methyl-N'- nitro-N-nitrosoguanidine (MNNG) and 4-nitroquinoline N-oxide (4NQO). Primary DNA damage was evaluated by the alkaline single-cell microgel-electrophoresis ("comet") assay. Control cells (leukocytes not exposed to ELF-MF, nor treated with genotoxins) from the different blood donors showed a comparable level of basal DNA damage, whereas the contribution of individual susceptibility toward ELF-MF and the tested genotoxic compounds led to differences in the extent of DNA damage observed following exposure to the genotoxins, both in the presence and in the absence of an applied ELF-MF. A 3 mT ELF-MF alone was unable to cause direct primary DNA damage. In leukocytes exposed to ELF-MF and genotoxins, the extent of MNNG-induced DNA damage increased with exposure duration compared to sham-exposed cells. The opposite was observed in cells treated with 4NQO. In this case the extent of 4NQOinduced DNA damage was somewhat reduced in leukocytes exposed to ELF-MF compared to sham-exposed cells. Moreover, in cells exposed to ELF-MF an increased concentration of GSH was always observed, compared to sham-exposed cells. Since following GSH conjugation the genotoxic pattern of MNNG and 4NQO is quite different, an influence of ELF-MF on the activity of the enzyme involved in the synthesis of GSH leading to different activation/deactivation of the model mutagens used was hypothesized to explain the different trends observed in MNNG and 4NQO genotoxic activity in the presence of an applied ELF-MF. The possibility that ELF-MF might interfere with the genotoxic activity of xenobiotics has important implications, since human populations are likely to be exposed to a variety of genotoxic agents concomitantly with exposure to this type of physical agent.

(NE) (VT, AE, IAO) Villarini M, Gambelunghe A, Giustarini D, Ambrosini MV, Fatigoni C, Rossi R, Dominici L, Levorato S, Muzi G, Piobbico D, Mariucci G. No evidence of DNA damage by co-exposure to extremely low frequency magnetic fields and aluminum on neuroblastoma cell lines. Mutat Res. 823:11-21, 2017.

Whether exposure to 50-60Hz extremely low frequency magnetic fields (ELF-MF) exerts neurotoxic effects is a debated issue. Analogously, the potential role of Aluminum (Al) in neurodegeneration is a matter of controversial debate. As all living organisms are exposed to ELF-MF and/or Al daily, we found investigating the early effects of co-exposure to ELF-MF and Al in SH-SY5Y and SK-N-BE-2 human neuroblastoma (NB) cells intriguing. SH-SY5Y5 and SK-N-BE-2 cells underwent exposure to 50Hz ELF-MF (0.01, 0.1 or 1mT) or $AlCl_3$ (4 or 40μM) or co-exposure to 50Hz ELF-MF and $AlCl_3$ for 1h continuously or 5h intermittently. The effects of the treatment were evaluated in terms of DNA damage, redox status changes and Hsp70 expression. The DNA damage was assessed by Comet assay; the cellular redox status was investigated by measuring the amount of reduced glutathione (GSH) and glutathione disulfide (GSSG) while the inducible Hsp70 expression was evaluated by western blot analysis and real-time RT-PCR. Neither exposure to ELF-MF or $AlCl_3$ alone induced DNA damage, changes in GSH/GSSG ratio or variations in Hsp70 expression with respect to the controls in both NB cell lines. Similarly, co-exposure to ELF-MF and $AlCl_3$ did not have any synergic toxic effects. The results of this in vitro study, which deals with the effects of co-exposure to 50Hz MF and Aluminum, seem to exclude that short-term exposure to ELF-MF in combination with Al can have harmful effects on human SH-SY5Y and SK-N-BE-2 cells.

Vojtísek M, Knotková J, Kasparová L, Svandová E, Markvartová V, Tůma J, Vozeh F, Patková J. Metal, EMF, and brain energy metabolism. Electromagn Biol Med. 28(2):188-193, 2009. (Review)

Some implications of cooperative potential of metal ions and electromagnetic fields' radiation (EMF) in carcinogenic processes are discussed. It is known that these factors, chemical and physical individually have connections with processes of oxidative stress. Special attention was paid to possible manifestation within the brain. Therefore, the entry of a few potentially neurotoxic metals into the brain is discussed.

(E) (VT, AE, IFR) Wang D, Zhang L, Shao G, Yang S, Tao S, Fang K, Zhang X. 6-mT 0-120-Hz magnetic fields differentially affect cellular ATP levels. Environ Sci Pollut Res Int 25(28):28237-28247, 2018.

Adenosine triphosphate (ATP), an indispensable molecule that provides energy for essentially all cellular processes, has been shown to be affected by some magnetic fields (MFs). Although people are frequently exposed to various static and power frequency MFs in their daily lives, the exact effects of these MFs of different frequencies have not been systematically investigated. Here, we tested 6-mT MFs with 0, 50, and 120 Hz for their effects on cellular ATP levels in 11 different cell lines. We found that the 6-mT static magnetic field (SMF) either does not affect or increase cellular ATP levels, while 6-mT 50-Hz MF either does not affect or decrease cellular ATP levels. In contrast, 6-mT 120-Hz MF has variable effects. We examined the mitochondrial membrane potential (MMP) as well as reactive oxygen species (ROS) in four different cell lines, but did not find their direct correlation with ATP levels. Although

none of the ATP level changes induced by these three different frequencies of 6-mT MFs are dramatic, these results may be used to explain some differential cellular responses of various cell lines to different frequency MFs.

Wang H, Zhang X. Magnetic fields and reactive oxygen species. Int J Mol Sci. 18(10), 2017, pii: E2175. doi: 10.3390/ijms18102175 Review. (Review)

Reactive oxygen species (ROS) ubiquitously exist in mammalian cells to participate in various cellular signaling pathways. The intracellular ROS levels are dependent on the dynamic balance between ROS generation and elimination. In this review, we summarize reported studies about the influences of magnetic fields (MFs) on ROS levels. Although in most cases, MFs increased ROS levels in human, mouse, rat cells, and tissues, there are also studies showing that ROS levels were decreased or not affected by MFs. Multiple factors could cause these discrepancies, including but not limited to MF type/intensity/frequency, exposure time and assay time-point, as well as different biological samples examined. It will be necessary to investigate the influences of different MFs on ROS in various biological samples systematically and mechanistically, which will be helpful for people to get a more complete understanding about MF-induced biological effects. In addition, reviewing the roles of MFs in ROS modulation may open up new scenarios of MF application, which could be further and more widely adopted into clinical applications, particularly in diseases that ROS have documented pathophysiological roles.

Wang S, Luo J, Zhang Z, Dong D, Shen Y, Fang Y, Hu L, Liu M, Dai C, Peng S, Fang Z, Shang P. Iron and magnetic: new research direction of the ferroptosis-based cancer therapy. Am J Cancer Res. 8(10):1933-1946, 2018. (Review)

Ferroptosis is an iron depend cell death which caused by lipid peroxidation. Abnormal iron metabolism and high intracellular iron content are the characteristics of most cancer cells. Iron is a promoter of cell growth and proliferation. However, iron also could take part in Fenton reaction to produce reactive oxygen species (ROS). The intercellular ROS could induce lipid peroxidation, which is necessary for ferroptosis. Iron metabolism mainly includes three parts: iron uptake, storage and efflux. Therefore, iron metabolism-related genes could regulate intercellular iron content and status, which can be involved ferroptosis. In recent years, the application of nanoparticles in cancer therapy research has become more and more extensive. The iron-based nanoparticles (iron-based NPs) can release ferrous (Fe^{2+}) or ferric (Fe^{3+}) in acidic lysosomes and inducing ferroptosis. Magnetic field is widely used in the targeted concentration of iron-based NPs related disease therapy. Furthermore, multiple studies showed that magnetic fields can inhibit cancer cell proliferation by promoting intracellular ROS production. Herein, we focus on the relationship of between ferroptosis and iron metabolism in cancer cells, the application of nanoparticles and magnetic field in inducing ferroptosis of cancer cells, and trying to provide new ideas for cancer treatment research.

(NE) (VT, VO, AE, LE. IFR) Wang Y, Liu X, Zhang Y, Wan B, Zhang J, He W, Hu D, Yang Y, Lai J, He M, Chen C. Exposure to a 50 Hz magnetic field at 100 μT exerts no DNA damage in cardiomyocytes. Biol Open. 2019;8(8). pii: bio041293.

The effects of exposure to magnetic fields (MFs) at electric frequencies (50-60 Hz) on carcinogenicity are still in debate. Whether exposure to MFs affects the heart is also a debated issue. This study aimed to determine whether exposure to extremely low frequency MFs (ELF-MFs) induced DNA damage in cardiomyocytes both *in vitro* and *in vivo* Human ventricular cardiomyocytes were exposed to 50 Hz ELF-MF at 100 μT for 1 h continuously or 75 min intermittently. The effects of the treatments were evaluated by DNA damage, redox status changes and relative signal molecular expression. Moreover, ten male Sprague-Dawley rats were exposed to a 50 Hz MF at 100 μT for 7 days, while another 10 rats were sham exposed. The protein levels of p53 and Hsp70 in heart tissue were analyzed by western blot. The results showed that exposure to ELF-MF did not induce DNA damage, changes to cell cycle distribution or increased reactive oxygen species level. No significant differences were detected in p53 and Hsp70 expression level between the ELF-MF and sham-exposure groups both *in vitro* and *in vivo* All these data indicate that MFs at power-frequency may not cause DNA damage in cardiomyocytes.

(E) (CE) (IAO) Wang **Y,** Sun **Y,** Zhang **Z,** Li **Z,** Zhang **H,** Liao **Y,** Tang **C,** Cai **P. Enhancement in the ATP level and antioxidant capacity of *Caenorhabditis elegans* under continuous exposure to extremely low-frequency electromagnetic field for multiple generations. Int J Radiat Biol 96(12): 1633-1640, 2020.**

Purpose: Safety concerns about the effects of long-term extremely low-frequency electromagnetic field (ELF-EMF) exposure on human health have been raised. To explore the effects of continuous exposure to ELF-EMF on organisms for multiple generations, we selected *Caenorhabditis elegans* as a model organism and conducted long-term continuous exposure studies for multiple generations under 20 °C, 50 Hz, and 3 mT ELF-EMF. **Materials and methods:** Each generation of worms was treated with ELF-EMF from the egg in the same environment. After long-term exposure to ELF-EMF, the body length of the worms was detected, and 15th generation adult worms were selected as the research object. The ATP level and ATPase were detected, and the expression levels of genes encoding ATP synthase (*r53.4, hpo-18, atp-5, unc-32, atp-3*) were detected by RT-PCR. In worm's antioxidant system, the level of reactive oxygen species (ROS) was detected by dichlorofluorescein staining, and the total antioxidant capacity (T-AOC), superoxide dismutase (SOD) and catalase (CAT) activity were investigated. The expression of genes encoding superoxide dismutase (*sod-1, sod-2, sod-3*) was detected in adult (60 h) worms of the fifteenth generation (F15). **Results:** These results showed that the body length of F15 worms increased significantly, ATP content increased significantly, ATP synthase activity was significantly enhanced, and the expression levels of the *r53.4, hpo-18, atp-5*, and *atp-3* genes encoding ATPase were significantly upregulated in F15 worms. In addition, SOD activity increased significantly, and the expression levels of the *sod-1, sod-2,* and *sod-3* genes encoding SOD were also significantly upregulated in F15 worms. **Conclusions:** These results indicated that continuous exposure to 50 Hz, 3 mT ELF-EMF for multiple generations can increase the body length of worms, induce the synthesis of ATP and enhance the antioxidant capacity of worms.

(E) (VT, AE, AO, IAO, AO) Wartenberg M, Wirtz N, Grob A, Niedermeier W, Hescheler J, Peters SC, Sauer H. Direct current electrical fields induce apoptosis in oral mucosa cancer cells by NADPH oxidase-derived reactive oxygen species. Bioelectromagnetics. 29(1):47-54, 2008.

The presence of more than one dental alloy in the oral cavity often causes pathological galvanic currents and voltage resulting in superficial erosions of the oral mucosa and eventually in the emergence of oral cancer. In the present study the mechanisms of apoptosis of oral mucosa cancer cells in response to electromagnetic fields was investigated. Direct current (DC) electrical fields with field strengths between 2 and 16 V/m, applied for 24 h to UM-SCC-14-C oral mucosa cancer cells, dose-dependently resulted in decreased cell proliferation as evaluated by Ki-67 immunohistochemistry and upregulation of the cyclin-dependent kinase (CDK) inhibitors p21(cip1/waf1) and p27(kip1), which are associated with cell cycle arrest. Electrical field treatment (4 V/m, 24 h) increased apoptosis as evaluated by immunohistochemical analysis of cleaved caspase-3 and poly-(ADP-ribose)-polymerase-1 (PARP-1). Furthermore, robust reactive oxygen species (ROS) generation, increased expression of NADPH oxidase subunits as well as Hsp70 was observed. Electrical field treatment (4 V/m, 24 h) resulted in increased expression of Cu/Zn superoxide dismutase and decreased intracellular concentration of reduced glutathione (GSH), whereas the expression of catalase remained unchanged. Pre-treatment with the free radical scavenger N-acetyl cysteine (NAC) and the superoxide dismutase mimetic EUK-8 abolished caspase-3 and PARP-1 induction, suggesting that apoptosis in oral mucosa cancer cells is initated by ROS generation in response to DC electrical field treatment.

E) (VT, CE, IFR. DAO) Wójcik-Piotrowicz K, Kaszuba-Zwoińska J, Piszczek P, Nowak B, Guzdek P, Gil K, Rokita E. Low-frequency electromagnetic fields influence the expression of calcium metabolism related proteins in leukocytic cell lines. Environ Toxicol Pharmacol 104:104320, 2023. (cell-types and wave-form dependent)

Our study aimed to verify the hypothesis concerning low-frequency magnetic fields (LF-MFs)-related changes in cell viability through the biomechanism(s) based on calcineurin (CaN)-mediated signaling pathways triggered via ROS-like molecules. For experiments, Mono Mac 6 and U937 leukocytic cell lines were chosen and exposed to various LF-MFs and/or puromycin (PMC). The protein expression level of key regulatory proteins of calcium metabolism was examined by Western Blot analysis. In turn, the reactive oxygen species (ROS) and cell viability parameters were evaluated by cytochrome C reduction assay and flow cytometry, respectively. The simultaneous action of applied MF and PMC influenced cell viability in a MF-dependent manner. The changes in cell viability were correlated with protein expression and ROS levels. It was verified experimentally that applied stress stimuli influence cell susceptibility to undergo cell death. Moreover, the evoked bioeffects might be recognized as specific to both types of leukocyte populations.

(E) (VT, AE, IOD, IFR, AO) Wolf FI, Torsello A, Tedesco B, Fasanella S, Boninsegna A, D'Ascenzo M, Grassi C, Azzena GB, Cittadini A. 50-Hz extremely low frequency electromagnetic fields enhance cell proliferation and DNA damage: possible involvement of a redox mechanism. Biochim Biophys Acta. 1743(1-2):120-129, 2005.

HL-60 leukemia cells, Rat-1 fibroblasts and WI-38 diploid fibroblasts were exposed for 24-72 h to 0.5-1.0-mT 50-Hz extremely low frequency electromagnetic field (ELF-EMF). This treatment induced a dose-dependent increase in the proliferation rate of all cell types, namely about 30% increase of cell proliferation after 72-h exposure to 1.0 mT. This was accompanied by increased percentage of cells in the S-phase after 12- and 48-h exposure. The ability of ELF-EMF to induce DNA damage was also investigated by measuring DNA strand breaks. A dose-dependent increase in DNA damage was observed in all cell lines, with two peaks occurring at 24 and 72 h. A similar pattern of DNA damage was observed by measuring formation of 8-OHdG adducts. The effects of ELF-EMF on cell proliferation and DNA damage were prevented by pretreatment of cells with an antioxidant like alpha-tocopherol, suggesting that redox reactions were involved. Accordingly, Rat-1 fibroblasts that had been exposed to ELF-EMF for 3 or 24 h exhibited a significant increase in dichlorofluorescein-detectable reactive oxygen species, which was blunted by alpha-tocopherol pretreatment. Cells exposed to ELF-EMF and examined as early as 6 h after treatment initiation also exhibited modifications of NF kappa B-related proteins (p65-p50 and I kappa B alpha), which were suggestive of increased formation of p65-p50 or p65-p65 active forms, a process usually attributed to redox reactions. These results suggest that ELF-EMF influence proliferation and DNA damage in both normal and tumor cells through the action of free radical species. This information may be of value for appraising the pathophysiologic consequences of an exposure to ELF-EMF.

(E) (VO, CE, IAO) Wu SX, Xu YQ, Di GQ, Jiang JH, Xin L, Wu TY. Influence of environmental static electric field on antioxidant enzymes activities in hepatocytes of mice. Genet Mol Res. Genet Mol Res. 15(3), 2016. doi: 10.4238/gmr.15038800.

With the increasing voltage of direct current transmission line, the intensity of the environmental static electric field has also increased. Thus, whether static electric fields cause biological injury is an important question. In this study, the effects of chronic exposure to environmental static electric fields on some antioxidant enzymes activities in the hepatocytes of mice were investigated. Male Institute of Cancer Research mice were exposed for 35 days to environmental static electric fields of different electric field intensities of 9.2-21.85 kV/m (experiment group I, EG-I), 2.3-15.4 kV/m (experiment group II, EG-II), and 0 kV/m (control group, CG). On days 7, 14, 21, and 35 of the exposure cycle, liver homogenates were obtained and the activities of antioxidant enzymes like superoxide dismutase, glutathione S-transferase, and glutathione peroxidase were determined, as well as the concentration of malonaldehyde. The results revealed a significant increase in superoxide dismutase activity in both EG-I and EG-II on the 7th ($P < 0.05$) and 35th days ($P < 0.01$) of the exposure cycle compared to that in the control group. However, the other test indices such as glutathione S-transferase, glutathione peroxidase, and malonaldehyde showed only minimal changes during the exposure cycle. These

results revealed a weak relationship between the exposure to environmental static electric fields and hepatic oxidative stress in living organisms.

