Chapter-1

Introduction

1.1 Electromagnetic field

In the 21st century, the environment is continually surrounded by natural or artificial fields or electromagnetic (EM) radiation of varying intensities, such as those from power transmission lines, mobile phones, televisions, radios, microwave ovens, and computers (Eliyahu et al., 2017 Swanson et al., 2019). EM radiation is a form of energy that is omnipresent and takes numerous forms, such as radio waves, microwaves, X-rays, and gamma rays. EM radiation is part of an enormous range of photon energies, wavelengths, and frequencies collectively called the EM spectrum. The EM spectrum is categorized into different sections depending on the frequencies and energy they possess. The EM spectrum is further divided into two groups: ionizing radiation and non-ionizing radiation, resulting from the differing physical characteristics of the various EM fields. Typically, lower energy radiation, such as radio waves, is expressed in terms of low-frequency (i.e., low energy/photon), and higher energy radiation or ionizing radiation, such as gamma and X-rays, are expressed in terms of high-frequency (i.e., high energy/photon). High-energy radiation has enough energy to damage DNA, lipids, and proteins directly or indirectly by removing and ionizing electrons from their orbits and producing free radicals (Powell and McMillan, 1990).

The frequency of an EM field is expressed in Hertz (Hz), which measures the number of sinusoidal cycles the wave completes each second. The following equation describes the relationship between frequency (f) and wavelength (λ):

$$\lambda = \frac{C}{f} \qquad (1.1)$$

Here,

$C = \text{Speed of light in vacuum}\ \left(3 \times 10^{8}\,\frac{\text{m}}{\text{sec}}\right) (M^{0}L^{1}T^{-1})$

$f = \text{Frequency in Hertz (Hz)}\ (M^{0}L^{0}T^{-1})$

$\lambda =$ Wavelength (meter) $(M^0L^1T^0)$

1.2 Characteristics for EM wave

The characteristics of EM wave is dependent on their energy and frequency, which can be represented in mathematical expression:

$$E \approx \upsilon \qquad (1.2)$$

$$E = h * \upsilon \qquad (1.3)$$

Here,

$E =$ Energy (Joule)$(M^1L^2T^{-2})$

$h =$ Plank′s constant

$\upsilon =$ Frequency in Hertz(Hz) $(M^0L^0T^{-1})$

EM waves are the combinations of electric and magnetic field (MF) components vibrating in the same phase but perpendicular in the direction of propagation.

1.3 Ionizing Radiation

Ionization radiation (f $\geq 30 \times 10^{15}$ Hz) contains enough EM energy to destabilize the atomic and molecular structure of matter or biological tissues (Ryan, 2012). X-ray and Gamma rays are the two most prominent forms of ionizing radiations known to cause cellular and tissue damage. The natural sources of ionizing radiations are sunlight, radioactive materials on Earth, radioactive gases, and cosmic rays from space.

1.4 Non-ionizing Radiation

Non-ionizing radiations are commonly referred to as lower frequencies of the electromagnetic spectrum. They consist of extremely low-frequency (ELF) and very-low-frequency (VLF)

($f \leq 30$ kHz), radio frequency (RF)(30 kHz $\leq f \leq 300$ GHz), infrared, visible, and ultraviolet light ($f \geq 300$ GHz) (Saliev et al., 2019).

The interaction of EM waves of a particular frequency range can benefit biological systems or vice versa. The interaction between EM waves and materials (living or non-living) is a complex issue due to the diversity of materials and the physical processes that come into play. In the past several decades, the therapeutic applications of ELF-EM field exposure to humans has grown considerably (Sackeim et al., 2020; Serafini et al., 2015; Watts et al., 2012). Numerous studies explored the applications of MF exposure in the treatment of sports injuries, non-union fractures, osteoarthritis in the knee and spine, migraine headaches, drug-resistant depression, and post-traumatic stress disorders (PTSD) (Belpomme et al., 2018; Hu et al., 2020; Pooam et al., 2020; Sherman et al., 1998; Sobiś et al., 2010; Trock et al., 1993; Watts et al., 2012).

1.5 Extremely low-frequency electromagnetic field (ELF-EMF)

Initially, it was believed that the forces of electricity and magnetism were distinct. However, in 1873, James Clerk Maxwell proposed a unified theory of electromagnetism. EM fields propagate wave-like motion through time-varying electric (E) and magnetic (M) fields. The study of electromagnetism deals with the interaction of charged particles with each other and MFs (Ishimaru, 2017). EM interactions are categorized into four types:

- Electric charges repel or attract one another with force inversely proportional to the square of their separation distance.
- Magnetic poles (north and south) act similarly to electric charges.
- A wire carrying an electric current generates a MF whose orientation is determined by the current's flow.
- MFs are created by moving electric charges and vice versa.

1.5.1 Electric field (EF)

The EF is created when two objects with different voltages or charges are brought together, and the greater the potential difference, the stronger the resulting EF. According to Coulomb's law, the force (F) experienced by the objects is

$$F = \frac{1}{4\pi\epsilon_0}\left(\frac{q_1 * q_2}{r^2}\right) \qquad (1.4)$$

$$\vec{E} = \frac{\vec{F}}{q_1} \qquad (1.5)$$

$$\vec{E} = \frac{1}{4\pi\epsilon_0}\left(\frac{q_2}{r^2}\right) \qquad (1.6)$$

$$\vec{E} = \frac{k * Q}{r^2} \qquad (1.7)$$

Here,

$\vec{E}$ = Electric field strength $(\frac{V}{m})(M^1L^1A^{-1}T^{-3})$)

q_1 = Absolute value of charge on first object (A*T)$(M^0L^0A^1T^1)$

q_2 = Absolute value of charge on second object $(A * T)(M^0L^0A^1T^1)$

k = Coulomb′s constant $(8.99 \times 10^9)(\frac{N*m^2}{C^2})(M^1L^3A^{-2}T^{-4})$

EFs exist in the environment, typically modified by various materials, i.e., walls and metal encasing. The measurement of the ELF-EF is complicated, and the role of ELF-EFs as a possible carcinogen is not supported by scientific investigations (Burdak-Rothkamm et al., 2009; Diab, 2020; Focke et al., 2010; Gholipour Hamedani et al., 2022).