(E) (VO, AE, DFR) Xu J, Liu K, Chen T, Zhan T, Ouyang Z, Wang Y, Liu W, Zhang X, Sun Y, Xu G, Wang X. Rotating magnetic field delays human umbilical vein endothelial cell aging and prolongs the lifespan of *Caenorhabditis elegans*. Aging (Albany NY). 11(22):10385-10408, 2019.

The biological effects of magnetic fields are a research hotspot in the field of biomedical engineering. In this study, we further investigated the effects of a rotating magnetic field (RMF; 0.2 T, 4 Hz) on the growth of human umbilical vein endothelial cells (HUVECs) and *Caenorhabditis elegans*. The results showed that RMF exposure prolonged the lifespan of *C. elegans* and slowed the aging of HUVECs. RMF treatment of HUVECs showed that activation of adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) was associated with decreased mitochondrial membrane potential (MMP) due to increased intracellular Ca^{2+} concentrations induced by endoplasmic reticulum stress in anti-aging mechanisms. RMF also promoted the health status of *C. elegans* by improving activity, reducing age-related pigment accumulation, delaying Aβ-induced paralysis and increasing resistance to heat and oxidative stress. The prolonged lifespan of *C. elegans* was associated with decreased levels of daf-16 which related to the insulin/insulin-like growth factor signaling pathway (IIS) activity and reactive oxygen species (ROS), whereas the heat shock transcription factor-1 (hsf-1) pathway was not involved. Moreover, the level of autophagy was increased after RMF treatment. These findings expand our understanding of the potential mechanisms by which RMF treatment prolongs lifespan.

(E) (VT, AE, IFR, AO) Yang ML, Ye ZM. [Extremely low frequency electromagnetic field induces apoptosis of osteosarcoma cells via oxidative stress]. Zhejiang Da Xue Xue Bao Yi Xue Ban. 44(3):323-328, 2015. [Article in Chinese]

OBJECTIVE: To investigate the effects of extremely low frequency electromagnetic field (ELF-EMF) on human osteosarcoma cells and its mechanisms. METHODS: Human osteosarcoma MG-63 cells were exposed to 50 Hz,1 mT ELF-EMF for 1, 2 and 3 h in vitro, with or without pretreatment by reactive oxygen species (ROS) inhibitor N acetylcysteine (NAC) or p38MAPK inhibitor SB203580. The proliferation of MG-63 cells was determined by MTT method; the apoptosis rate and ROS level in MG-63 cells were detected by flow cytometry. The expression of p38MAPK in MG-63 cells was determined by Western blotting. RESULTS: ELF-EMF decreased the viability of MG-63 cells, inhibited cell growth, induced cell apoptosis and increased the level of ROS significantly. The apoptosis rate declined significantly after treatment with ROS inhibitor NAC or p38MAPK inhibitor SB203580. After exposure to ELF-EMF, p38MAPK in MG-63 cells was activated, and the phosphorylation level was also inhibited after

treatment with NAC. CONCLUSION: ELF-EMF can induce the apoptosis of MG-63 cells. Increased ROS and p38MAPK activation may be involved in the mechanism.

(E)(VO, IV, IFR) Yang LL, Zhou Y, Tian WD, Li HJ, Kang-Chu-Li, Miao X, An GZ, Wang XW, Guo GZ, Ding GR.· Electromagnetic pulse activated brain microglia via the p38 MAPK pathway. Neurotoxicology. 52:144-149, 2016.
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Previously, we found that electromagnetic pulses (EMP) induced an increase in blood brain barrier permeability and the leakage of albumin from blood into brain tissue. Albumin is known to activate microglia cells. Thus, we hypothesised that microglia activation could occur in the brain after EMP exposure. To test this hypothesis, the morphology and secretory function of microglia cells, including the expression of OX-42 (a marker of microglia activation), and levels of TNF-α, IL-10, IL-1β, and NO were determined in the rat cerebral cortex after EMP exposure. In addition, to examine the signalling pathway of EMP-induced microglia activation, protein and phosphorylated protein levels of p38, JNK and ERK were determined. It was found that the expression of OX-42increased significantly at 1, 6 and 12h ($p<0.05$) and recovered to the sham group level at 24h after EMP exposure. Levels of NO, TNF-α and IL-10 also changed significantly in vivo and in vitro after EMP exposure. The protein level of p38 and phosphorylated p38 increased significantly after EMP exposure ($p<0.05$) and recovered to sham levels at 12 and 24h, respectively. Protein and phosphorylated protein levels of ERK and JNK did not change. SB203580 (p38 inhibitor) partly prevented the change in NO, IL-10, IL-1β, TNF-α levels induced by EMP exposure. Taken together, these results suggested that EMP exposure (200kV/m, 200 pulses) could activate microglia in rat brain and affect its secretory function both in vivo and in vitro, and the p38 pathway is involved in this process.

(E) (VT, AE, IFR, AO)Yin C, Luo X, Duan Y, Duan W, Zhang H, He Y, Sun G, Sun X. Neuroprotective effects of lotus seedpod procyanidins on extremely low frequency electromagnetic field-induced neurotoxicity in primary cultured hippocampal neurons. Biomed Pharmacother. 82:628-639, 2016.

The present study investigated the protective effects of lotus seedpod procyanidins (LSPCs) on extremely low frequency electromagnetic field (ELF-EMF)-induced neurotoxicity in primary cultured rat hippocampal neurons and the underlying molecular mechanism. The results of MTT, morphological observation, superoxide dismutase (SOD) and malondialdehyde (MDA) assays showed that compared with control, incubating neurons under ELF-EMF exposure significantly decreased cell viability and increased

the number of apoptotic cells, whereas LSPCs evidently protected the hippocampal neurons against ELF-EMF-induced cell damage. Moreover, a certain concentration of LSPCs inhibited the elevation of intracellular reactive oxygen species (ROS) and Ca(2+) level, as well as prevented the disruption of mitochondrial membrane potential induced by ELF-EMF exposure. In addition, supplementation with LSPCs could alleviate DNA damage, block cell cycle arrest at S phase, and inhibit apoptosis and necrosis of hippocampal neurons under ELF-EMF exposure. Further study demonstrated that LSPCs up-regulated the activations of Bcl-2, Bcl-xl proteins and suppressed the expressions of Bad, Bax proteins caused by ELF-EMF exposure. In conclusion, these findings revealed that LSPCs protected against ELF-EMF-induced neurotoxicity through inhibiting oxidative stress and mitochondrial apoptotic pathway.

(E) (VO, CE, IOD) Yokus B, Cakir DU, Akdag MZ, Sert C, Mete N. Oxidative DNA damage in rats exposed to extremely low frequency electromagnetic fields. Free Radic Res. 39(3):317-323, 2005.

Extremely low frequency (ELF) electromagnetic field (EMF) is thought to prolong the life of free radicals and can act as a promoter or co-promoter of cancer. 8-hydroxy-2'-deoxyguanosine (8OHdG) is one of the predominant forms of radical-induced lesions to DNA and is a potential tool to asses the cancer risk. We examined the effects of extremely low frequency electro magnetic field (ELF-EMF) (50 Hz, 0.97 mT) on 8OHdG levels in DNA and thiobarbituric acid reactive substances (TBARS) in plasma. To examine the possible time-dependent changes resulting from magnetic field, 8OHdG and TBARS were quantitated at 50 and 100 days. Our results showed that the exposure to ELF-EMF induced oxidative DNA damage and lipid peroxidation (LPO). The 8OHdG levels of exposed group (4.39+/-0.88 and 5.29+/-1.16 8OHdG/dG.10(5), respectively) were significantly higher than sham group at 50 and 100 days (3.02+/-0.63 and 3.46+/-0.38 8OHdG/dG.10(5)) ($p<0.001$, $p<0.001$). The higher TBARS levels were also detected in the exposure group both on 50 and 100 days ($p<0.001$, $p<0.001$). In addition, the extent of DNA damage and LPO would depend on the exposure time ($p<0.05$ and $p<0.05$). Our data may have important implications for the long-term exposure to ELF-EMF which may cause oxidative DNA damage.

(E) (VO, CE, IOD) Yokus B, Akdag MZ, Dasdag S, Cakir DU, Kizil M. Extremely low frequency magnetic fields cause oxidative DNA damage in rats. Int J Radiat Biol. 84(10):789-795, 2008.

PURPOSE: To detect the genotoxic effects of extremely low frequency (ELF) -magnetic fields (MF) on oxidative DNA base modifications [8-hydroxyguanine (8-OH-Gua), 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua) and 4,6-diamino-5-formamidopyrimidine (FapyAde)] in rat leucocytes, measured following exposure to ELF-MF. MATERIALS AND METHODS: After exposure to ELF-MF (50 Hz, 100 and 500 microT, for 2 hours/day during 10 months), DNA was extracted, and measurement of DNA lesions was achieved by gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS). RESULTS: Levels of FapyAde, FapyGua and 8OHdG in DNA were increased by both 100 microT and 500 microT ELF-MF as compared to a cage-control and a sham group; however, statistical significance was observed only in the group exposed to 100

microT. CONCLUSION: This is the first study to report that ELF-MF exposure generates oxidatively induced DNA base modifications which are mutagenic in mammalian cells, such as FapyGua, FapyAde and 8-OH-Gua, in vivo. This may explain previous studies showing DNA damage and genomic instability. These findings support the hypothesis that chronic exposure to 50-Hz MF may be potentially genotoxic. However, the intensity of ELF-MF has an important influence on the extent of DNA damage.

(NE) (VT, AE) Yoon HE, Lee JS, Myung SH, Lee YS. Increased γ-H2AX by exposure to a 60-Hz magnetic fields combined with ionizing radiation, but not hydrogen peroxide, in non-tumorigenic human cell lines. Int J Radiat Biol. 90(4):291-298, 2014.

Abstract Purpose: Genotoxic effects have been considered the gold standard to determine if an environmental factor is a carcinogen, but the currently available data for extremely low frequency time-varying magnetic fields (ELF-MFs) remain controversial. As an environmental stimulus, the effect of ELF-MF on cellular DNA may be subtle. Therefore, a more sensitive method and systematic research strategy are warranted to evaluate genotoxicity. Materials and methods: We investigated the effect of ELF-MFs in combination with ionizing radiation (IR) or H_2O_2 on the DNA damage response of expression of phosphorylated H2AX (γ-H2AX) and production of γ-H2AX foci in non-tumorigenic human cell systems consisting of human lung fibroblast WI38 cells and human lung epithelial L132 cells. Results: Exposure to a 60-Hz, 2 mT ELF-MFs for 6 h produced increased γ-H2AX expression, as well as γ-H2AX foci production, a common DNA double-strand break (DSB) marker. However, exposure to a 1 mT ELF-MFs did not have the same effect. Moreover, 2 mT ELF-MFs exposure potentiated the expression of γ-H2AX and γ-H2AX foci production when combined with IR, but not when combined with H_2O_2. Conclusions: ELF-MFs could affect the DNA damage response and, in combination with different stimuli, provide different effects on γ-H2AX.

(NE) (VO, AE, IX) Yoshikawa T, Tanigawa M, Tanigawa T, Imai A, Hongo H, Kondo M. Enhancement of nitric oxide generation by low frequency electromagnetic field. Pathophysiology. 7(2):131-135, 2000.

Oxidative stress is implicated in the intracellular signal transduction pathways for nitric oxide synthase (NOS) induction. The electromagnetic field (EMF) is believed to increase the free radical lifespan [S. Roy, Y. Noda, V. Eckert, M.G. Traber, A. Mori, R. Liburdy, L. Packer, The phorbol 12-myristate 13-acetate (PMA)-induced oxidative burst in rat peritoneal neutrophils is increased by a 0.1 mT (60 Hz) magnetic field, FEBS Lett. 376 (1995) 164-6; F.S. Prato, M. Kavaliers, J.J. Carson, Behavioural evidence that magnetic field effects in the land snail, Cepaea nemoralis, might not depend on magnetite or induced electric currents, Bioelectromagnetics 17 (1996) 123-30; A.L. Hulbert, J. Metcalfe, R. Hesketh, Biological response to electromagnetic fields, FASEB 12 (1998) 395-420]. We tested the effects of EMF on endotoxin induced nitric oxide (NO) generation in vivo. Male BALB/C mice were injected with lipopolysaccharide (LPS) intraperitoneously (i.p.), followed by the exposure to EMF (0.1 mT, 60 Hz). Five hours and 30 min after the LPS administration, mice were administered with a NO spin trap, ferrous N-methyl-D-glucaminedithiocarbamate

(MGD-Fe). Thirty minutes later, mice were sacrificed, and their livers were removed. The results were compared to three control groups: group A (LPS (-) EMF(-)); group B (LPS(-) EMF(+)); group C (LPS(+) EMF(-)). The ESR spectra of obtained livers were examined at room temperature. Three-line spectra of NO adducts were observed in the livers of all groups. In groups A and B very weak signals were observed, but in groups C and D strong spectra were observed. The signal intensity of the NO adducts in Group D was also significantly stronger than that in Group C. EMF itself did not induce NO generation, however, it enhanced LPS induced NO generation in vivo.

(E) (VT, CE, IOD, IFR, AO)Yuan LQ, Wang C, Lu DF, Zhao XD, Tan LH, Chen X. Induction of apoptosis and ferroptosis by a tumor suppressing magnetic field through ROS-mediated DNA damage. Aging (Albany NY). 12:3662-3681, 2020.

Magnetic field (MF) is being used in antitumor treatment; however, the underlying biological mechanisms remain unclear. In this study, the potency and mechanism of a previously published tumor suppressing MF exposure protocol were further investigated. This protocol, characterized as a 50 Hz electromagnetic field modulated by static MF with time-average intensity of 5.1 mT, when applied for 2 h daily for over 3 consecutive days, selectively inhibited the growth of a broad spectrum of tumor cell lines including lung cancer, gastric cancer, pancreatic cancer and nephroblastoma. The level of intracellular reactive oxygen species (ROS) increased shortly after field exposure and persisted. Subsequently, pronounced DNA damage and activation of DNA repair pathways were identified both in vitro and in vivo. Furthermore, use of free radical scavenger alleviated DNA damage and partially reduced cell death. Finally, this field was found to inhibit cell proliferation, and simultaneously induced two types of programmed cell death, apoptosis and ferroptosis. In conclusion, this tumor suppressing MF could determine cell fate through ROS-induced DNA damage, inducing oxidative stress and activation of the DNA damage repair pathways, eventually lead to apoptosis and ferroptosis, as well as inhibition of tumor growth.

(NE) (VT, AE, IFR) Zastko L, Makinistian L, Tvarožná A, Belyaev I. Intermittent ELF-MF Induce an Amplitude-Window Effect on Umbilical Cord Blood Lymphocytes. Int J Mol Sci 23(22):14391, 2022.

In a previous study of the effects of intermittent extremely low frequency (ELF) magnetic fields (MF) on umbilical cord blood lymphocytes (UCBL), we evaluated MF amplitudes between 6 μT and 24 μT and found an effect only for those below 13 μT. This suggested the existence of an amplitude window. In this brief communication, we further tested this hypothesis. UCBLs from healthy newborns were isolated and exposed for 72 h to an intermittent ELF-MF (triangular, 7.8 Hz, 250 s ON/250 s OFF) with 6 different amplitudes between 3 μT and 12 μT, utilizing an oblong coil. Percentage of viable, early apoptotic (EA), and late apoptotic/necrotic (LAN) cells were determined by flow cytometry. Moreover, reactive oxygen species (ROS) were determined at 1 h and 3 h of the exposure. Like in our previous work, neither EA, nor LAN, nor ROS were statistically significantly affected by the intermittent ELF-MF. However, the percentage of viable cells was decreased by exposure to the fields with intensities of 6.5 μT and 12 μT (p < 0.05; and $p = 0.057$ for 8.5 μT). ELF-MF decreased the percentage of viable cells for fields down to 6.5 μT, but not for 5 μT, 4 μT, or 3 μT. Combined with our previous findings, the results reported here indicate an amplitude window effect between 6 μT and 13 μT. The

obtained data are in line with a notion of amplitude and frequency windows, which request scanning of both amplitude and frequency while studying the ELF-MF effects.

(E) (VO, AE, DAO, IOD) Zeng L, Ji X, Zhang Y, Miao X, Zou C, Lang H, Zhang J, Li Y, Wang X, Qi H, Ren D, Guo G. MnSOD expression inhibited by electromagnetic pulse radiation in the rat testis. Electromagn Biol Med. 30(4):205-218, 2011

Male Sprague Dawley rats were exposed to EMP irradiation of 100 kV/m peak-to-peak e-field intensity and different numbers of pulses. Rat sperm samples were prepared for analysis of sperm qualities; Testes were assessed by transmission electron microscopy and serum hormone concentrations were examined by radioimmunoassay; Enzymatic activities of Total-superoxide dismutase(T-SOD) and manganese-superoxide dismutase (MnSOD), the mRNA levels of MnSOD and cuprozinc-superoxide dismutase (CuZnSOD), and the density of malondialdehyde (MDA) were also determined. EMP irradiation did not affect spermatozoon morphology, micronucleus formation rate, sperm number or viability, but the acrosin reaction rate decreased at 24 h and 48 h and recovered by 72 h after irradiation as compared to the controls. The ultrastructure of rat testis displayed more serious damage at 24 h than at other time points (6 h, 12 h, 48 h). Serum levels of luteotrophic hormone (LH) and testosterone (T) were elevated in irradiated rats as compared to controls. After irradiation, enzymatic activities of T-SOD and MnSOD were reduced by 24 h, consistent with the changes observed in MnSOD mRNA expression; MDA content increased at 6 h in turn. These studies have quantified the morphological damage and dysfunction in the rat reproductive system induced by EMP. The mechanism of EMP induced damage may be associated with the inhibition of MnSOD expression.