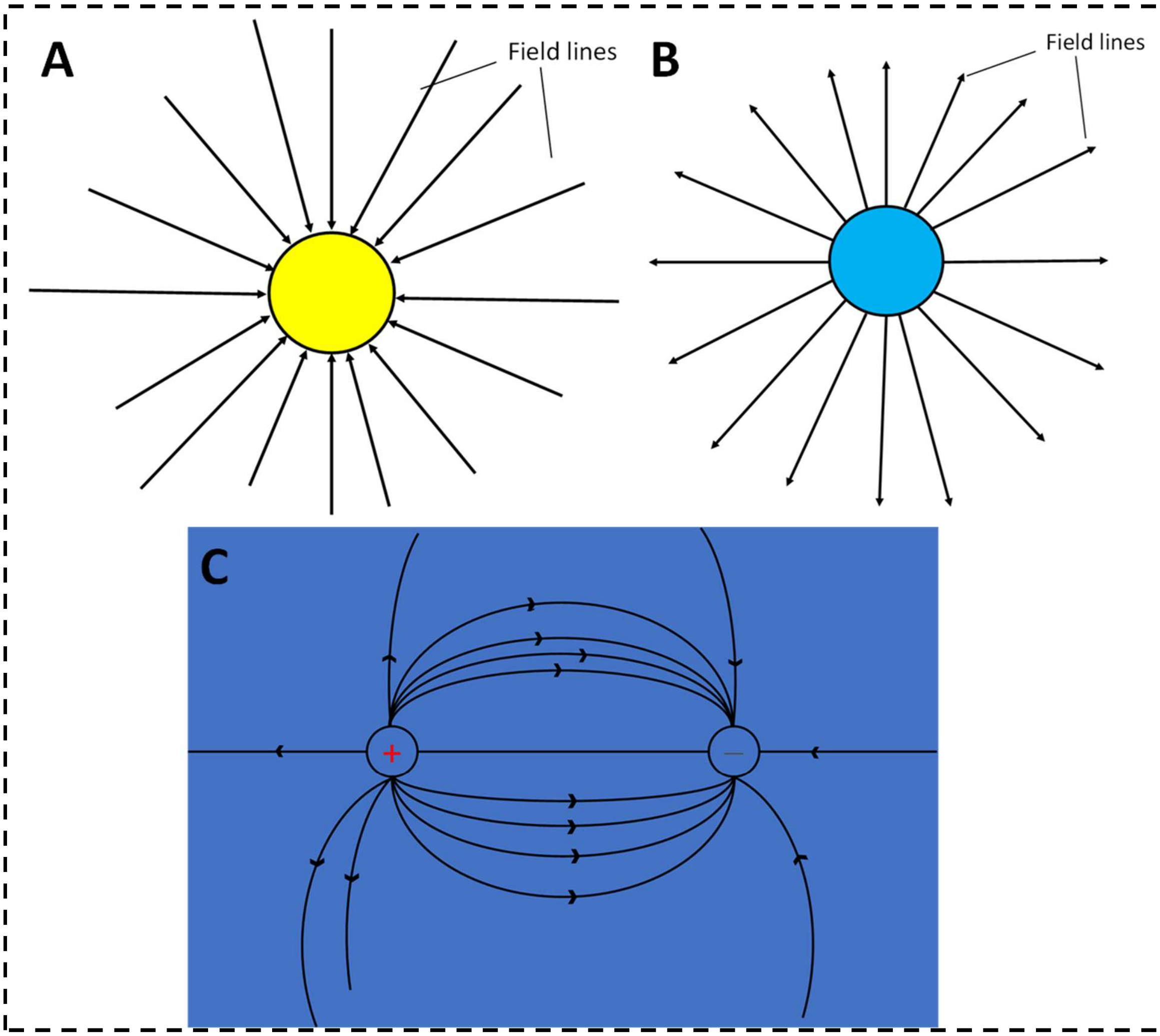

Figure 1.1 Schematic representation of EFs. (A) EF from an isolated negative charge, (B) EF from an isolated positive charge, (C) EFs lines from the opposite charges (Anita and Yadav, 2019).

1.5.2 Magnetic field (MF)

The MF is a vector field generated by moving electric charges through conducting wire in the form of current. It has two components: magnetic force (F) and magnetic flux (ϕ). It is arranged in concentric circles across the length of the conductor (Grant and Phillips, 2013). The strength of the MF at any point in space is known as magnetic flux density (B), measured in tesla (T), but field strength decreases with increasing distance from the wire.

The unit of the MF is Gauss (G) or Tesla (T), and the relation is

$$1\ \text{Tesla} = 10{,}000\ \text{Gauss} \qquad (1.8)$$

Electrical current is a sinusoidal wave and electric current's magnitude determines the MFs strength. Additionally, MF strength (H) is expressed as amperes per meter ($\frac{A}{m}$) since the motion of charged particles through conducting wires creates the MF.

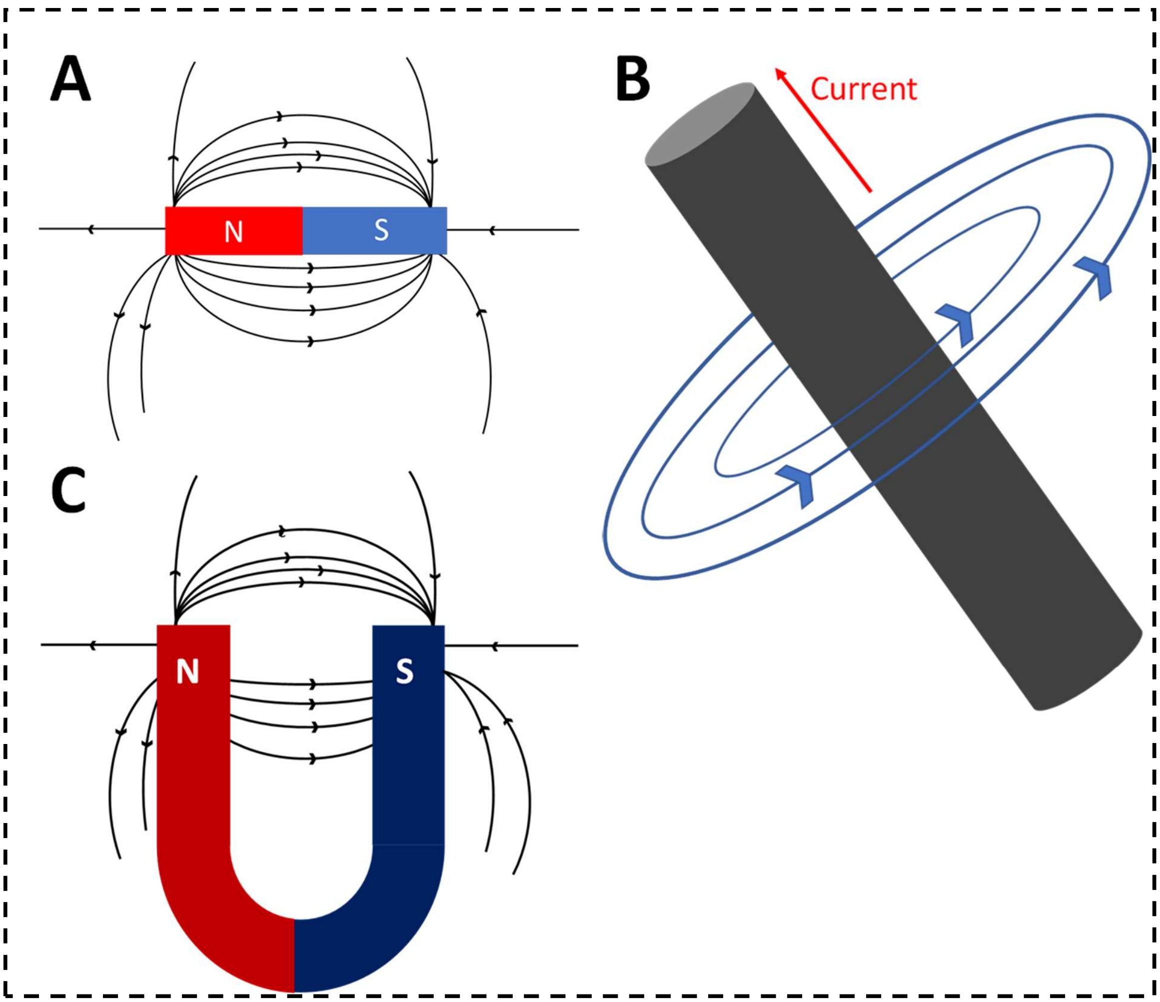

Figure 1.2 Schematic representation of MFs from different sources. (A) Bar magnet, (B) Current carrying wire, (C) Horseshoe magnet ("Magnetic field | Definition & Facts | Britannica," 2023).

1.5.2.1 Magnetic force

The magnetic force can be experienced by the current-carrying conductor of length (l), area of cross-section (A), charge (q), and due to current (i). The force (F) exerted on charge (q) is represented by the following expression

$$F = q * \upsilon * B * \sin\theta \qquad (1.9)$$

Here,

$F =$ Magnetic force in Newton (N) $(M^1L^0T^{-2}A^{-1})$

$q =$ Charge of moving particle in Coulomb (C)$(M^0L^0T^1A^1)$

$\upsilon =$ Particle velocity in meter per sec $(\frac{m}{sec})$ $(M^0L^1T^{-1})$

$B =$ Magnetic flux density in Tesla $(M^1L^0T^{-2}A^{-1})$

$\Theta =$ Angle between velocity and magnetic field

For N charges,

$$N = n * I * A \qquad (1.10)$$

Now, the total force (F_T) exerted on the conductor is

$$F_T = F * N \qquad (1.11)$$

$$F_T = B * i * I * \sin\theta \qquad (1.12)$$

also,

$$i = n * q * \upsilon * A \qquad (1.13)$$

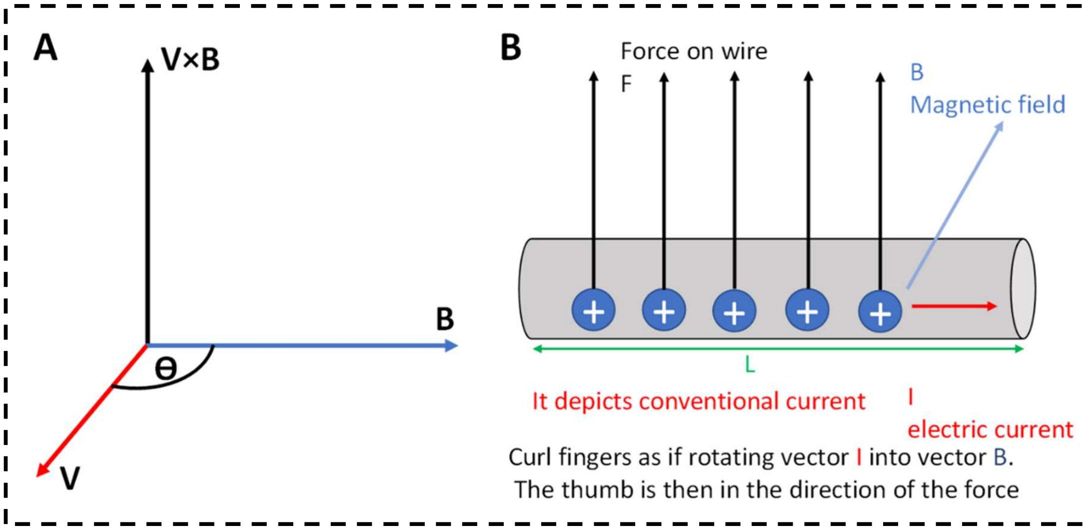

Figure 1.3 Schematic representation of magnetic force. (A) Magnetic force on moving charge, (B) Magnetic force on straight wire of length L (Jones, 2013).