(E) (IV, AE, CE, IFR) Zeng Y, Shen Y, Hong L, Chen Y, Shi X, Zeng Q, Yu P. Effects of single and repeated exposure to a 50-Hz 2-mT electromagnetic field on rrimary cultured hippocampal neurons. Neurosci Bull. 33(3):299-306, 2017.

The prevalence of domestic and industrial electrical appliances has raised concerns about the health risk of extremely low-frequency magnetic fields (ELF-MFs). At present, the effects of ELF-MFs on the central nervous system are still highly controversial, and few studies have investigated its effects on cultured neurons. Here, we evaluated the biological effects of different patterns of ELF-MF exposure on primary cultured hippocampal neurons in terms of viability, apoptosis, genomic instability, and oxidative stress. The results showed that repeated exposure to 50-Hz 2-mT ELF-MF for 8 h per day after different times in culture decreased the viability and increased the production of intracellular reactive oxidative species in hippocampal neurons. The mechanism was potentially related to the up-regulation of Nox2 expression. Moreover, none of the repeated exposure patterns had significant effects on DNA

damage, apoptosis, or autophagy, which suggested that ELF-MF exposure has no severe biological consequences in cultured hippocampal neurons.

(E) (VO, CE, IAO, DFR, DOD) Zhai M, Zhang C, Cui J, Liu J, Li Y, Xie K, Luo E, Tang C. Electromagnetic fields ameliorate hepatic lipid accumulation and oxidative stress: potential role of CaMKKβ/AMPK/SREBP-1c and Nrf2 pathways. Biomed Eng Online 22(1):51, 2023.

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, and is related to disturbed lipid metabolism and redox homeostasis. However, a definitive drug treatment has not been approved for this disease. Studies have found that electromagnetic fields (EMF) can ameliorate hepatic steatosis and oxidative stress. Nevertheless, the mechanism remains unclear. **Methods:** NAFLD models were established by feeding mice a high-fat diet. Simultaneously, EMF exposure is performed. The effects of the EMF on hepatic lipid deposition and oxidative stress were investigated. Additionally, the AMPK and Nrf2 pathways were analysed to confirm whether they were activated by the EMF. **Results:** Exposure to EMF decreased the body weight, liver weight and serum triglyceride (TG) levels and restrained the excessive hepatic lipid accumulation caused by feeding the HFD. The EMF boosted CaMKKβ protein expression, activated AMPK phosphorylation and suppressed mature SREBP-1c protein expression. Meanwhile, the activity of GSH-Px was enhanced following an increase in nuclear Nrf2 protein expression by PEMF. However, no change was observed in the activities of SOD and CAT. Consequently, EMF reduced hepatic reactive oxygen species (ROS) and MDA levels, which means that EMF relieved liver damage caused by oxidative stress in HFD-fed mice. **Conclusions:** EMF may activate the CaMKKβ/AMPK/SREBP-1c and Nrf2 pathways to control hepatic lipid deposition and oxidative stress. This investigation indicates that EMF may be a novel therapeutic method for NAFLD.

(E) (VO, CE, IFR) Zhan A, Luo Y, Qin H, Lin W, Tian L. Hypomagnetic Field Exposure Affecting Gut Microbiota, Reactive Oxygen Species Levels, and Colonic Cell Proliferation in Mice. Bioelectromagnetics 43(8):462-475, 2022.

The gut microbiota has been considered one of the key factors in host health, which is influenced by many environmental factors. The geomagnetic field (GMF) represents one of the important environmental conditions for living organisms. Previous studies have shown that the elimination of GMF, the so-called hypomagnetic field (HMF), could affect the physiological functions and resistance to antibiotics of some microorganisms. However, whether long-term HMF exposure could alter the gut microbiota to some extent in mammals remains unclear. Here, we investigated the effects of long-term (8- and 12-week) HMF exposure on the gut microbiota in C57BL/6J mice. Our results clearly showed that 8-week HMF significantly affected the diversity and function of the mouse gut microbiota. Compared with the GMF group, the concentrations of short-chain fatty acids tended to decrease in the HMF group.

Immunofluorescence analysis showed that HMF promoted colonic cell proliferation, concomitant with an increased level of reactive oxygen species (ROS). To our knowledge, this is the first *in vivo* finding that long-term HMF exposure could affect the mouse gut microbiota, ROS levels, and colonic cell proliferation in the colon. Moreover, the changes in gut microbiota can be restored by returning mice to the GMF environment, thus the possible harm to the microbiota caused by HMF exposure can be alleviated.

(E) (VO, CE, DFR) Zhang, B.F.; Wang, L.; Zhan, A.S.; Wang, M.; Tian, L.X.; Guo, W.X.; Pan, Y.X. Long-term exposure to a hypomagnetic field attenuates adult hippocampal neurogenesis and cognition. Nat. Commun. 2021, 12, 1174.

Adult hippocampal neurogenesis contributes to learning and memory, and is sensitive to a variety of environmental stimuli. Exposure to a hypomagnetic field (HMF) influences the cognitive processes of various animals, from insects to human beings. However, whether HMF exposure affect adult hippocampal neurogenesis and hippocampus-dependent cognitions is still an enigma. Here, we showed that male C57BL/6 J mice exposed to HMF by means of near elimination of the geomagnetic field (GMF) exhibit significant impairments of adult hippocampal neurogenesis and hippocampus-dependent learning, which is strongly correlated with a reduction in the content of reactive oxygen species (ROS). However, these deficits seen in HMF-exposed mice could be rescued either by elevating ROS levels through pharmacological inhibition of ROS removal or by returning them back to GMF. Therefore, our results suggest that GMF plays an important role in adult hippocampal neurogenesis through maintaining appropriate endogenous ROS levels.

Zhang B, Tian L. Reactive Oxygen Species: Potential Regulatory Molecules in Response to Hypomagnetic Field Exposure. Bioelectromagnetics 41:573-580, 2020. (review)

Organisms, including humans, could be exposed to hypomagnetic fields (HMFs, intensity <5 μT), e.g. in some artificially shielded magnetic environments and during deep-space flights. Previous studies have demonstrated that HMF exposure could have negative effects on the central nervous system and embryonic development in many animals. However, the underlying mechanisms remain unknown. Studies have revealed that HMFs affect cellular reactive oxygen species (ROS) levels and thereby alter physiological and biological processes in organisms. ROS, the major component of highly active free radicals, which are ubiquitous in biological systems, were hypothesized to be the candidate signaling molecules that regulate diverse physiological processes in response to changes in magnetic fields. Here, we summarize the recent advances in the study of HMF-induced negative effects on the central nervous system and early embryonic development in animals, focusing on cellular ROS and their role in response to HMFs. Furthermore, we discuss the potential mechanism through which HMFs regulate ROS levels in cells.

(E) (HU, CE, IOD, AO) Zhang D, Zhang Y, Zhu B, Zhang H, Sun Y, Sun C. Resveratrol may reverse the effects of long-term occupational exposure to electromagnetic fields on workers of a power plant. Oncotarget. 8(29):47497-47506, 2017.

High-voltage electricity lines are known to generate extremely low-frequency electromagnetic fields (ELF-EMFs). With the process of urbanization, increasing concerns has been focused on the potentially hazardous impacts of ELF-EMF on human health, and the conclusions are controversial. Little is known about the method of prevention against ELF-EMF induced healthy problems. A total of 186 male workers with occupational exposure to high-voltage electricity lines, and 154 male subjects with insignificant exposure as reference control were enrolled in this study. Resveratrol or placebo was given as dietary supplements (500 mg twice daily), and several inflammatory biomarkers and biomarkers of oxidative stress were assessed. Workers who had long-term exposure to high-voltage electricity lines exhibited elevated urinary levels of 8-hydroxy-2-deoxy-guanosine (8-OHdG) and F2-isoprostane, compared to the reference group. Lower plasma nuclear factor kappa B (NF-κB) and interleukin (IL)-6 were observed in exposed workers compared to the reference group. Resveratrol significantly reversed the adverse impacts of ELF-EMF. Stimulated cytokine production by resveratrol was found in exposed workers but not in the reference group. This study supported that occupational and long-term exposure to high-voltage electricity lines has an adverse effect on homeostasis of human body, and resveratrol supplement could be an effective protection strategy against the adverse effects induced by ELF-EMFs.

Zhang J, Ding C, Ren L, Zhou Y, Shang P. The effects of static magnetic fields on bone. Prog Biophys Mol Biol. 114(3):146-152, 2014. (review)

All the living beings live and evolve under geomagnetic field (25-65 μT). Besides, opportunities for human exposed to different intensities of static magnetic fields (SMF) in the workplace have increased progressively, such SMF range from weak magnetic field (<1 mT), moderate SMF (1 mT-1 T) to high SMF (>1 T). Given this, numerous scientific studies focus on the health effects and have demonstrated that certain magnetic fields have positive influence on our skeleton systems. Therefore, SMF is considered as a potential physical therapy to improve bone healing and keep bones healthy nowadays. Here, we review the mechanisms of effects of SMF on bone tissue, ranging from physical interactions, animal studies to cellular studies.

(E) (VT, AE, IFR, DRF) Zhang J, Ding C, Meng X, Shang P. Nitric oxide modulates the responses of osteoclast formation to static magnetic fields. Electromagn Biol Med. 37(1):23-34, 2018.

Nitric oxide (NO) is involved in osteoclast differentiation. Our previous studies showed that static magnetic fields (SMFs) could affect osteoclast differentiation. The inhibitory effects of 16 T of high SMF (HiMF) on osteoclast differentiation was correlated with

increased production of NO. We raised the hypothesis that NO mediated the regulatory role of SMFs on osteoclast formation. In this study, 500 nT of hypomagnetic field (HyMF), 0.2 T of moderate SMF (MMF) and 16 T of high SMF (HiMF) were utilized as SMF treatment. Under 16 T, osteoclast formation was markedly decreased with enhanced NO synthase (NOS) activity, thus producing a high level of NO. When treated with NOS inhibitor N-Nitro-L-Arginine Methyl Ester (L-NAME), NO production could be inhibited, and osteoclast formation was restored to control group level in a concentration-dependent manner. However, 500 nT and 0.2 T increased osteoclast formation with decreased NOS activity and NO production. When treated with NOS substrate L-Arginine (L-Arg) or NO donor sodium nitroprusside (SNP), the NO level in the culture medium was obviously elevated, thus inhibiting osteoclast differentiation in a concentration-dependent manner under 500 nT or 0.2 T. Therefore, these findings indicate that NO mediates the regulatory role of SMF on osteoclast formation.

(E) (HU, CE, IOD) Zhang Y, Zhang D, Zhu B, Zhang H, Sun Y, Sun C. Effects of dietary green tea polyphenol supplementation on the health of workers exposed to high-voltage power lines. Environ Toxicol Pharmacol. 46:183-187, 2016.

Although it has been several decades since the focus on the effect of extremely low frequency electromagnetic fields (ELF-EMF) of high-voltage power lines on human health, no consistent conclusion has been drawn. The present study aimed to investigate the change in oxidative stress after exposure to ELF-EMFs, and potential protective effects of green tea polyphenol supplementation (GTPS) on ELF-EMFs induced oxidative stress. A total of 867 subjects, including workers with or without exposure to ELF-EMFs of 110-420kV power lines, participated and were randomized into GTPS and placebo treatment groups. Oxidative stress and oxidative damage to DNA were assessed by urinary tests of 8-isoprostane and 8-OHdG. Significant increased urinary 8-isoprostane and 8-OHdG were observed in workers with ELF-EMFs exposure, which were diminished after 12 months of GTPS. No protective effects of GTPS on oxidative stress and oxidative damage to DNA were observed after three months of GTPS withdraw. We found a negative impact of high-voltage power lines on the health of workers. Long-term GTPS could be an efficient protection against the health issues induced by high-voltage power lines.

(E) (VO, AE, IOD, DFR, IAO) Zhang Z, Zhang J, Yang C-J, Lian H-Y, Yu H, Huang X-M, Cai P. Coupling Mechanism of Electromagnetic Field and Thermal Stress on Drosophila melanogaster. PLoS One 11(9):e0162675, 2016.

Temperature is an important factor in research on the biological effects of extremely low-frequency electromagnetic field (ELF-EMF), but interactions between ELF-EMF and temperature remain unknown. The effects of ELF-EMF (50 Hz, 3 mT) on the lifespan, locomotion, heat shock response (HSR), and oxidative stress (OS) of Canton-Special (CS) and mutant w1118 flies were investigated at 25°C and 35°C (thermal stress). Results showed that thermal stress accelerated the death rates of CS and w1118 flies, shortened their lifespan, and influenced their locomotion rhythm and activity. The upregulated expression levels of heat shock protein (HSP) 22, HSP26, and HSP70 indicated that HSR was enhanced. Thermal stress-induced OS response increased malondialdehyde content,

enhanced superoxide dismutase activity, and decreased reactive oxygen species level. The effects of thermal stress on the death rates, lifespan, locomotion, and HSP gene expression of flies, especially w1118 line, were also enhanced by ELF-EMF. In conclusion, thermal stress weakened the physiological function and promoted the HSR and OS of flies. ELF-EMF aggravated damages and enhanced thermal stress-induced HSP and OS response. Therefore, thermal stress and ELF-EMF elicited a synergistic effect.

(E) (VO, CE, IFR, MC) Zhao B, Yu T, Wang S, Che J, Zhou L, Shang P. Static Magnetic Field (0.2-0.4 T) Stimulates the Self-Renewal Ability of Osteosarcoma Stem Cells Through Autophagic Degradation of Ferritin. Bioelectromagnetics 42(5):371-383, 2021.

Static magnetic field (SMF) can alter cell fate decisions in many ways. However, the effects of SMF on cancer stem cells (CSCs) are little-known. In this particular study, we evaluate the biological effect of moderate-intensity SMF on osteosarcoma stem cells (OSCs) and try to clarify the underlying mechanisms of action. First, we demonstrated that prolonged exposure to SMF induced the proliferation and tumorsphere formation in K7M2 and MG63 OSCs. Moreover, SMF promoted the release of ferrous iron (Fe^{2+}) and provoked reactive oxygen species (ROS) in OSCs. Interestingly, SMF evidently triggered the autophagic degradation of ferritin, which is characterized by the activation of microtubule-associated protein 1 light chain 3 (LC3) and nuclear receptor co-activator 4 (NCOA4), and downregulation of ferritin heavy chain 1 (FTH1) in OSCs. Particularly, the colony-forming ability of K7M2 OSCs promoted by SMF was obviously abolished by using a small interfering RNA (siRNA) against NCOA4. Finally, treatment of the tumor-bearing mice with SMF did not affect the tumor volume or tumor mass, nor pulmonary metastasis of K7M2 OSCs, but the SMF-treated K7M2 OSCs caused a preference of pulmonary metastasis in a mouse model, which suggested that SMF might induce the metastatic characteristic of OSCs. Consequently, this paper demonstrates for the first time that the cumulative SMF exposure promoted the self-renewal ability of OSCs via autophagic degradation of ferritin, implying that ferritinophagy may be a potential molecular target for cancer.

(E) (VT, AE, IFR) Zhao G, Chen S, Wang L, Zhao Y, Wang J, Wang X, Zhang W, Wu R, Wu L, Wu Y, Xu A. Cellular ATP content was decreased by a homogeneous 8.5 T static magnetic field exposure: role of reactive oxygen species. Bioelectromagnetics. 32(2):94-101, 2011.

The literature on the impact of strong static magnetic fields (SMF) on human health is vast and contradictory. The present study focused on the cellular effects of strong homogeneous SMF in human-hamster hybrid (A(L)) cells, mitochondria-deficient (ρ(0) A(L)) cells, and double-strand break (DSB) repair-deficient (XRS-5) cells. Adenosine triphosphate (ATP) content was significantly decreased in A(L) cells exposed to 8.5 Tesla (T) but not 1 or 4 T SMF for either 3 or 5 h. In addition, ATP content significantly decreased in the two deficient cell lines exposed to 8.5 T SMF for 3 h. With further incubation of 12 or 24 h without SMF exposure,

ATP content could retrieve to the control level in the A(L) cells but not ρ(0) A(L) and XRS-5 cells. Under a fluorescence reader, the levels of reactive oxygen species (ROS) in the three cell lines were significantly increased by exposure to 8.5 T SMF for 3 h. Concurrent treatment with ROS inhibitor, DMSO, dramatically suppressed the ATP content in exposed A(L) cells. However, the CD59 mutation frequency and the cell cycle distribution were not significantly affected by exposure to 8.5 T SMF for 3 h. Our results indicated that the cellular ATP content was reduced by 8.5 T SMF for 3 h exposure, which was partially mediated by mitochondria and the DNA DSB repair process. Moreover, ROS were involved in the process of the cellular perturbations from the SMF.

(E) (VT, VO, LE, IAO, IX)
Zheng Y, Hao Y, Xia B, Mei L, Li S, Gao X, Ma T, Wei B, Tan Z, Lan P, Luo Z, Jing D, Huang J. Circadian Rhythm Modulates the Therapeutic Activity of Pulsed Electromagnetic Fields on Intervertebral Disc Degeneration in Rats. Oxid Med Cell Longev 2022:9067611, 2022.