1.5.2.2 Magnetic flux

Magnetic flux lines are many MF lines originating at one pole and ending as closed loops at the other (Grant and Phillips, 2013). The relationship between magnetic flux density (B) and MF strength (H) can be expressed by the following equations

$$B = \mu * H \qquad (1.14)$$

$$\mu = \mu_0 * \mu_r \qquad (1.15)$$

$$B = \mu_0 * \mu_r * H \qquad (1.16)$$

Here,

$H =$ Magnetic field strength $(\frac{\text{Ampere}}{meter})$ $(M^0 L^{-1} T^0 A^1)$

$\mu_r =$ Permeability of magnetic material

$\mu_0 =$ Permeability of free space $(4\pi \times 10^{-7}\frac{H}{M})(M^1 L^1 T^{-2} A^{-2})$

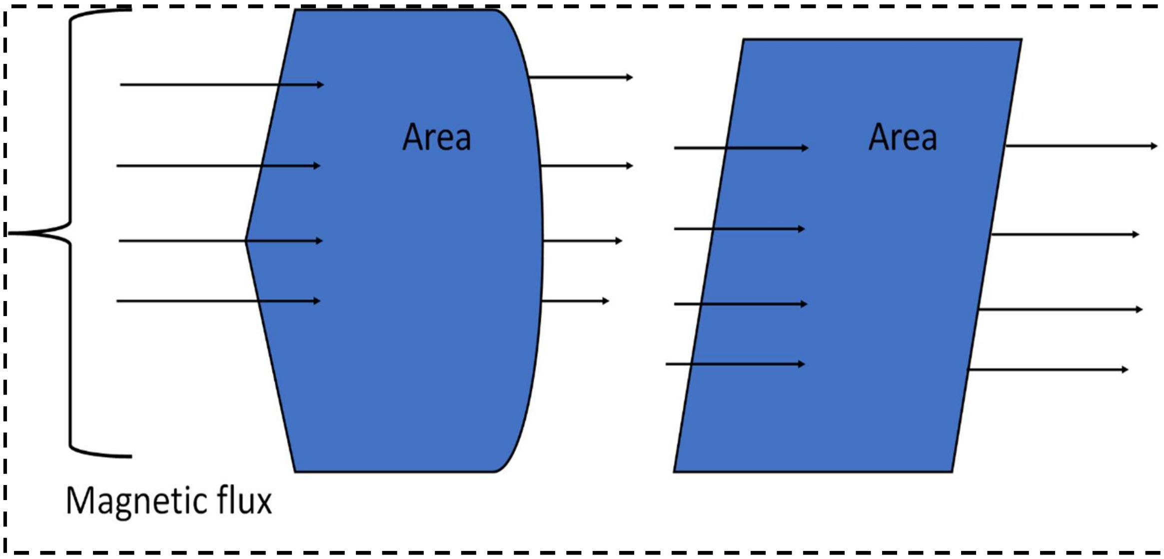

Figure 1.4 Schematic representation of magnetic flux through flat surface areas (Jones, 2013).

1.6 Sources of EM field

1.6.1 Geomagnetic field

The geomagnetic field is omnipresent and extended from the Earth's core to space. It is generated by the movement of molten metal in the outer core subjected to constant fluctuations (Campbell, 2003). Earth's MF ranges from 67 micro Tesla (μT) & 30 μT (approx.) at the poles and equator, respectively, but fluctuates by lunar disparity (Erdmann et al., 2021; Skiles, 1985). Alternatively, MFs are also generated by thunderstorms and lightning discharges between the Earth and the ionosphere. The lightning discharges can largely influence the EM waves in the ELF spectrum at 7.83 Hz (Chand et al., 2009).