Circadian rhythm (CR) imparts significant benefits in treating multiple diseases, such as heart diseases and arthritis. But the CR effect on intervertebral disc degeneration (IVDD) therapy remains unclear. Recent studies revealed that pulsed electromagnetic fields (PEMF) are capable of alleviating IVDD. In this study, we evaluated the CR-mediated regulation of PEMF therapeutic effect on IVDD induced by rat tail disc needle puncture. Our results demonstrated that the daytime PEMF stimulation (DPEMF) is more effective than the nighttime PEMF (NPEMF) in delaying IVDD. Moreover, the rats treated with DPEMF maintained better disc stability and histology after 8 weeks, relative to NPEMF. CR and PEMF cotherapies were also examined in cellular models, whereby serum shock was used to induce different levels of clock gene expression in the nucleus pulposus (NP), thus imitating CR *in vitro*. PEMF at ZT8 (higher level of clock gene expression) correlated with a higher extracellular matrix (ECM) component expression, compared to ZT20 (lower level of clock gene expression). Taken together, these data suggest a strong role of CR in regulating the beneficial effect of PEMF on IVDD. Our findings provide a potential clinical significance of CR in optimizing PEMF positive effects on IVDD.

(E) (VT, AE, IOD, IAO) Zwirska-Korczala K, Adamczyk-Sowa M, Polaniak R, Sowa P, Birkner E, Drzazga Z, Brzozowski T, Konturek SJ. Influence of extremely-low-frequency magnetic field on antioxidative melatonin properties in AT478 murine squamous cell carcinoma culture. Biol Trace Elem Res. 102(1-3):227-243, 2004.

Effects of melatonin, extremely-low-frequency magnetic field (ELF-MF), and their combination on AT478 murine squamous cell carcinoma line were studied. Manganese superoxide dismutase (MnSOD), copper-zinc superoxide dismutase (Cu/ZnSOD), and glutathione peroxidase (GSH-Px) were used as markers of cells antioxidative status, and malondialdehyde (MDA) level was used as a marker of lipid peroxidation. After melatonin treatment, antioxidative enzyme activities were increased and MDA level was decreased. Application of ELF-MF on treated cells caused an increase of both superoxide dismutases activity and MDA level, but

influence of ELF-MF on GSH-Px activity was negligible. All enzyme activity in culture medium containing melatonin (10(-3), 10(-4), 10(-5) M) after exposure to ELF-MF were significantly diminished compared to cells treated only with melatonin. Also MDA levels after combined treatment with melatonin and ELF-MF were significantly decreased. Observed changes were statistically significant ($p<0.05$). These results strongly suggest that ELF-MF attenuates antioxidative actions of melatonin on cellular level.

(E) (VT, AE, IX, LI) Zmyslony M, Rajkowska E, Mamrot P, Politanski P, Jajte J. The effect of weak 50 Hz magnetic fields on the number of free oxygen radicals in rat lymphocytes in vitro. Bioelectromagnetics. 25(8):607-612, 2004a.

The aim of the work was verification of the hypothesis that weak power frequency (50 Hz) magnetic fields (MF) affected the number of free oxygen radicals in living biological cells and that these changes could be qualitatively explained by the radical pair mechanism. The experiments were performed on rat lymphocytes. One-hour exposure to 50 Hz MF at 20, 40, or 200 microT flux densities was performed inside a pair of Helmholtz coils with axis along or crosswise to the Earth's static MF. Iron ions (FeCl2) were used as a stimulator of the oxidation processes. Oxygen radicals were measured by fluorimetry using a DCF-DA fluorescent probe. Only in the lymphocytes exposed at 40 microT MF directed along the Earth's static MF there was a decrease of fluorescence in relation to non-exposed samples. Our observation seems to confirm the hypothesis that low level power frequency MF affects oxidative processes which occur in living biological cells and that this effect can be explained by the radical pair mechanism.

(E) (VT, AE, IX, LI) Zmyślony M, Palus J, Dziubałtowska E, Politański P, Mamrot P, Rajkowska E, Kameduła M. Effects of in vitro exposure to power frequency magnetic fields on UV-induced DNA damage of rat lymphocytes. Bioelectromagnetics. 25(7):560-562, 2004b.

The mechanisms of biological effects of 50/60 Hz (power frequency) magnetic fields (MF) are still poorly understood. There are a number of studies indicating that MF affect biochemical processes in which free radicals are involved, such as the biological objects' response to ultraviolet radiation (UVA). Therefore, the present study was aimed to assess the effect of 50 Hz MFs on the oxidative deterioration of DNA in rat lymphocytes irradiated in vitro by UVA. UVA radiation (150 J/m2) was applied for 5 min for all groups and 50 Hz MF (40 microT rms) exposure was applied for some of the groups for 5 or 60 min. The level of DNA damage was assessed using the alkaline comet assay, the fluorescence microscope, and image analysis. It has been found that the 1 h exposure to MF caused an evident increase in all parameters consistent with damaged DNA. This suggests that MF affects the radical pairs generated during the oxidative or enzymatic processes of DNA repair.

Literature on free radical generation after expsore to static and extremely-low-frequency electromagnetic fields

Two types of free radicals can be generated: reactive oxygen species (ROS) and reactive nitrogen species (RNS). Activity in the mitochondrial electron transport chain leads to the production of superoxide radical anion ($O_2^{\bullet -}$) which can be converted to hydrogen peroxide (H_2O_2) by various forms of superoxide dismutate (SOD). H_2O_2 can be degraded by catalase (CAT) into water and oxygen or converted by the iron-dependent Fenton reaction into the potent hydroxyl radical ($OH^{\bullet}$). In the cytoplasm, nitric oxide ($NO^{\bullet}$) is generated by various forms of nitric oxide synthase (NOS) by conversion of L-arginine to L-citrulline. $NO^{\bullet}$ reacts with $O_2^{\bullet -}$ to generate the potent oxidant peroxynitrite ($ONOO^-$). $O_2^{\bullet -}$ can also be produced by NOS by transfer of electron from NADPH to O_2. Other enzymatic processes, such as cytochrome P_{450}, also generate ROS in normal cellular activities.

Major anti-oxidative processes in cells include catalase/peroxidase that converts $O_2^{\bullet -}$ to H_2O and O_2. In the process, glutathione (GSH) is oxidized to glutathione disulfide (GSSG). GSSG is reduced back to GSH by the enzyme glutathione reductase with the conversion of NADPH to NADP. GSH and NADPH are the most common electron donors participating in cellular anti-oxidation processes. $ONOO^-$ is decomposed by peroxiredoxin and glutathione peroxidase into less potent nitrogen free radicals ($NO_3^{\bullet}/NO_2^{\bullet}$).

ROS react with cellular macromolecules, e.g., DNA, protein, and lipid. The most common form of DNA oxidative damage is the formation of hydroxylated bases. 8-hydroxy-2'-deoxyguanosine (8-OHdG) is generally used as an index of oxidative DNA damage. ROS react with lipids to produce lipid peroxyl radicals and lipid hydroperoxides. Lipid peroxyl can subsequently form malondialdehyde (MDA), which is commonly used as an index of oxidative lipid damage. Lipid radicals can diffuse through membrane leading to protein oxidation and formation of DNA-MDA adduct. Oxidative lipid damage affects the structure and function of cell membrane. ROS attack proteins directly and indirectly. Protein carbonyl is a form of protein oxidative damage. Changes in protein structure lead to alteration in enzymatic activities, particularly, damage to membrane transport proteins leads to ionic imbalance such as intracellular concentrations of calcium and potassium. Oxidative stress could also cause changes in regulation of transcription factors in cells, e.g., the Nrf2 antioxidant pathway.

More than 300 papers have been published on effects of *in vitro* and in *vivo* exposure to static and extremely–low frequency electromagnetic fields on various aspects of the free radical processes in living organisms. The following table is a summary of these papers.

Table Summary of papers on the effects of static/ELF-EMF on oxidative processes in cells and animals. (* Study reported no significant effect on oxidative processes; ↑ increase; ↓ decrease; Ø no significant effect; MF= magnetic field; EF = electric field; CAT= catalase; GR= glutathione reductase; GSH= glutathione; GST = glutathione S-transferase; GPx = glutathione peroxidase; NOS= nitric oxide synthase; MPO= myeloperoxidase; O_2. = superoxide; ROS = reactive oxygen species; SOD= superoxide dismutase; TOS=total oxdant status; TAS=total antioxidant status) In some studies, the term EMF (electromagnetic field) was used. The authors may mean magnetic field or a combination of magnetic and electric fields, since most exposure systems emit both fields when not properly shielded and grounded. On the other hand, fields labelled as magnetic field in some studies may contain also electric component.,

			Oxidative damages (DNA, protein, lipid)	*ROS (O_2^{-}, OH, H_2O_2, NO)*	*NOS*	*Antioxidative processes (SOD, CAT/ peroxidase, GSH, GPx)*	*Effect of antioxidants/ scavengers*	*Remarks*
Agrawal et al. (2021)	Drosophila melanogaster	75 Hz MF, 0.55 mT, 6 hat third stage instar larva or adult fly stage, or 6 h/day from egg to adult fly		↑ROS (H_2O_2)				
Ahmad et al. (2023)	Blood of human subject	Imaging professionals occupationally exposed to nonionizing EMF		↑ O_2^{-}		↑ SOD and CAT		
Ahmadi-Zeidabadi et al. (2019)	Human glioblastoma U87 cells	100 Hz MF, 10 mT, 120-144 h	↑ lipid peroxidation			↑ SOD		
Akan et al. (2010)	Activated THP-1 cells (human monocytic leukemia cells)	50-Hz EMF, 1 mT, 4-6 h		↑NO	↓ iNOS			↑cGMP

Akbarnejad et al. (2017)	two human glioma cells line U87 and T98G	100 Hz MF, 10 mT, up to 144 h		↑ROS				↑heme oxygenase -1
Akdag et al. (2007)	Sprague-Dawley rat serum in vivo	50-Hz MF, 0.1 and 0.5 mT, 2 h/day, 10 months		↓NO				
Akdag et al. (2010)	Sprague-Dawley rat brain in vivo	50-Hz MF,0.1 and 0.5 mT, 2 h/day, 10 months	↑ lipid peroxidation			↓ CAT		↑ total oxidant status, ↓ total anti-oxidative capacity
Akdag et al. (2013a)	Sprague-Dawley rat brain in vivo	50-Hz MF, 0.1 and 0.5 mT, 2 h/day, 10 months	↑ protein carboxylation ↑ lipid peroxidation					
*Akdag et al. (2013b)	Sprague-Dawley rat testes in vivo	50-Hz MF, 0.1 and 0.5 mT, 2 h/day, 10 months	Ø lipid peroxidation			Ø CAT		No change in total oxidant status and total anti-oxidative capacity
Akpinar et al. (2012)	Wister rat brain and retina in vivo	50-Hz EF, 12 and 18 kV/m, 1 h/day, 14 days	↑ lipid peroxidation					↑ total oxidant status, ↓ total anti-oxidative capacity

Akpinar et al. (2016)	Wister rat brain in vivo	50-Hz EF,12 kV/m, 1 h/day, prenatal (Pr), postnatal (Po, 30 days), and prenatal + postnatal (PP)	↑lipid peroxidation in Po, ↓in PP (cf. Pr and Po) ↓ protein carboxylation in PP					
Aksen et al. (2006)	Wister rat uterus and ovary in vivo	50-Hz EMF, 1 mT, 3 h/day, 50 or 100 days	↑ lipid peroxidation					
*Alcaraz et al. (2014)	Micronucleated cells induced by EMF in bone morrow of mouse	50-Hz EMF, 0.2 mT, for 7, 14, 21, or 28 days					Effect not blocked by 4 types of antioxidant	
Alipour et al. (2022)	Mesenchymal stem cells	Static MF (20 mT); 50 HZ EMF (20 mT)		↑ROS		↑SOD, GST		Static and ELF fields have different effects on cell cycle, apotosis and cell viability.
Amara et al. (2009)	Frontal cortex and hippocampus of exposed rats	Static MF, 128 mT, 1 h/day for 30 days	↑ lipid peroxidation in hippocampus			↓CuZnSOD, MnSOD in hippocampus; ↓ GPx, CuZnSOD, CAT in frontal cortex;		Ø DNA oxidation
Amara et al. (2011)	Frontal cortx of exposed rats	Static MF, 128 mT, 1 h/day for 30 days						Synergistic with cadmium to decrease CuZnSOD, MnSOD;

								effects not foiund in ippocampus
Ansari et al. (2016)	NMRI mice	50-Hz MF, 0.5 mT, 2 h or 2 h/day for 2 weeks		↑ NO				Blocked effect of L-NAME, a NOS inhibitor, long ter exposure reversed depressive disorder in mice
Asghar et al. (2016)	Soybean seeds and seedlings	50-Hz MF, 50, 75, or 100 mT for 3 or 5 min	↑ lipid peroxidation at 50 mT for 3 min (not at other exposure conditions)	↑H_2O_2 at 50 and 100 mT for 3 min		↑ SOD at 75 mT for 3 and 5 min; ↑CAT/peroxidase at 50, 75 and 100 mT for 3 min;		↑ ascorbic acid
Ashta et al. (2020)	human glioblastoma cell line (A172)	10 Hz EMF (5 mT) and static MF (5 mT) up to 96 h		10 Hz field increased ROS (no effect with satic field)				
Ayşe et al. (2010)	K562 cells, in vitro	50-Hz EMF, 5 mT, 1 h or 1 h/day for 4 days		↑ $O_2^{\cdot-}$				Effect disappeared at 2 h post-exposure, no interaction with hemin
Barat et al. (2021)	MC4-L2 breast cancer cells	In vitro: 100 Hz EMF 1 mT, 2 h/day for 5 days					Necroptosis attenuated by N-acetyl cysteine (a ROS scavenger)	Effect also attenuated by verapamil (a calcium channel inhibitor)

Bawin et al. (1996)	Electrical activity of rat hippocampal slices	1-Hz MF, 0.56 and 0.056 mT, 10 min			Effect blocked by NOS inhibitor			60-Hz MF has no significant effect
Bediz et al. (2006)	Sprague-Dawley rat blood and brain in vivo	50-Hz EMF, 0.005 mT, 5 min every other day for 6 months	↑ lipid peroxidation			↓GSH		Effect attenuated by zinc
Belova et al. (2010)	Activated mouse peritoneal neutrophils	Combined magnetic field (CMF) tuned to calcium ion (DC 40.6 μT, AC 74.7 μT at 31 Hz): pulsed MF (225 μs, 20 pulses packet at 15 Hz, 1500 μT); up to 30 min exposure		CMF ↓ ROS, pulsed MF ↑ ROS				
Benassi et al. (2016)	SH-SY5Y cells (human used to study Parkinson's disease)	50-Hz MF, 1 mT, 6-72 h	↑ protein carboxylation					
Bertea et al. (2015)	Arabidopsis thaliana	Reversed geomagnetic field				↑ SOD-1. CAT-3 gene expression		↑ Redox responsive transcription factor-1, ascorbate oxidase, thylakoidal ascorbate peroxidase

								gene expression
Bhardwaj et al. (2012)	Germinating cucumber seeds	Static MF,100 to 250 mT for 1, 2 or 3 h				↑ SOD, CAT, GR		
Bhardwaj et al. (2016)	Aged garden pea seeds	Pulsed MF, 6 min ON/6 min OFF, 100 mT, 1 h	↑ protein carboxylation	↑ O2., H_2O2		↑ SOD		
Brucu et al. (2020)	Ovary tissue of rats	50 Hz, 3 mT EMF prenatal and to 42 days postnatal			↑NOS			
Buczyński et al. (2005)	Human blood platelets	1 kHz MF, 0.5 mT, 30, 60 or 90 min	↑ lipid peroxidation					Effect observed only after 30 and 90 min exposure, not at 60 min
Budziosz et al. (2018)	Male Wistar rats, frontal cortex, hippocampus, brainstem, hypothalamus, striatum, cerebellum	50-HZ EMF, 22 h/day, 28 days, 4.4 pT	Ø lipid peroxidation	Ø total oxidant status		Changes (↑ and ↓) in SOD, CAT and glutathione-related enzymes depended on barin region		
Buldak et al. (2012)	AT478 murine squamous carcinoma cells	EMF 50-Hz, 1 mT, 16 min	↓ lipid peroxidation			↑SOD ↑GPx		MF lessens oxidative effects of cisplatin