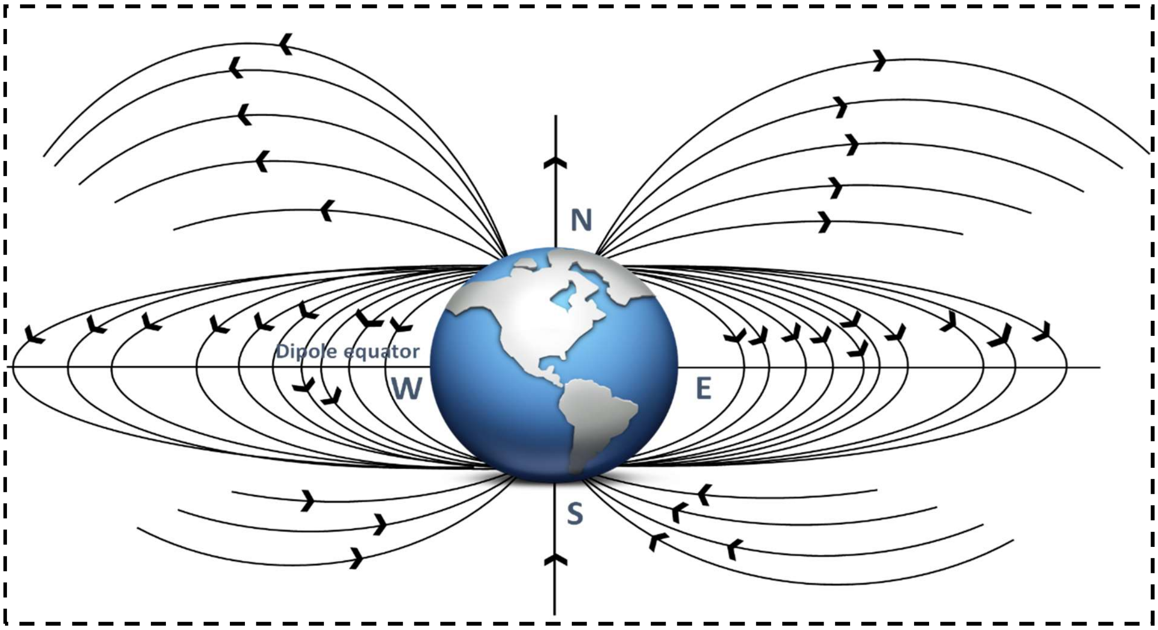

Figure 1.5 Schematic representation of geomagnetic field of Earth (Campbell, 2003).

1.6.2 Artificial magnetic field

1.6.2.1 Background magnetic fields

Background MFs primarily emitted from high-voltage transmission lines, mobile phones, and household appliances (i.e., T.V., microwave oven, dryer, etc.). Numerous scientific studies have been conducted to determine the biological effects of background MFs (Baaken et al., 2020; Karipidis, 2015; Magne et al., 2017), but the data disparity in the recorded background fields caused uncertainty in an approximation of background field. Numerous studies have also proposed that the incongruity of background MF is due to different supply voltages, and the field is subjected to vary according to electrical demand in household appliances during daytime or night-time (Banks et al., 2002; Gajšek et al., 2016; Kheifets and Oksuzyan, 2008).

1.6.2.2 Electrical appliances

In household appliances, background fields are more likely to emanate from those with looped heating elements, i.e., microwave ovens and mobile phones, as depicted in table 1.1. Numerous studies suspected that a large MFs could be a probable cause for the onset of hormone-dependent cancers, breast cancer, meningioma, and brain cancer (Levitt et al., 2022; Mumtaz et al., 2022).

Table 1.1 Typical magnetic field levels near household appliances (Baliah et al., 2022; Garrido et al., 2003; Misek et al., 2023).

Household appliances	**Distance from source in meters (m)**		
	0.00	**0.3**	**1**
Clothes washer	8-400 mG	2–30 mG	0.1–2 mG
Television	25-500 mG	0.4-20 mG	0.1–2 mG
Electric range	60-2000 mG	0-40 mG	0.1-1 mG
Microwave oven	730-2000 mG	40-80 mG	3-8 mG
Fluorescent lamp	400-4000 mG	5-20 mG	0.1-3 mG
Electric shaver	150-150000 mG	1-90 mG	0.4-3 mG
Dryer	60-20000 mG	1-70 mG	0.1-3 mG
Electric blanket	0.1 m (100 mG)	Average in the body (13 mG)	1 m (< 1 mG)
Mobile phones (2G-5G)	80-200 mG (front) 350-750 mG (back)	100 mG (front) 300 mG (back)	60 mG (front) 100 mG (back)
Antenna	>20230 µA/m	2023-8721 µA/m	674.60-2907 µA/m

mG = milligauss; µA= microampere

1.6.2.3 Power lines

The electrical power supply to household appliances occurs through a broad range of voltages and currents, primarily dependent on the distance of transmission (Halgamuge and McLean, 2018; Kroll et al., 2010; Salceanu et al., 2020). Hence, population exposure to EM fields is associated with the properties of power distribution lines. Long-distance transmission is conducted by $33 - 765$ kilovolts (kV) and $275/400$ kV high voltage transmission lines in India, but electricity is supplied in homes at a voltage ranging from $220 - 240$ volts. Hence, the strongest MF is near electrical appliances but field intensity is inversely proportional to the distance from devices. Table 1.2 illustrates the typical MF near power lines. Various studies have observed the impact of ELF-MF exposure in homes or near high-voltage power lines on the induction of neoplastic effects (Panagopoulos, 2013; Panagopoulos et al., 2021). However, some studies have found no link between living near high-voltage power lines and risk of cancer development (Kleinerman et al., 2000; Pedersen et al., 2014).

Table 1.2 Typical MF levels near power lines (Ahlbom et al., 2008).

Transmission lines	**Distance from power lines in meters**			
	0	**10**	**20**	**30**
500 kV line	81 mG	72 mG	51 mG	33 mG
230 kV line	38 mG	28 mG	15 mG	8 mG
138 kV line	33 mG	22 mG	11 mG	5 mG
69 kV line	18 mG	6 mG	3 mG	1 mG
25 kV line	10 mG	5 mG	2 mG	1 mG

mG = milligauss

1.7 Exposure guidelines

The ELF-MF exposure guidelines state that within the ELF range (≤ 100 kHz), which also includes power frequencies ($50/60$ Hz), are considered safe for household applications. In 2020, ICNIRP updated the guidelines for occupational exposure to represent workers and chronic exposure to more vital fields. Moreover, the reference limits of 500 μT and 100 μT were decided for occupational workers and the general population, respectively. ELF-MF can incite carcinogenesis, and mutation after-effects on living tissues are vaguely proposed hypotheses but not strongly backed up by valid scientific evidences. However, the application of ELF-MF as a treatment methodology for bone disorders (osteoarthritis, non-union fractures), wound healing, and selected cancers has been gaining considerable attention (Bagheri et al., 2018; Saliev et al., 2014).

1.8 Review of the existing literature

A detailed assessment of the existing work has been conducted to showcase our research findings within the context of current literature. The review has been carried out while exploring the therapeutic potential of ELF-EMF in treatment of various diseases.

1.8.1 Biophysical model of action of AC EM fields

Panagopoulos et al. proposed a biophysical model to explain the action of oscillating MFs on cells and the suitability of pulsed electromagnetic fields (PEMF) as more bioactive than continuous fields (Dj et al., 2000). This model is based on the simple hypothesis that an oscillating EM field will exert force on the free ions and incite movement/vibration through transmembrane proteins of the cell membrane. Each free ion will experience forced vibration as a result of the external electromagnetic field. When the amplitude of this forced vibration increases beyond a certain point, it will produce a false signal that will cause voltage or mechanically gated channels to open, disrupting the electrochemical balance of the plasma membrane and ultimately the function of the entire cell. The potential difference across the cell membrane under equilibrium conditions, caused by a specific type of ions, is given by the Nernst equation.

$$\Psi_0 - \Psi_i = -\frac{RT}{ZF_c} ln \frac{C_0}{C_i} \tag{1.17}$$

Here,

Ψ_0 = Electrical potential on the external surface of the membrane in volt ($M^1L^2T^{-3}A^{-1}$)

Ψ_i = Electrical potential on the internal surface of the membrane in volt ($M^1L^2T^{-3}A^{-1}$)

R = Global constant of the perfect gases ($8.314\ \mathrm{J^1K^{-1}mol^{-1}}$)($\mathrm{M^1L^2T^{-2}K^{-1}}$)

T = Absolute temperature in Kelvin (K)($\mathrm{M^0L^0T^0K^1}$)

z = Ions electric charge or valence

$\mathrm{F_c}$ = Faradays constant ($9.648 \times 10^4\mathrm{s\ A.mol^{-1}}$)($\mathrm{M^0L^0T^1A^1mol^{-1}}$)

$\mathrm{C_0}$ = Concentration of ions on the external side of the membrane

$\mathrm{C_i}$ = Concentration of ions on the internal side of the membrane

At equilibrium, the net flux of the ion is zero. The total electrical difference across the membrane will be the sum of the contributions from all the existing ions, restoring the final balance between osmotic and electrical forces.

1.8.2 Magnetic susceptibility

Magnetic susceptibility is a fundamental electromagnetic property that measures the ability of the material to become magnetized when placed in an external MF. The biological samples exhibit either positive or negative susceptibility (paramagnetic/diamagnetic), respectively (Klohs and Hirt, 2021). The volume magnetic susceptibility of a material is commonly symbolized by χ , which is represented by the following equation

$$\chi = \frac{M}{H} \qquad (1.18)$$

Here,

χ= Magnetic suceptibility

M = Magnetization (Ampere/meter)($\mathrm{M^0L^{-1}T^0A^1}$)

Both M and H are measured in A/m. Thus, magnetic susceptibility (χ) is a dimensionless unit.