Calabro et al. (2013)	SH-SY5Y cells	Static MF, 2.2 mT, 24 h		↑ ROS production				Mitochondria involved
Calcabrini et al. (2017)	Human keratinocyte (NCTC 2544)	50 Hz MF, 0.025 – 0.2 mT, 1 h	↑ lipid peroxidation at 0.05 and 0.1 mT	↑ ROS at 0.05 and 0.1 mT		↓ SOD and ↑GSH at 0.05 and 0.1 mT		↑ ROS blocked by the iron chelator o-phenanthroline
Calota et al. (2006)	Human blood serum	50-Hz EF, 5, 7.5 10, 15, 20 kV/m, 1-2 h		↓ ROS production				
Calota et al. (2007)	Human blood serum	50-Hz MF, 0.357, 0.596, 1.788, 2.384 mT, 1-2 h		↑ ROS production, enhanced by $FeCl_2$ and H_2O_2				
Canseven et al. (2008)	Guinea pig, liver and heart tissues	50-Hz MF, 1, 2, or 3 mT, 4 or 8 h/day for 5 days	↑ and ↓ in lipid peroxidation	↑ and ↓ in NO		MPO (↑ or ↓) depending on exposure condition (duration and intensity) and tissue studied; ↑ and ↓ in GSH		
Chen Y. et al. (2014)	Mouse embryonic fibroblast	50-Hz MF, 2 mT, 0.5, 2, 6, 12, 24 h		↑ ROS				
Chen Y. et al. (2021)	Human macrophages	51.8 Hz and 52.3 Hz with different pulsing properties		↑ ROS with one of the fields				
Chen YB et al. (2011)	Brain of exposed mice	Electromagnetic pulses (peak-intensity 400 kV/m,	↑ lipid peroxidation			↓ SOD, GPx, CAT, GSH		Effects observed at 3 h and returned to

		rise-time 10 ns, pulse-width 350 ns, 0.5 Hz and total 200 pulses)						normal 2 days after exposure.
Cheun et al. (2007)	Canine kidney MDCK cells	60-Hz MF, 1.4 mT, seconds		MF affected ROS kinetics when H_2O_2 was added to cells.				
Chu et al. (2011)	Mouse cerebellum in vitro	60-Hz MF, 2.3 mT, 3 h	↑ lipid peroxidation	↑OH		↑SOD Ø GPx		
Chung et al. (2015)	Rat brain in vivo	60-Hz MF, 2.0 mT, 2 or 5 days		↑NO in striatum, thalamus and hippocampus				
Cichon et al. (2017a)	Post-stroke patients	40-Hz, 7 mT for 15 min/day for 4 weeks (5 days a week)				↑ SOD and CAT in hemolysates		Ø total antioxidant status in plasma; exposed patients showed better improvement in functional and mental status
Cichon et al. (2017b)	Post-stroke patients	40-Hz, 7 mT for 15 min/day for 4weeks (5 days a week)		↑ 3-nitrotyrosine ↑ nitrate/nitrite ratio				ELF-EMF promotes recovery of post-stroke patients
Cichon et al. (2018a)	Post-stroke patients,	Rectangular, bipolar waves, 5 mT, 40 Hz, 15						↑ CAT, SOD1, SOD2,

	blood mRNA	min/session, 10 sessions in 14 days,						GPx1, GPx4 mRNA
Cichon et al. (2018b)	Post-stroke patients, blood	Rectangular, bipolar waves, 5 mT, 40 Hz, 15 min/session, 20 sessions in 20 days,	↓ lipid peroxidation ↓ protein carboxlation					Improved psychophysical abilities of patients
Ciejka et al. (2009)	Sprague-Dawley rats in vivo (plasma)	40-Hz MF, 7 mT, 30 or 60 min per day for 14 days						Repeated 30-min and 60-min exposure increased and decreased plasma antioxidant activity, respectively.
Ciejka et al. (2010)	Sprague-Dawley rats in vivo (muscle)	40-Hz MF, 7 mT, 30 or 60 min per day for 14 days						Both exposures caused an increase in -SH and decrease in proteins in muscle
Ciejka et al. (2011)	Sprague-Dawley rats in vivo (brain)	40-Hz MF, 7 mT, 30 or 60 min per day for 14 days	↑ lipid peroxidation in brain of 30-min per day exposed rats					Rats exposed for 60 min per day, 14 days showed increases in

								-SH and proteins in brain (adaptation).
Ciejka et al. (2014)	Sprague-Dawley rats in vivo (muscle)	40-Hz MF, 7 mT, 30 or 60 min per day for 14 days				↑GSH		
Cios et al. (2021)	HEK293, 786-O 769-P, and Caki1cells (renal carcinoma cells)	50-HZEMF, 4.5 mT. 30 min/day for 5 days		↑ ROS				G1 cell cycle arrest and aoptosis
Coballase-Urrutia et al. (2018)	Restraint Wistar rats	Static MF, 0.8 mT, 30, 60, 240 min/day, 5 days						Attenuated restaint stress-induced increases in NO and MDA and decreases in SOD and GSH
Consales et al. (2018)	SH-SY5Y human neuroblastoma cells and mouse primary cortical neurons	50-Hz MF. 1 mT, 24, 48 or 72 h	↑ $O_2^{\cdot-}$, H_2O_2,					Some ROS produced by mitochondria; affected by microRNA (miR-34) Mitochondria involved

*Consales et al. (2019)	SH-SY5Y human neuroblastoma cells (wild type and two mutants)	50-Hz MF, 1 mT, 24-72 h	Ø $O_2^{\cdot-}$, H_2O_2,					↓ iron cotent and ron-gene expression in a mutant cell-type; Ø viability and proliferation
Coskun et al. (2009)	Guinea pig in vivo-plasma, brain, and liver	50-Hz MF, 1.5 mT, continuous (4h/day) or intermittent (2 h on/2 h off/2h on) for 4 days	Plasma: I ↑ lipid peroxidation Brain: C, ↓ lipid peroxidation Liver: C, I ↑lipid peroxidation	Plasma: C, I ↑ NO		MPO: Plasma C ↑, Brain C, I ↑, Liver C, I ↓ GSH: C ↑ I ↓ in brain		
Cui et al. (2012)	C57BL/6 mice in vivo, striatum and hippocampus	50-Hz MF, 1 or 0.1 mT, 4h/day, 12 days	↑ lipid peroxidation in 1 mT group			↓ CAT and ↓GSH in 1 mT group		↓Total antioxidant capability in 1 mT group
Da Costa et al. (2021)	Neonatal rat normal cortical astrocytes	Static MF, 305 mT, 5-40 min/day for 7 days	↑ lipid peroxidation	Ø SOD, CAT				↓Total antioxidant capability Mitochondria involved
*de Groot et al. (2014)	Normal and chemically-stressed PC12 cells	50-Hz EMF, 30 min or 48 h, up to 1 mT		No effect on ROS production as measured by H_2-DCFDA				
* De Mattei et al. (2003)	Bovine articular cartilage explants	75-Hz EMF 1.3 ms pulses, 2.3 mT peak, 24 h		Ø NO				Pulses enhanced Interleukin-1β–induced

								NO production
De Nicola et al. (2006)	U937 cells	Static MF, 6 mT, 2 h; 50-Hz MF, 0.07-0.1 mT, 2 h		↑ ROS		↓GSH		Decreased apoptosis
Deng B. et al. (2014)	Rat primary cerebral cortical neurons	Electromagnetic pulses (peak 400 KV/m, width 350 ns, 0.5 pps, I Hz)	↑ lipid peroxidation			↓SOD		Decreased cell viability observed, effects antagonized by sevoflurane
Deng Y. et al. (2013)	SPF Kunming mouse in vivo, serum and brain	50-Hz MF, 2 mT, 4 h/day, 8 weeks	↑ lipid peroxidation			↓SOD		No interaction with aluminum
Di G. et al. (2021)	Testis of exposed mice	Electric field, 56.3 kV/m; 24 h/day for 28 days	↑ lipid peroxidation			↓GPx		Simulation of high voltage power line exposure; Mitochondria involved
Di S. et al. (2012)	Human preosteoclast FLG29.1 cells	Large gradient high magnetic fields (12 T, -1370 T^2/m; 12 T, 1370 T^2/m), 72 h		↓ NO				
*Di Loreto et al. (2009)	Rat cortical neurons	50-Hz MF, 0.1 or 1 mT, 7 days	Ø lipid peroxidation	Ø total ROS		Ø GSH		↑ cell viability, ↓ apoptosis

Dinčić et al. (2018)	Wistae albino rats	Static magnetic field, 1 mT, 50 days	↑ lipid peroxidation			↓ synaptosomal CAT depending on oritentation of static MF		↑ ATPase and AchE in synaptosomes
Ding et al. (2004)	Human leukemia HL-60 cells	60-Hz MF, 5 mT, 24 h						Enhanced apoptotic effect of H_2O_2
Djordjevic et al. (2017)	Wistar male rats	50-Hz MF, 10 mT, 7 days, 24 h/day		↑ $O_2^{\cdot-}$ *and* NO; Ø peroxynitrite (ONOO-) in hypothalamus				
Dornelles et al. (2017)	Human peripheral mononuclear cells with different polymorphism at Vali1la-MnSOD gene	Static magnetic field, 5 mT; 0,1,3,6 h	↑ and Ø lipid peroxidation, ↑ and ↓ protein carboxylation	↑, ↓ and Ø ROS		↑, ↓ and Ø in SOD1, SOD2, GPX, CAT		Response depended on genetic makeup of the cells
Dong D. et al. (2019)	Osteoclastic formation from mouse RAW264.7 cells	Static MF, 16 T, 2 or 4 days	↓ lipid peroxidation	↓ ROS		↑ GSH		Mitochondria involved
Dong L. et al. (2022)	Spleen of exposed mice	Tatic electric field, 56.3 kV/m, 21 days	↑ lipid peroxidation		↑NOS	↑SOD		Mitochondria involved
Duan Y. et al. (2013)	ICR mouse, Serum and hippocampus	50-Hz MF, 8 mT, 4 h/day, 28 days	↑ lipid peroxidation	↑NO	↑NOS	↓SOD ↓ CAT ↓GPx		Effects reversed by lotus seedpot procyanidins

*Duan W. et al. (2015)	Mouse spermatocyte-devrived GC-2 cells	50-Hz EMF, 1, 2, or 3 mT, 5-min on /10-min off, 24 h	Ø oxidative DNA base damage					
Duong and Kim (2016)	Human microglial HMO6	50-Hz EMF, 1 mT, 4 h						EMF exposure decreased ROS induced by oxygen-glucose deprivation; Mitochondria involved.
Ehnert et al. (2017)	Human osteoblasts	Pulsed EMF, 16-Hz, 6 - 282 μT; 7 min or 7min/day (>3 days)		Single exposure ↑ ROS; Repeated exposure ↓ ROS; mainly $O_2^{\cdot-}$ and H_2O_2		↑GPX3, SOD2, CAT, GSR	Effects of EMF blocked by $O_2^{\cdot-}$ and H_2O_2 scavengers	EMF promotes osteoblast differentiation via free radicals
Elexpuru-Zabaleta et al. (2022)	Human MDA-MB-231 and MCF-7 breast cancer cells and MCF-10A breast cells	50Hz MF, 0.1 or 1 mT, up to 96 h		↑ ROS				Effects depended on intensity and duration of exposure and cell type; Mitochondria involved
Emre et al. (2011)	Wistar rat in vivo, liver	Pulsed EMF (0.5 ms rise time, 9.5 ms fall time) EF 0.6 V/m, MF 1.5 mT, each frequency train of 1 Hz,	↑ lipid peroxidation			↑SOD		No effect on apotosis, decreased necrosis.

		10 Hz, 20 Hz and 40 Hz was given for 4-min and with 1-min interval between each frequency (together 20 min.); on each day, three exposure cycles performed (1 h), 1 h per day for 30 days						
Erdal et al. (2008)	Male and female Wistar rat in vivo, liver	50-Hz MF, 1 mT, 4/day, 45 days	Ø lipid peroxidation					Increased 3-nitrotyrosine (oxidative/ nitrosative stress) in liver of female rats.
Errico Provenzano et al. (2018)	NB4 cells (human acute promyelocytic leukemia)	50 Hz MF, 2 mT, 8, 16, 24 h		↑ROS				
Ersoy et al. (2022)	Testis of male pups exposed prental and postnatal (to 28 or 42 days)	50 Hz EMF, 3 mT, 4 h/day, 5 days/week.	↑ lipid peroxidation in both 28 and 42 postnatal-day groups			↓GSH in 28 postnatal group		
Falone et al. (2007)	Human neuroblastoma cells SH-SY5Y	59-Hz MF, 1 mT, 96-192 h		Ø ROS		Ø SOD, CAT ↑ GST, GPx		Increased cell viability; Ø cell circle, apoptosis and DNA

						5x ↑ reduced/total GSH ratio		damage, but enhanced these effects induced by H_2O_2.
Falone et al. (2008)	Female Sprague-Dawley rat in vivo, 3- and 19-month old, brain cortex	50-Hz MF, 0.1 mT, 10 days				↑SOD_2 in young rats; ↓ catalase and GPx in old rats		↓Glutathione reductase in old and young rats, ↓ glutathione-s-transferase in old rats: old and young rats responded differently.
Falone et al. (2016)	Human drug-resistant neuroblastoma SK-N-BE(2) cells	72-Hz pulsed EMF, 1.3 ms pulse duration, 2 mT, 15 min, 3 times over 5 days						Pulsed EMF increased MnSOD-based antioxidant protection and reduced ROS production induced by H_2O_2 .
Falone et al. (2017)	SH-SY5Y human neuroblastoma cells	50-Hz MF, 0.1 or 1 mT, 5 and 10 days	↓ protein carboxylation and DNA oxidation			↑ GPx/SOD and catalase/SOD ratios, i.e., increase antioxidating defense; ↑ GPx activity		Protects cell death by H_2O_2, ↑ Nrf2 activity
Faraji et al.. (2021)	Serum of exposed rats	50-Hz EMF, 1 h/day for 8 weeks; 0.001, 0.1, 0.5, or 2 mT	↑ lipid peroxidation					↑ TAS, TOS, thiol

Feng et al.. (2016a)	Human amniotic epithelial cells	50-HZ MF, 0.4 mT, 5, 15, 30 or 60 min		↑ ROS			MF-induced mitochondrial permeability transition blocked by NAC	Mitochondria involved
Feng et al. (2016b)	Human amniotic epithelial cells	50-HZ MF, 0.1, 0.2, or 0.4 mT, 5, 15, 30, or 60 min		↑ ROS				↑ total ROS at 0.2 mT and higher, ↑NADPH oxidase-produced superoxide; Mitochondria involved
Feng et al. (2016c)	Human amniotic epithelial cells	50-Hz MF, 0.2-2 mT, 30, 60, 120 min		↑ mitochondrial ROS				↑ ROS led to activation of Akt and anti-apoptotic effect; Mitochondria involved
Feng et al. (2022)	Blood of genetically obese leptin receptor-deficient db/db diabetic mice	Static MF; 0.5 T; 24 h/day for 7 weeks	↓ lipid peroxidation	↓ ROS				
Fernie & Bird (2001)	American kestrel	60-Hz EMF, 30 μT,10 kV/m, 91 days, 23.5 h/day						Decreased plasma carotenoids

Fiorani et al. (1997)	Rabbit red blood cells	50-Hz MF, 0.2-0.5 mT, 90 min in the presence of an oxygen-generating system (Fe(II)/ascorbate)						Enhanced GSH reduction and hemoglobin oxidation caused by Fe(II)/ascorbate at 0.5 mT
Fitzsimmons et al. (2008)	Human chondrocyte	Pulsed electric field, EF in culture medium 0.2 mV/cm, 30 min		↑NO				↑cGMP, calcium involved
Frahm et al. (2006)	Mouse bone-marrow derived macrophage	50-Hz MF, 0.05, 0.1, 0.5, 1.0 mT, 45 min		↑ROS				
Frahm et al. (2010)	Mouse bone-marrow derived macrophage	50-Hz MF, 1.0 mT, 45 min		↑ROS				Activated enzymes (NAD(P)H oxidases) and proteins involved in redox homeostasis
Garip and Akan (2010)	K562 human leukemia cells, normal or treated with H_2O_2	50-Hz EMF 1 mT, 3 h		↑ROS				Decreased and increased apoptosis in untreated and H_2O_2-treated cells, respectively.

Ghodbane et al. (2011a)	Wistar male rat in vivo, plasma	Static MF, 128 mT, 1 h/day, 5 days	Ø lipid peroxidation			↑ GPx		Decreased vitamin A and E levels, effects blocked by selenium
Ghodbane et al. (2011b)	Wistar male rat in vivo, liver, kidney, muscle , brain	Static MF, 128 mT, 1 h/day, 5 days				↑ SOD in liver, ↓ GPx in kidney and muscle, ↑ GSH in liver		Selenium reversed GPx effect in kidney and muscle
Ghodbane et al. (2014)	Wistar male rat in vivo, plasma	Static MF, 128 mT, 1 h/day, 5 days					Vitamin E blocked static MF effects on blood glucose and liver glycogen	
Ghodbane et al. (2015a)	Wistar male rat in vivo, brain and liver	Static MF, 128 mT, 1 h/day, 5 days	Ø lipid peroxidation in brain and liver			↑ CAT in liver	selenium and vitamin E reversed liver catalase effect.	↑ apoptosis in liver through a mitochondrial capase-independent pathway; Mitochondria involved
Ghodbane et al. (2015b)	Wistar male rat in vivo, kidney and muscle	Static MF, 128 mT, 1 h/day, 5 days	↑ lipid peroxidation in kidney			↑ CAT in kidney	vitamin E reversed lipid peroxidation effect.	Selenium reversed ↑ lipid peroxidation and CAT effects in kidney

*Giorgi et al. (2014)	Human neuroblastoma BE(2) cells	Bipolar pulsed square wave MF, 50 Hz, 1 mT, up to 72 h	MF did not affect H_2O_2-induced DNA double strand break.					
Giorgi et al. (2017)	Human neuroblastoma BE(2) cells	Bipolar pulsed square wave MF, 50 Hz, 1 mT, (average rate of change in MF 3.3 T/s) 24 or 48 h	MF ↑DNA methylation with 24 h exposure (not with 48 h)					Oxidative stress (300 μM H_2O_2) decreased DNA methylation compared to PMF alone
Glinka et al. (2013)	Male Sprague-Dawley rat in vivo, blood serum and liver	40-Hz MF, 10 mT, 30 min /day for 6, 10, or 14 days	↓ lipid peroxidation in liver of 6-day exposure			↑SOD-Mn in serum only in 6 day exposure, ↓SOD-Mn in liver in 14-day exposure. No effect on SOD-ZnCu ↑ GPx in serum in 10- and 14-day exposure		↑glutathione s-transferase in liver of 6-day exposure; Mitochondria involved
Glinka et al. (2018)	Mouse fibroblasts	Static magnetic field, 0.1-0.7 T, 72 h	Ø lipid peroxidation			↓ SOD and GPx		
Gok et al (2016)	Wistar rat in vivo, brain and retina	50-Hz EF, 12 kV/m, I h/day during prenatal, postnatal, and prenatal + postnatal period	↑ lipid peroxidation in brain and retina of exposed animals					Prolonged visual evoked potentials were observed in exposed animals.
Goraca et al. (2010)	Male Wistar rat in vivo, heart and plasma	40-Hz MF,7 mT, 30 or 60 min/day, 14 days	↑ lipid peroxidation in heart in 30 and 60 min/day exposure	↑ H_2O_2 in heart in 30 and 60 min/day exposure		↓ GSH in heart 60min/day		Total free –SH decreased in heart of 60 min/day,

								decreased reducing capability in plasma of 60 min/day
Groiss et al. (2021)	Lipopolysaccharide-stimulated human leukemic THP1 cells and peripheral blood mononuclear cells	16.7 Hz MF(10-min ON/10-min OFF) 1-24 h, 0.05-4.8 mT		↑ ROS in mitochrondia at 4,8 mT				↑ Lipid-related anti-oxidative enzymes PRDX6 and DHCR24 in THP1; TPH1 ans mononuclear cells reponded to different flux densities
Guleken et al. (2022)	Brain and liver tisues from exposed rats (from day 0 of gestation through to day 21 of lactation)	50-Hz MF, 0.5 mT	↑ lipid peroxidation			↓GSH		
Guo et al. (2023)	Zebrafish lavae	59-Hz MF 100-800 μT , 1 or 24 h/day for 5 days.						Behavioral and gene expression effects blocked by free radical scavenger.
Güler et al (2008)	Male guinea pig in vivo, liver	50-Hz EF, 12 kV/m, 8 h/day, 7 days	↑ lipid peroxidation	↑NO		↓SOD ↓ GPx	Blocked by NAC	

						↓ MPO		
*Güler et al (2009a)	Male guinea pig in vivo, plasma	50-Hz EF, 12 kV/m, 8 h/day, 7 days	Ø oxidative protein damage					
Güler et al (2009b)	Male guinea pig in vivo, lung	50-Hz EF, 12 kV/m, 8 h/day, 7 days	↑ protein carboxylation Ø lipid peroxidation	Ø NO				
Gurhan et al. (2021)	HT-1080 human fibrosarcoma cells	Static MF; 0.0005- 0.6 mT, 4 days		H_2O_2 increased, decreased, and increase with increasing flux density, ↓ O2.-and NO				Calcium influx into mitochondria
Haghighat et al. (2014)	Seeds of Vicia faba (broad bean)	Static MF, 30 mT, 8 days		↑ H_2O_2		↑ CAT level and gene expression		
Hajipour Verdom et al. (2018)	Human MCF-7 breast cancer cels and HFF normal fibroblasts	Static magnetic field 10 mT, 24 and 48 h		↑ ROS		↑ GSH in HFF cells		Decreased viability and differentiation in both cell types; Synergistic with doxorubicin
Hajnorouzi et al. (2011)	Maize seedling	Combination of geomagnetic field (47 μT) and perpendicular 10-kHz MF (22 μT), 5 h/day for 4 days				↓SOD		↑Total antioxidant capacity, faster growth of seedlings, decrease iron increased growth

Hambarde et al. (2023)	Human glioblastoma and diffusion intrinsic pontine glioma cells	Static or oscillating (77, 135, 277 Hz) MF at 0.4-50 mT for 2h or 2X 2h,		↑ ROS				Oscillating field mor potent than static field; cell death observed; possible cancer treatment application
Hanini et al. (2017)	Mutant Pseudomonas aeruginosa without Mn- and Fe-SOD	Static magnetic field, 200 mT	↑ lipid peroxidation			↑ SOD, CAT, peroxidases		Wide type bacteria less responsive to the field
*Harakawa et al. (2005)	Sprague-Dawley rat in vivo, plasma	50-Hz EF, 17.5 kV/m, 15 min/day, 7 days	Ø lipid peroxidation (↓ in oxidatively stressed rats)					No effect on total antioxidant activity
Hashish et al., (2008)	Male Swiss (BALB/c) mouse in vivo, liver	Static MF (+/- 2.9 μT), or 50-Hz MF 1.4 mT, 30 days	↑ lipid peroxidation			↓GSH in ELF-MF exposure only		↑glutathione s-transferase
He et al. (2022)	Rat calvarial osteoblasts	50 Hz pulsed EMF (50% duty ratio), 90 min/day for 3 days; 0.6 mT			↑ iNOS, eNOS			
Henrykowska et al. (2009)	Human blood platelet	50-Hz MF, 10 mT, 15 min (sinusoidal, triangular, or rectangular)	↑ lipid peroxidation	↑ ROS		↓SOD-1 ↑catalase		Effects not wave-shape dependent
*Hong et al. (2012)	Human breast epithelial	60-Hz MF, 1 mT, 4 h		Ø ROS level		Ø SOD		

	cells (MCF10A)					Ø GSH		
Hosseinabadi and Khanjani (2019)	Serum from 152 power plant workers	Mean exposure of electric and magnetic fields were 4.09 V/m (standard deviation [SD] = 4.08) and 16.27 μT (SD = 22.99), respectively	↑ lipid peroxidation			↑ SOD, CAT, GPx		
Hosseinabadi et al (2020)	Serum from power plant workers	Mean time as power plant worker 7.1 yr; average MF(50/60 Hz) 16.7 μT					biochemical parameters changes in immune system attenuated by antioxidant vitamins	
Hosseinabadi et al (2021)	Serum from power plant workers and office workers as controls	10.4 - 25.2 V/m	↑ lipid peroxidation			↑ SOD, CAT		
Höytö et al. (2017)	Human SH-SY5Y neuroblastoma cells	50-Hz MF, 0.1 mT, 24 h		↑ cytosolic $O_2^{\cdot-}$ production; ↓ mitochondrial $O_2^{\cdot-}$ production				Mitochondria involved
Hu et al., (2016)	3xTG mouse. hippocampus	50-Hz MF, 0.5 mT, 20 h/day for three months		↑ ROS				Decreased cognitive deficits, decreaed apoptosis;

								decreased molecules involved in oxidative stress
Jajte et al. (2001)	Rat lymphocyte	50-Hz MF, 7 mT, 3 h	DNA strand breaks				DNA strand breaks induced by MF and $FeCl_2$ blocked by melatonin.	
Jajte et al. (2002)	Rat lymphocyte	Static MF, 7 mT, 3 h	↑ lipid peroxidation with MF + $FeCl_2$					
Jajte et al. (2003)	Rat lymphocyte	Static MF, 7 mT, 3 h	↑ lipid peroxidation with MF + $FeCl_2$				Effect blocked by melatonin and vitamin E	
Jakubowska-Lehrmann et al. (2022)	Bivalves Cerastoderma glaucum	Static MF or 50-Hz EMF, 6.4 mT; 8 days	↑ protein carboxylation			Ø antioxidative enzymes		
Jedrzejczak-Silicka et al. (2021)	Mouse fibroblast L929 and human keratinocytes HaCat cells	Rotating MF (30 or 50 Hz); 5.9 - 284 mT		L929 cells: ↑ ROS at 50 Hz ↓ at 30 Hz HaCaT cells: ↑ ROS at 30 and 50 Hz; ROS level inversely proportional to magnetic flux density				
Jelenković et al. (2006)	Male Wistar rat in vivo, different brain regions	50-Hz MF, 0.5 mT, 7 days	↑ lipid peroxidation in basal forebrain only	↑ $O_2^{\cdot-}$ ↑ NO		↑ SOD in basal forebrain only		Different brain regions responded differently.

Jeong et al. (2006)	Male ICR mouse in vivo, brain and spinal cord	60-Hz MF, 2 mT, 48 h		↑NO	Ø nNOS, eNOS, iNOS			Hyperalgesia observed, blocked by Ca^{2+} channel blocker
*Jin et al. (2015)	Human lung epithelial L132 cell	60-Hz MF, 1 or 2 mT, 9 h						MF did not affect H_2O_2-induced G2/M-arrested or aneuploid cells.
*Jin et al. (2012)	Mouse embryonic fibroblast NIH3T3 and human lung fibroblast WI-38 cells	60-Hz MF, I mT, 4 h						MF did not affect H_2O_2-induced micronucleus formation.
*Jin et al. (2014)	Mouse embryonic fibroblast NIH3T3, human lung fibroblast WI-38, human lung epithelial L132, and human mammary epithelial MCF10A cells	60-Hz MF,1 mT, 4 or 16 h						MF did not affect H_2O_2-induced DNA strand breaks.
Jouni et al. (2012)	Broad bean (Vicia faba L.)	Static MF, 15 mT, 8 h/day, 8 days	↑ lipid peroxidation			↑SOD ↓ CAT and peroxidase		

Kamalipooya et al. (2017)	Human cervicle cancer (HeLa) Cell, human fibroblasts	Static MF; 7, 10-16 mT, 24 or 48 h	Synergistic ↑ lipid peroxidation in cisplatin-treated cancer cells	Synergistic ↑ ROS in cisplatin-treated cancer cells				Generally, no effect on normal fibroblast cells; 10 mT caused highest effects in cancer cells
Kantar Gok et al. (2014)	Male Wistar rat in vivo, brain	50-Hz EF, 12 or 18 kV/m for 2 or 4 weeks, 1 h/day	↑ protein carboxylation in 18 kV/m 2 wk and 12 and 18 kV/m 4 wk ↑ lipid peroxidation in all exposed groups					
Karimi et al. (2019)	Male Wistar rats	50-Hz EMF, 1,100. 500, 2000 μT, 2h/day 60 days	↑ lipid peroxidation	↑total thio molecules, ↑ total oxidant staus		↑ total antioxidant activity		Rats showed improved memory retention.
Kataria et al. (2019)	soybean (Glycine max) seedlings under salt stress	Static MF, 200 mT, 1 h		↑ NO				
Kavaliers et al. (1998)	Land snail (Cepaea nemoralis) in vivo	60-Hz MF, 0.141 mT, 15 min		↑NO (possible)				MF attenuated opioid-induced analgesia by increasing NO activity
*Kesari et al. (2015)	Human neuroblastoma SH-SY5Y cells	50-Hz MF, 0.1 mT, 24 h	Ø lipid peroxidation	Ø ROS change at 15, 30, and 45 days after exposure				

Kesari et al. (2016)	Human neuroblastoma SH-SY5Y cells and rat C6 glioma cells, cells treated with menadione	50-Hz MF, 10 or 30 μT, 24 h		↑ $O_2^{\cdot-}$ cytosolic and mitochondrial in C6 cells				Increased micronucleus in SH-SY5Y cells at 30 μT; Mitochondria involved
Khadir et al. (1999)	Human neutrophils simulated by phorbol 12-myristate13-acetate	60-Hz MF, 22 mT, 10 min		↑ $O_2^{\cdot-}$				
Kim et al. (2017)	RAW 264.7 macrophage	60-Hz MF, 0.8 mT, up to 20 h		↑NO				Decreased effectiveness of antioxidant; increased macrophage activation
*Kimsa-Dudek et al (2018)	Human dermal fibroblast	Static magnetic field, 0.65T, 24 h		Ø ROS				Changes in antioxidant defense system – related gene expression; Attenuate floride-induced changes in antioxidant defense system gene expression

Kimsa-Dudek et al (2022)	Human C32 melanoma cells	Staic MF, 0.75 T	↑ DNA oxidative damage	↑ ROS				
Klimek et al. (2022)	Prefrontal cortex ofexposed rats	50-Hz EMF, 1 h/day for 7 days, 1 or 7 mT						Repeated exposure changed the oxidative/antioxidative status depending on the intensity of the EMF and the number of exposures
Koh et al. (2008)	Human prostate cancer cells (DU145, PC3, and LNCaP)	60-Hz MF, 1 mT, 6, 24, 48, 72 h		↑ H_2O_2			Blocked by NAC	Apoptosis and cell cycle arrest observed.
Kostyn et al. (2023)	Flax seedling	50 Hz, 0.5 mT, 30 min						Incaresed antioxidant potential, increased expression of ROS processing genes
Koyama et al. (2004)	pTN89 plasmids	60-Hz MF, 5 mT, 4 h						MF potentiated H_2O_2-induced mutation

Koyama et al. (2008)	Human glioblastoma A172 cell	60-Hz MF, 5 mT, 2, 4, 8, 16, or 24 h						MF potentiated H_2O_2-induced increase in apurinic/apyrimidinic sites (DNA lesion)
Kthiri et al. (2019)	Saccharomyces cerevisiae (yeast)	Static magnetic field, 250 mT, 6 and 9 h	↑ lipid peroxidation and protein carboxylation			↑ SOD and CAT ↓GP_X after 9 h exposure		Decrease in growth after 6 h and an increase between between 6 and 9 h
Kunt et al. (2016)	47 electrical workers in power transmission facility, serum	Mean working period 15.9 ± 6.72 yrs						↑ oxidative stress index (increased total oxidant status, decreased antioxidant status)
Kurzeja et al. (2013)	Mouse fibroblast	Static MF, 0.4, 0.6, and 0.7 T, 4 days						Static MF reduced oxidative stress induced by fluoride ion by normalizing antioxidant enzymes.
Kuzay et al. (2017)	Healthy and diabetic male Wistar	50-Hz MF, 8.2 mT, 20 min/day. 5	↑ lipid peroxidation	↑NO		↓GSH		

	rats, testis tissue	days/week. 1 month						
Lai and Singh (1997)	Sprague-Dawley rat in vivo, brain	60-Hz MF, 0.5 mT, 2 h	↑ DNA strand breaks				DNA strand breaks blocked by melatonin and a spin-trap compound.	
Lai and Singh (2004)	Sprague-Dawley rat in vivo, brain	60-Hz MF, 0.01 mT, 24 or 48 h	↑ DNA strand breaks				DNA strand breaks blocked by Trolox and a nitric oxide synthase inhibitor.	Effects blocked by the iron chelator deferiprone
Lai et al. (2016)	Molt-4 human leukemia cells	0.2 Hz pulses, carrier modulated 134 KHz field from radiofrequency ID chip, 1 h					Effect blocked by the spin-trap compound N-tert-butyl-alpha-phenylnitrone	Cell death, effect also bloked by the iron-chelator deferoxamine
Lazzarini et al. (2023)	Human MDA-MB-231 breast cancer cells and MCF-10A normal breast cells	50 Hz MF, 1 mt, 4h		↑ $O_2^{\cdot-}$ in mitochondria in both cell lines				
Lee et al. (2004)	Balb/c mouse in vivo, brain	60-Hz MF, 1.2 mT, 3 h	↑ lipid peroxidation	Ø $O_2^{\cdot-}$		↑SOD		
*Lee et al. (2012)	Mouse fibroblast NIH3T3	60-Hz MF, 1 mT, 4 h						MF did not affect H_2O_2-induced cellular

								transformation
Lee et al. (2010)	Human intervertebral disc cells	60-Hz EMF, 1.8 mT, 72 h						EMF induced DNA synthesis blocked by NMDA, a NO blocker
Lewicka et al. (2015)	Human blood platelet	EMF (1 kHz, 0.5 mT; 50 Hz, 10 mT, 1 kHz, 220 V/m), 30 min	↑ lipid peroxidation			↑ CAT		
*Li et al. (2015)	Human workers performed inspection near transformers and power lines, plasma	8-h time weighed average magnetic flux intensity 7.3 μT (1.56-26.33 μT), controls 0.07-0.72 μT	Ø lipid peroxidation			ØSOD Ø GPx		Ø Total antioxidant capacity, no change in micronucleus frequency
Li et al. (2013)	Male Drosophila melanogaster in vivo	50-Hz EMF, 72 h or long term (312 h), 3 mT						Short term exposure down-regulated CAT gene (endogenous antioxidant enzymes), trend of recovery with long term exposure

Lian et al. (2018)	Yeast (NT64C and SB34)	50-Hz-MF, 6 mT, 0.5- 24 h		↑ ROS at 0.5, 1 ad 2 h		↑ SOD at 1 h, ↑ CAT at 0.5 and 2 h		↑ generation and propagation of yeast prions; no ahnge in molecular chaperones (several heat-shock proteins)
Liu et al. (2014)	Sprague-Dawley rat cerebellum neurons	50-Hz MF, 1 mT, 1 h					Melatonin (MT) blocked MF-induced Na_v current, MT_2 receptor involved	
Liu et al. (2002)	Mouse in vivo, brain and liver	50-Hz EMF, 0.2 or 6 mT, 2 weeks	↑ lipid peroxidation, brain and liver			↓ GSH in liver		↓ decreased total antioxidant capacity in brain and liver, decreased cell membrane fluidity, synergism with lead
Luo et al. (2016)	ICR mouse Blood and cerebral cortex	50-Hz, 2-10 mT, 4 h/days. 28 days	↑ lipid peroxidation in serum and cerebral cortex			↓ SOD, ↓ CAT, ↓ glutathione reductase, ↓GSH-Px, and glutathione-s-transferase in serum and cerebral cortex		
Luo et al. (2019)	Sitobion avenae Fabricius (a	High-voltage electric field (HVEF); 2, 4. or 6 kV/cm; 20, 40, or 60				↓ SOD, ↓ CAT, ↓peroxidase over multiple gererations		Exposed insects have higher Co2

	herbivorous insect)	min; assayed up to 21 generations						production rate
Lupi et al. (2020)	Bees lived closed to high voltage power lines					↑ CAT, GST		
Lupi et al. (2020)	Bees lived closed to high voltage power lines and exposed to pesticides	50 Hz MF; average 1.49 μT with a mean daily peak intensity of 2.43		↑ ROS		↑ CAT, GST		
Lupke et al. (2004)	Human umbilical cord blood derived monocyte and human mono Mac 6 cells	50-Hz MF, 1 mT, 45 min		↑ total ROS, ↑ $O_2^{\cdot-}$				Mono Mac 6 cells more sensitive, activation of NADPH oxidase not NADH oxidase.
Luukkonen et al. (2014)	Human SH-SY5Y neuroblastoma cell	50-Hz MF, 0.1 mT, 24 h		↑ ROS, ↑ H_2O_2 in mitochondria				interacts with menadione; effects observed days after exposure; Mitochondria involved
Mahmoudinasab et al. (2016)	Human MCF-7 cells	50-Hz EMF, 0.25 and 0.5 mT; 5-min on/5-min off; 15-min on/15-min-off, or 30						Changes in mRNA levels of 7 antioxidant genes

		min continuously; total exposure time 30 min						
Mahmoudinasab and Saadat (2018a)	Human SH-SY5Y and MCF-7 cells	50-Hz EMF, 0.5 mT, 15 min on/ 15 min off						Up-regulation of antioxidant genes and protection of Cisplatin cytotoxicity in SH-SY5Y cells, but not MCF-7 cells
Mahmoudinasab and Saadat (2018b)	Human SHSY5Y cells	50-Hz EMFm 0.5 mT, 15 min on/15 min off or 30 min continuously						Changes in antioxidant gene NQO1↓ and NQO2↑
Maiullari et al. (2023	Human skeletal muscle cells	75 Hz pulsed EMF, 1.msec pulses, 1.5 mT; 4 h/day for 2 days				↓ SOD2		Promoted skeletal muscle cell regeneration
Maliszewska et al. (2018)	American cockroach (Periplaneta Americana L)	50-Hz EMF, 7 mT, 24, or 72 h or 7 days	↑ lipid peroxidation			↓ GSH		
Manikonda et al. (2014)	Male Wistar rat in vivo, brain (hippocampus, cerebellum and cortex)	50-Hz MF, 0.05 and 0.1 mT, 90 days	↑ lipid peroxidation	↑ ROS		↑SOD ↓ GSH/GSSG ratio		Larger response at 0.1 mT

Mannerling et al. (2010)	Human leukemia cell K562	50-Hz MF, 0.025-0.1 mT, 1 h		↑ $O_2^{\cdot-}$			Melatonin blocked MF-induced HSP70	
*Markkanen et al. (2010)	Murine L929 fibroblast	50-Hz MF, 0.1-0.3 mT, 1 h						Did not affect ROS production induced by UV.
Martinez et al. (2016)	Human neuroblastoma NB69 cells	50-Hz MF, 0.1 mT, 3-h on/3-h off for 24, 42, or 63 h, or continuously for 15-120 min					MF-induced MAPK-p38 and ERK1/2 activation blocked by NAC	
Martinez et al. (2021)	Human neuroblastoma NB69 cells	50-Hz MF, 0.1 mT, 5-30 min at day 4 after plating	↑ ROS					↑ NADPH oxidase expression
Martinez-Samano et al. (2010)	Male Wistar rat in vivo, plasma , liver, kidney and heart	60-Hz EMF, 2.4 mT, 2 h	Ø lipid peoxidation			↓ SOD in plasma of MF and restrained rats Ø CAT ↓ GSH in heart		Interacts with restraint stress
Martinez-Samano et al. (2012)	Male Wistar rat in vivo, brain	60-Hz EMF, 2.4 mT, 2 h				↓SOD ↓ CAT Ø GSH		Interacts with restraint stress
Martinez-Samano et al. (2018)	Male Wistar rat in vivo, brain	60-Hz EMF, 2.4 mT, 2 h/day, 21days	↑ lipid peroxidation in cortex and cerebellum					↑ plasma corticosterone

Martino (2011)	Human umbilical vein endothelial cell	Static MF, 0.12 and 0.03 mT (compared to 0.2-1 μT), 2 days					Increased cell proliferation attenuated by SOD	
Martino and Castello (2011)	Human fibrosarcoma HT1080, pancreatic AsPC-1 cancer cells, and bovine pulmonary artery endothelial cells	Static MF, geomagnetic field (45-60 μT) or shielded field (0.2-2 μT), 24 h		↓ H_2O_2 in shielded samples compared to geomagnetic field			MnTBAP (a ROS scavenger) inhibited MF effect.	
Medina-Fernandez et al. (2017)	Rat multiple sclerosis (MS)-like experimental model-brain and spinal cord	Transcranial magnetic stimulation (TMS); 60-Hz MF; 0.7 mT; 2 h/day,5 days/week for 3 weeks						TSM attenuated MS -like increased in lipid peroxidation, protein oxidation, and total GSH Mitochondria involved
Medina-Fernandez et al. (2018)	Rat multiple sclerosis (MS)-like experimental model-blood, brain and spinal cord	Transcranial magnetic stimulation (TMS); 60-Hz MF; 0.7 mT; 2 h/day,5 days/week for 3 weeks						TSM attenuated MS -like increased in lipid peroxidation, protein oxidation, and total GSH

Merla et al. (2019)	SH-SY5Y human neuroblastoma cells	50 Hz MF; 1 mT; 24 h		↑ ROS				Effect attenuated by NADPH oxidase inhibitor (involvement of plasma membrane)
Merighi et al. (2020)	lipopolysaccharide (LPS)-activated murine N9 microglial cells	Pulsed EMF, 1.3 ms pulses, 75 Hz, 0.1 duty cycle; 1.5 mT; 48-72 h		↑ ROS				
Miao et al. (2017)	Male BALB/c mice, in vio, testicle	Electromagnetic pulse, 200 kV/m, pulse edge 25nsm pulse width 15 ns, 0.1 Hz, 40 pulses/day, 5 days/week, 4 weeks				↓ Testicular antioxidativ capacity at 28 and 60 days after exposure		↓ spermatozoa formation
Migdal et al. (2020)	Bees	50 Hz electric field; 12 h; 5-34.5 kV/m				↑SOD; intensity-dependent changes in CAT		

Miliša et al. (2017)	Euglena viridis and Parameciumcaudatum	50-Hz EF, 2.5, 5.0, 9.3 and 13.6 kV/m, 24 h		↑ $O_2^{\cdot-}$ and H_2O_2,		↑SOD		
Mohamad EA et al. (2022)	Mosquito larvae (*Culex pipiens*)	Pulsed electric field, 4 ms; 67-117 V/cm; 20-80 pulses	↑and ↓ lipid peroxidation Depended on exposure parameterss			↓ SOD; ↑ GST, ↑and ↓ CAT Depended on exposure parameterss		
Mohamad AF et al. (2022)	S. aureus, K. pneumonia, breast cancer (MCF-7) cells	ELF-EMF, 1 mT, 2 h		↑ ROS		↑ SOD, ↓ CAT		
Mohammadi et al. (2018)	Tobacco cells	Static Magnetic field, 0.2 mT, 24 h		↑ H_2O_2 , ↑ NO				Delayed G1-S transition, increased cyclic nucleotides
Morabito et al. (2010a)	Rat pheochromocytoma PC-12 cell	50-Hz MF. 0.1 or 1 mT, 30 min or 7 days		↑ ROS in 30 min exposure at 1 mT.		↓ CAT in 0.1 and 1 mT 30-min exposure, ↑ catalase in 1 mT 7-day exposure		All effects were observed in undifferentiated and not in differentiated cells. Calcium probably involved.
Morabito et al. (2010b)	Undifferentiated C2C12 myoblast	50-Hz MF. 0.1 or 1 mT, 30 min		Ø $O_2^{\cdot-}$ ↑ H_2O_2 in 1 mT exposure		↑ CAT and GPx	NAC attenuated free radical increase by MF	Calcium probably involved; Mitochondria involved

Mshenskaya et al. (2022)	Wheat and peas	7.8 Hz, 14.3 Hz, 20.8 Hz EMF (Schumann resonances); 30 min or 18 days; 18 μT	↑and ↓ lipid peroxidation			↑CAT ↑ SOD		More pronounced effects with short term (30 min) expsoure
Mustafa et al. (2022)	Human SH-SY5Y neuroblastoma cells	50/60 Hz MF; 24 h, 0.1 mT						Effect on ROS signalling
Muti et al. (2023)	Human spermatozoa	50 Hz EMF, 1 mT, 2 h		↑ Mitochondrial $O_2^{\cdot-}$				Mitochondria involved
Naarala et al. (2017)	Rat glioma C6 cells	Nearly vertical 33 μT static MF plus a horizontal or a vertical 50-Hz 30 μT MF, 2 h		↑ cytosolic $O_2^{\cdot-}$ in vertical static field plus horizontal 50-Hz MF (but not vertical 50-Hz MF); Mitochondrial $O_2^{\cdot-}$ not affected				Cell viability not affected.
*Nakayama et al. (2016)	Mouse macrophage (RAW 264) with or without LPS stimulation	50-Hz MF, 0.5 mT, 24 h		Ø NO				
Noda et al. (2000)	Rat brain cerebellum tissues	Pulsed DC MF, 0.1 mT, 1 h			↑NOS			No effect from pulsed DC at 0.3 and 0.6 mT, 60 Hz (0.1 mT), and DC (3 or 20 mT) MF, no effect in hippocampus, cortex, medulla

								oblongagta, hypothalamus, striatum, and midbrain.
Oliva et al. (2023)	Sperm from reef forming serpulid	static MF at 0.5- 1 mT for 30 min - 48 h	↑ lipid peroxidation					
Orel et al. (2021)	Liver of Walker-256 carcinosarcoma-bearing rats	50 Hz EMF, 2040 A/m; every other day 5x after tumor implanation.	↓ lipid peroxidation			↓ SOD, CAT, GSH		
Osera et al. (2011)	Human neuroblastoma SH-SY5Y cells	72-Hz pulsed EMF, 1.3 ms pulse duration, 2 mT, 72 h				↑SOD-1		Increased quiescent cells; Mitochondria involved
Osera et al. (2015)	Human neuroblastoma SH-SY5Y cells	72-Hz pulsed EMF, 1.3 ms pulse duration, 2 mT, 10, 15, or 30 min for 4 times over 7 days, or 72 h				↑Mn-SOD		Interacts with H_2O_2. Pulsed EMF prevented H_2O_2 – induced decrease in cell number and protein expression (HSP70).
Pakhomova et al. (2012)	Jurket cells	Nanosecond pulsed electric field (300 ns, 1-12 kV/cm)		↑ROS proportional to pulse number				No effect on U937 cells

Pandir and Sahingoz (2014)	Moth Ephesta kuehniella larvae	Static MF, 1.4 T; 3, 6, 12, 24, 48, or 72 h	↑ lipid peroxidation			Exposure-time dependent ↓ SOD, CAT, GPx and GST		
Park et al. (2013)	Human bone marrow mesenchymal stem cells	50-Hz EMF, 1 mT, 90 min		↑ROS			Blocked by NAC	
Patruno et al. (2010)	Human epidermal keratinocyte cell HaCaT	50-Hz MF, 1 mT, 3, 18, 48 h		↓ $O_2^{\cdot-}$ ↑NO	↑iNOS and eNOS	↓ CAT		Increased cell proliferation.
Patruno et al. (2011)	Human epidermal keratinocyte cell HaCaT and acute myeloid leukemia THP-1 cell	50-Hz MF, 1 mT, 24 h			↑iNOS activity	↑ CAT activity		
Patruno et al. (2012)	Human acute myeloid leukemia THP-1 cell	50-Hz MF, 1 mT, 24 h		↑ $O_2^{\cdot-}$	↑iNOS	↓SOD ↓ CAT		
Patruno et al. (2015)	Human erythro-leukemic K562 cell	50-Hz MF, 1 mT, 24 h			↓ iNOS reaction velocity	↑ CAT activity		
Pilla (2012)	Human dopaminergic MN9D cells and fibroblasts	Pulsed radiofrequency signal, 2 Hz, with 127.2 MHz carrier; 2.5 μT, 15 min		↑NO				May involve activation of calcium/calmodulin nitric oxide synthase (cNOS)

*Piszczek et al (2023)	human monocytic Mono Mac 6 (MM6) cells	7 Hz, 30 mT, 3 h						No effect on ROS
Politanski et al. (2010)	C57BL/g mouse in vivo, cochlear	Static MF, 5 mT, 2 h, repeated over 14 days (also exposed to noise once)	↑ lipid peroxidation in 'MF + noise'			↑ SOD in MF, noise, and 'MF + noise', ↑ CAT activity in MF, noise, and 'MF + noise'		MF interacted with noise
Poniedziałek et al. (2013a)	Human neutrophil	EMF tuned to calcium ion cyclotron resonance frequency (up to 60 μT)		↓ ROS in unstimulated cells, ↑ in phorbol 12-myristate 13-acetate stimulated cells				
Poniedziałek et al. (2013b)	Human neutrophil	Gradient static MF, maximum value 60 mT, 15, 30 or 45 min		↓ ROS in 15-min exposure, ↑ in 45-min exposure in both unstimulated and phorbol 12-myristate 13-acetate stimulated cells, effect depended on whether samples were placed close to south or north pole of magnet.				
Pooam et al. (2017)	Human macrophage RAW264	50 Hz MF, 0.1 or 0.5 mT, 1, 17 or 24 h		↑ $O_2^{\cdot-}$				Mitochondria involved
Potenza et al. (2010)	Human umbilical vein endothelial cells	Static MF, 300 mT, 4, 24, 48, and 72 h		↑ROS only at 4-h exposure coincided with DNA damage				Mitochondria involved
Rageh et al. (2012)	10 -day old rat in vivo, brain	50-Hz MF. 0.5 mT, 30 days (24 h/day)	↑ lipid peroxidation			↑ SOD Ø GSH		

Raggi et al. (2008)	Human blood sample	Magnetic therapy device based on ion cyclotron resonance	↓ lipid peroxidation immediately and one month after exposure					
Rajabbeigi et al. (2013)	Parsley cell	Static MF, 30 mT, 6 or 12 h				↑ CAT with MF ↓ CAT with 'MF + iron'		↓ ascorbate peroxidase
Ramazi et al. (2023)	MCF-7 human breast cancer cells	50 HZ, 20 mT, 2, 24, or 48 h		↑ROS				Synergistic with doxorubicin
*Rasaeifar et al. (2023)	Transplanted mouse ovary	4.5 msec pulses, 15 Hz, 1.2 mT; 8 h/day from 2nd to 5th day of tarnsplanttaion	Ø lipid peroxidation	Ø ROS		Ø GPX, SOD		
Rauš Balind et al. (2014)	Gerbil subjected to 10-min global cerebral Ischemia in vivo, brain(forebrain, striatum and hippocampus)	50-Hz MF, 0.5 mT, 7 days						MF decreased oxidative stress induced by ischemia (NO, SOD, MDA, $O_2^{\cdot-}$)
Reale et al. (2006)	Human blood monocytes	50-Hz EMF, 1 mT, overnight			↓ iNOS			

Reale et al. (2014)	Human neuroblastoma cell SH-SY5Y	50-Hz MF, 1 mT, 1, 3, 6 or 24 h		↑ $O_2^{\cdot-}$	↑ NOS, peaked at 1 h	↑ CAT		MF enhanced oxidative effects of H_2O_2 (↓catalase, ↑ $O_2^{\cdot-}$**).**
Regoli et al. (2005)	Snail Helix aspersa in vivo, digestive gland	50-Hz MF, 0.5, 2.5,10 and 50 μT, 10 days in lab; 2.88 and 0.75 μT for 10, 20, 40, 60 days in field	Lab: Ø lipid peroxidation Field: ↑ in 2.88 μT more than 10 days and 0.75 μT more than 20 days			Lab:↓ CAT in 50 μT 10 days Field: ↓ CAT in 2.88 μT more than 10 days and 0.75 μT more than 40 days Lab: Ø GSH, ↓ Glutathione reductase Field: ↓ glutathione reductase		Total oxyl-radical scavenger capacity: Lab: ↓OH and ROO; Field: ↑OH and ↓ROO
Rollwitz et al. (2004)	Mouse bone marrow-derived promonocytes and macrophage	50-Hz MF, 1 mT, 45 min-24 h		↑ ROS, ↑ $O_2^{\cdot-}$				NADH-oxidase (not NADPH pathway) involved.
*Romeo et al. (2016)	Human fetal lung fibroblasts (MRC-5)	Static MFm 370 mT, 1 h/day for 4 days		Ø ROS				Ø viability, DNA strand breaks, and apoptosis
Roy et al. (1995)	Phorbol 12-myristate 13-acetate-stimulated rat neutrophil	60-Hz MF, 0.1 mT		↑ ROS				

Sadeghipour et al. (2012)	Human breast carcinoma cell (T47D)	100 and 217 Hz pulsed EMF, 0.1 mT, 24-72 h		↑ ROS in 217 Hz 72-h, not in 100 Hz exposure				
Sahebjamei et al. (2007)	Cultured tobacco cell	Static MF, 10 and 30 mT, 5 h/day, 5 days	↑ lipid peroxidation			↑SOD ↓ CAT and ascorbate peroxidase		
Salek et al (2021).	Mouse spermatogonial stem cells	50 Hz EMF;1 h/day for 5 days; 2.5 mT		↑ ROS		↓ CAT		
Salunke et al. (2014)	Swiss albino mouse in vivo, brain	50-Hz MF, 1 mT, 8 h/day for 7, 30, 60, 90 and 120 days		↑ NO in cortex, hippocampus, and hypothalamus				
Seif et al. (2018)	Male Wistar rats, in vivo blood	50-Hz EMF, 0.7 mT, 2 h/day. 1 month	↑ plasma protein carboxylation, methemoglobin and hemichrome			↓ plasma anti-oxidation capacity		
Seifirad et al. (2014)	Male Wistar rat in vivo, serum	60-Hz MF, 0.5 mT, 4 h or 4 h/day 14 days	↑lipid peroxidation immediately after and at 72 h after chronic exposure, Ø acute exposure					Total antioxidant activity: ↑ immediately after acute exposure (not at 3 days post-exposure), ↓immediately and 3 days after chronic exposure.

Selaković et al. (2013)	Male gerbils 3- and 10-month old in vivo, Forebrain cortex, striatum hippocampus, and cerebellum	50-Hz MF, 0.5, 0.25 and 0.1 mT, 7 days	↑ lipid peroxidation	↑ $O_2^{\cdot-}$ ↑NO		↑SOD		Dose-response observed, effects smaller and recovered faster in 3-month than in 10-month old animals.
Senol et al. (2023)	Blood of exposed rats	50-Hz electric field, 21 h/day for 30 days				↑SOD		
Shabani et al. (2021)	Substantia nigra of exposed rats	50 Hz, 3 mT; 4 h/day for 60 days	↑ lipid peroxidation			↓SOD	Effects attenuated by vitamin E	
Sharifian et al. (2009)	Human welders occupational exposure, serum and red blood cells	50-Hz EMF, 8.8-84 μT, 20-133 V/m, 40 h/week (6 days/ week)				↓SOD ↓GPX		Ø Total serum antioxidant status, a significant negative correlation between SOD/GPX and MF intensity was observed.
Sherrard et al. (2018)	Insect sf21 cells, human embroyonic kidney cells, mouse embryonic fibroblasts	Pulsed EMF. 10 Hz, peak intensity 2 mT, 15 min; with blue light		↑ROS				Effects involved cryptochromes

Shine et al (2012)	Soybean seeds	Static MF 150 and 200 mT, 1 h		↑ $O_2^{\cdot-}$, OH, H_2O_2,		↓SOD & ascorbate peroxidase		
Shokrolahi et al. (2018)	Soybean plants	Static MF, 20 and 30 mT, 5 days, 5 h/day		At 20 mT, ↓ H_2O_2,; at 30 mT, ↑ H_2O_2,		At 20 mT, ↓ CAT,; at 30 mT, ↑ CAT,		At 20 mT, ↓ gene expression of Fe transporter, ferrous content,, and gene expression and content of ferritin;,; 30 mT produced the opposite effects of these parameters
Sieroń et al. (2021)	Various organs of exposed rats	50 Hz EMF; 10 kV/m.4.3 pT; 22 h/day for 28 days	↑ lipid peroxidation in the salivary glands, esophagus, and small intestine			↑ CuZn-SOD in tongue, salivary glands, and esophagus; ↓ CAT in tongue, esophagus, and small intestine		↑ TOS in the salivary glands, esophagus, and small intestine
Simko et al. (2001)	Mouse bone marrow-derived macrophage	50-Hz MF, 0.5-1.5 mT, 45 min		↑ $O_2^{\cdot-}$				Increased phagocytic activity.
Sirmatel et al. (2007a)	Male human blood	1,5 T static MF from a MRI machine, 30 min						↑ total antioxidant capacity; ↓ total oxidant ststus and oxidative stress index

Sirmatel et al. (2007b)	Male human blood	1,5 T static MF from a MRI machine, 30 min		↑ NO (based on nitrite and nitrate leveks)				
Solek et al. (2017)	Mouse spermatogenic cell lines	2, 50, 120 Hz pulsed (1 sec on/1 sec off) and continuous-wave EMF, 2.5-8 mT, 2 h		↑ $O_2^{\cdot-}$ ↑ NO				Cell cycle arrest and apoptosis observed; Mitochondria involved
Song et al. (2018)	Human cerical cancer cells (HeLa) and lung fibroblasts (IMR-90)	60-Hz EMF 1-10 mT, up to 72 h		↓ROS				Increased cell proliferation
Sullivan et al. (2011)	Various human cell lines	Static MF, 35-120 mT		Static MF ↑ ROS at 18 h (not at 5 days) of exposure in fetal lung (WI38) cells.				Effects observed in some cell types and not in others.
Sun et al. (2015)	Preosteoclast cell line RAW264.7	Large gradient high magnetic fields (12 T, -1370 T^2/m; 12 T, 1370 T^2/m), 48 h		↓ NO				
Sun L.et al. (2018)	Human amnion epithelial cells	50-Hz MF, 0.4 mT, 15 min		↑ ROS			Inhibited by N-accetyl-l-cysteine and pyrrolidine dithiocarbamate	Increase in free radicals correlated to clustering of cell surface epidermal growth

								factor receptor
Sun Y. et al. (2018)	Caenorhabditis elegans	50-Hz EMF, 3 mT. exposed from egg to fourth larva stage		↑ ROS				
Sun YY et al. (2019)	Caenorhabditis elegans	50-Hz EMF, 3 mT		↑ ROS				↑ TAS Mitochondria involved
Tang et al. (2016)	Human Jurket cell and stimulated mouse primary T cell	7.5 Hz MF, 0.4 T, 2 h		↑ ROS		↑Total anti-oxidant activity, Ø SOD, Ø CAT		Disruption of tricarboxylic acid cycle enzymes PGE2 and formation
Tasset et al. (2012)	Male Wistar rat in vivo, brain	60-Hz MF, 0.7 mT, 2 h in the morning and 2 h in the afternoon for 21 days (applied to the head)	Ø DNA oxidative damage Ø lipid peroxidation			Ø GSH ↓ GSSG		MF reversed 3-nitropropionic acid induced oxidative stress.
Tayefi et al. (2010)	Wistar rat pup in vivo, myocardium	50-Hz MF, 3 mT, 4/h per day during gestation and to 20 day postnatal	↑ lipid peroxidation			↓ SOD		Mitochondria involved
Tekutskaya et al. (2022)	Blood of exposed rats	50 Hz EMF		↑ H_2O_2				

Tian et al. (2022)	Hippocampus of exposed mice	Hypomagnetic field (<5 μT) (elimination of geomanetic field, 8 weeks		↑ ROS				
Towari et al. (2013)	Blood of electric utility workers	Subjects classified as administrative workers (low exposure), maintenance workers (medium exposure) and liveline workers (high exposure)	↑ lipid peroxidation with increased exposure	↑ NO with increased exposure		↓ antioxidant enzymes		Decreased plasma meatonin in high-expsoure subjects.
Towari et al. (2015)	Human subjects occupationally exposed to 132 kV high-voltage substations.	142 exposed subjects (average duration of occupation=9 yrs) and 151 non-exposed individuals	↑ lipid peroxidation in exposed group	↑NO peroxidation in exposed group				
Todorovic et al. (2012)	Eggs of Baculum extradentatum (insert also known as Vietnamese walking stick)	Static MF, 50 mT; 50-Hz MF, 6 mT; exposed until completion og embryonic development				↑SOD and CAT Ø GSH		

Todorovic et al. (2019)	One-month old Blaptica dubia (cockroach) nymphs; gut assayed	110 mT Static MF or 10 mT 50-Hz MF, for 5 months				↑ SOD and CAT; Ø GSH; ↓GST and glutathione reductase		MF exposure decreased gut mass of developing cockcoach
Tony et al. (2022)	Blood of exposed rats	50 Hz EMF; 5.4 kV/m; 2 or 4 /day for 25 days	↑ lipid peroxidation			↓CAT		
Túnez et al. (2006)	Male Wistar rat in vivo, striatum	60-Hz MF, 0.7 mT, 2 h in the morning and 2 h in the afternoon for 4 days (applied to the head)						MF itself had no effect on different oxidative parameters, but reduced 3-nitropropionic acid induced oxidative and nitrosative stress.
*Türközer et al. (2008)	Guinea pig in vivo, brain	50-Hz EF, 2, 2.5, 3, 3.5, 4, 4.5, 5 V/m, 8 h/day, 3 days	Ø lipid peroxidation			Ø SOD Ø CAT and GPx		
Van Huizen et al. (2019)	Schmidtea mediterranea (planarian), regeneration after amputation	Static magnetic field;100-400 μT and 500 μT; 12, 24 or 48 h		↓ ROS after 100-400 μT and ↑ ROS after 500 μT exposure				Reduced blastema (regrowth) size at 100-400 μT, increased at 500 μT; ROS altered stem cell proliferation and differentiatio

								n depending on field intensity, inhibiting SOD pharmacologically reversed decreased regeneration effect of 200 μT
*Vannoni et al. (2012)	Human osteoarthritic chondrocyte	100-Hz EMF and a field containing various frequencies		Ø ROS		Ø GSH		
Vergallo et al. (2020)	Human Lymphocytes	Static MF, 6 mT; up to 72 h	↑ lipid peroxidation	↑ ROS				
Vignola et al. (2012)	Female Wistar rat with drug-induced myopathy, in vivo, muscle	Pulsed EMF, 50-Hz carrier frequency, 20 mT, 30 min/day, 8 days, assayed 8 days after exposure		↓NO		↓SOD		Pulsed EMF caused muscle recovery.
Villarini et al. (2006)	blood leukocytes from 4 donors	50-Hz MF; 30, 60, or 120 min; 3 mT				↑ GSH		
*Villarini et al. (2017)	SH-SY5Y5 and SK-N-BE-2 human neuroblastoma cells	50-Hz MF; 0.01, 0.1, or 1 mT; 1 h continuously	Ø DNA damage			Ø GSH/GSSG ratio		

		or 5 h intermittently						
Wang et al. (2018)	11 cancer and normal cell lines	Static magnetic field and 50- and 120-Hz MF, 6 mT, 2, 4, or 6 h		ROS measured in 4 cell lines after 2 h exposure. ↑ and ↓ ROS observed depeding on cell line and field				No change in ATP levels, ↑ and ↓ in mitochondrial membrane potential depending on cell type
*Wang et al (2019)	Human ventricular cardiomyocytes and heart tssue of exposed rats	Cells: 50 Hz MF, 100 μT, I h continuously or imtermittently 15 min on/15 off for 75 min Rats: 50 Hz MF; 100 μT, 15 h/day for 7 days		Ø ROS		Ø GSH		
Wartenberg et al. (2008)	Oral mucosa cancer cell (UM-SCC-14-C)	DC EF, 4 V/m, 24 h				↑ Cu/Zn SOD Ø CAT ↓GSH	Effects blocked by NAC.	Increased apoptosis and decreased cell proliferation.
Wójcik-Piotrowicz et al. (2023)	Mono Mac 6 and U937 leukocytic cells	Static (6 mT) and/or AC-MF (6.5 mT) (7-50 Hz) 3 x 2.5 h		↑ ROS		↓SOD1		Cell-type and wave-form dependent
Wolf et al. (2005)	HL-60 leukemia cells, Rat-1 fibroblast,	50-Hz EMF, 0.5-1 mT, 24-72 h	↑ DNA oxidative damage	↑ ROS in Rat-1 fibroblast			Effect blocked by	Dose-dependent increase in cell

	WI-38 diploid fibroblast						alpha-tocopherol.	proliferation observed.
Wu et al. (2016)	Male mice, liver	Static E-field, 9.2-21.85 kV/m, 2.3-15.4 kV/m, and 0 kV/m, 35 days	Ø lipid peroxidation			↑ SOD		No effect on glutathione-transferase and glutathione peroxidase
Xu et al. (2019)	Caenorhabditis elegans	Rotating MF, 0.2 T, 4 Hz; 10 days						reduced ROS accumulation and enhanced resistance of C. elegans to oxidation
Yang and Ye (2015)	Human osteosarcoma MG-63 cells	50-Hz EMF; 1 mT; 1,2 or 3 h		↑ ROS			Blocked by N-acetylcysteine	↓ viability and cell growth; ↑ apoptosis
Yang et al. (2016)	Sprague-Dawley rats and isolated microglial cells	EMP, 200 kV/m, 200 pulses; assayed at 1, 6, 12 and 24 h after exposure		↑ NO in cerebral cortex of rats and microglial cells, effect returned to normal at 24 h				
Yin et al. (2016)	Primary cultured rat hippocampal neurons	50-Hz MF, 8 mT, 90 min	↑ lipid peroxidation	↑ ROS		↓SOD		Mitochondria involved
Yokus et al. (2005)	Female Wistar rat in vivo,	50-Hz MF, 0.97 mT, 3	↑ DNA oxidative damage ↑lipid peroxidation					Larger effects with

	leukocytes and plasma	h/day for 50 or 100 days						longer exposure.
Yokus et al. (2008)	Male Sprague-Dawley rat in vivo, leukocytes	50-Hz MF, 0.1 and 0.5 mT, 2 h/day for 10 months	↑ different forms of oxidative DNA damage in 0.1 mT group					
*Yoon et al. (2014)	Human lung fibroblast W138 and human lung epithelial L132 cells	60-Hz MF, 1 or 2 mT, 6 h						MF did not enhance H_2O_2-induced double strand DNA breaks.(MF potentiated infra-red induced breaks).
*Yoshikawa et al. (2000)	Male BALB/C mouse injected with lipopolysaccharide (LPS) in vivo, liver	60-Hz MF, 0.1 mT, 5.5 h						MF did not induce NO generation, but enhanced LPS-induced NO generation.
Yuan et al. (2020)	Tumor cell lines including lung cancer, gastric cancer, pancreatic cancer and nephroblastoma.	50 Hz EMF modulated by static MF, time average intensity 5.1 mT, 2 h/day for 3 days		↑ ROS			Cell death and DNA damage attenuated by free radical scavenger	

*Zastko et al. (2022)	Human umbilical cord blood lymphocytes	Triangular 7.8 Hz MF, 250s On/ 250s OFF; 3-12 μT, 1- 3 h		Ø ROS				Decreased viability with amplitude window
Zeng et al. (2011)	Male Sprague-Dawley rats	EMP, 100 kV/m, 50 pps 2.5-2.8 ns width, total pulses 4x 10^5	↑ lipid peroxidation in testes			↓total SOD and manganese-SOD in testes		Changes in ultrastructures of testes
Zeng et al. (2017)	Hippocampal neurons from embryonic Sprague-Dawley rats	50-Hz MF, 2 mT; acute; 30 min, 8 h or 24 h on DIV (days in vitro) 7or 14; repeated: 30 min or 8 h DIV1-7 or DIV 7-14		↑ ROS after repeated exposure				↓ cell viability; ↑ expression of NADPH oxidase (subunit Nox2), respobsible for ROS production
Zhai et al. (2023)	Liver from mice fed high fat diet	15-Hz 5 ms EMF pulse, 2 h/day for 2 weeks at 1.6 mT	↓ lipid peroxidation	↓ ROS		↑ GPx, Ø SOD, CAT		CaMKKβ/AMPK/SREBP-1c and Nrf2 pathways involved
Zhan et al. (2022)	gut microbiota in exposed mice	hypomagnetic field (elimination of geomagnetic field); 8 or 12 weeks		↑ ROS				
Zhang BF et al. (2021)	Hippocampus of exposed mice	Hypomagnetic field (0.17 μT) (elimination of geomanetic field, 12 weeks		↓ ROS				

Zhang D. et al. (2017)	Workers occupationally exposed to EMFin a power plant	>20 yrs	↑ DNA oxidative damage (8-OHdG measured in plasma)				Effects reversed by resveratrol (500 mg twice daily, 12 months)	Exposed subjects showed reduced inflammatory biomarkers
Zhang J. et al. (2018)	RAW264.7 bone monocytes	Static MF, 500 nT, 0.2 T, 16 T; 12 h to 4 days		↑ NO (16 T) ↓ NO (500 nT and 0.2 T)	↑ NOS (16 T) ↓ NOS (500 nT and 0.2 T)			NO mediates SMF effects on osteoclast formation; effect depends on intensity of MF
Zhang Y et al. (2016)	workers with or without exposure to ELF-EMFs of 110-420kV power lines		↑ 8)HdG in exposed group					
Zhang Z et al. (2016)	Canton Special and W1118 flies	50-Hz MF, 3 mT, 12 h						Acted synergistically with heat on oxidative stress and induction of heat shock proteins, effects depends on species and sex
Zhao et al. (2011)	Human-hamster hybrid(A9L)),	Static MF, 8.5 T, 3 h		↑ ROS				Mitochondria involved

	mitochondria-deficient (p(0)A(L)) cells, double-strand break repair-deficient (XRS-5) cells							
Zhao et al. (2021)	osteosarcoma stem cells	Static MF; 0.2-0.4 T; 7 days		↑ ROS				↑ release of ferrous iron from ferritin
Zheng et al. (2022)	Taildisc of rat model of intervertebral disc degeneration	Pulsed EMF, 15 Hz pulsed bursts (pulse width 5 ms, pulse width 0.2 ms); 4 h/day for 8 weeks						Circadian effect: Day=time EMF exposure had higher SOD and lower lipid peroxidation than night-time EMF
Zwirska-Korczala et al. (2004)	Murine squamous carcinoma AT478 cell	Mixture of frequencies up to 400 Hz, MF, 0.11 mT, 16 min, assayed 24 and 72 h after exposure	↑lipid peroxidation			↑ MnSOD and Cu/ZnSOD Ø GPx	Effects attenuated by melatonin	
Zmylony et al. (2004a)	Rat lymphocytes stimulate by $FeCl_2$	50-HZ MF, 20, 40, or 200 μT, 5 or 60 min		↓ ROS in Fe and 40 μT MF exposed cells (AC MF has to be directed along the earth's static MF).				

Zmylony et al. (2004b)	Rat lymphocytes	50-HZ MF, 40 μT, 5 or 60 min	MF enhanced DNA damage caused by ultraviolet radiation (UVA). (UVA damages DNA via free radicals.)					