Now, magnetic mass susceptibility (χ_{mass}) was calculated by:

$$\chi_{mass} = \frac{\chi}{\rho} \qquad (1.19)$$

Here,

χ_{mass} = Magnetic mass suceptibility ($M^{-1}L^3T^0A^0$)

ρ = Density of the tissues ($M^1L^{-3}T^0A^0$)

In general, human tissue and water both are diamagnetic and have volume susceptibility (χ_v) at -11.0×10^{-6} to -7.0×10^{-6} and -9.05×10^{-6} respectively (Klohs and Hirt, 2021). Red blood cells' volume magnetic susceptibility depends on the iron oxidation state in haemoglobin (Klohs and Hirt, 2021; Schenck, 1996). In the following sections, we have included the literature concerning the magnetic susceptibility of cells and tissues utilized in current work.

1.8.2.1 Magnetic susceptibility of animal tissues

The absolute value of magnetic field susceptibility is usually assumed to be close to water but the presence of grey and white matters (iron and myelin) is also contributed to the large difference between magnetic field susceptibility. Based on the literature, rat tissue samples (brain, liver and heart) are less diamagnetic ($\chi_{brain} = -9.2\ to - 8.8$ ppm) compared to the water ($\chi_{water} = -9.05$ ppm) due to the large abundance of water in tissues (Duyn and Schenck, 2017; Klohs and Hirt, 2021; Peprah et al., 2014). Moreover, pathological alterations in the brain, heart, and abdomen are associated with changes in respective magnetic susceptibilities of tissues (Klohs et al., 2011; Sharma et al., 2017; Straub et al., 2017).

Magnetic susceptibility is also an important parameter to detect the onset of neurodegenerative diseases. Kletetschka et al. studied the magnetic oscillations in brain with neurodegenerative disease and observed the possible interference in the synaptic function by the magnetic grains in human brain (Kletetschka et al., 2021).

1.8.2.2 Glial (C6) Cell line

C6 is a glial cell line isolated from the brain of a rat with glioma, and it is spindle-like cells that simulate human GBM when injected into the brain of neonatal rats (Auer et al., 1981; Xu et al., 2019). Moreover, C6 cell lines are widely used in toxicological studies to observe any harmful effects of novel therapeutic methods (Giakoumettis et al., 2018).

1.8.2.3 Mouse fibroblast red fluorescent protein (RFP-L929) cell line

RFP-L929 is an adherent type of mouse fibroblast cell line, and it is the primary constituent of the extracellular matrix and plays a critical role in wound healing. It is widely used for drug toxicity and phototoxicity assessment studies (Cannella et al., 2019; Ray et al., 2008). Previous studies explored the influence of different magnetic field exposure on ornithine decarboxylase (ODC) activity, fibroblast growth, metabolic activity and observed the difference in morphological clustering and orientation, no change in ODC activity, altered metabolic activity and cell response (Azadniv et al., 1995; Cress et al., 1999; Penafiel et al., 1997; Schuetz et al., 1985; Torricelli et al., 1998). Moreover, L929 cells also expressed the highest rate of wound healing on the lowest magnetic induction values (Jedrzejczak-Silicka et al., 2021). Based on the literature studies mentioned above RFP-L929 cell lines was seemed appropriate for *in vitro* studies in current thesis work.

1.8.2.4 Lung adenocarcinoma (A549) cell line

A549 is a human pulmonary adenocarcinoma that has morphologic and biochemical features of the pulmonary alveolar type II cell, and it was isolated from the lung tissue of a white, 58-

year-old male with lung cancer (Smith, 1977). This cell line is widely used in cancer, immuno-oncology, and toxicology research. Vu-Dinh et al. proposed effective isolation methods for lung carcinoma cells based on immunomagnetic separation, and the results showed that the concentration of A549 cells in the non-magnetic area is substantially less than in the magnetic area (Vu-Dinh et al., 2021).

1.8.2.5 Breast cancer (MCF-7) cell line

Michigan Cancer Foundation-7 (MCF-7) is a breast cancer cell line isolated in 1970 from a 69-year-old white woman, and it is widely used as a suitable model cell line for breast cancer investigations worldwide (Lee et al., 2015; Shirazi et al., 2011). Elexpuru-Zabaleta et al. studied the influence of a 50 Hz magnetic field on the viability of breast cancer cells. The result showed that cell viability is increased in short-term exposure but decreased in long-term exposure. Moreover, alteration in mitochondrial membrane potential and reactive oxygen species (ROS) production suggests that the mitochondria are a probable target of magnetic field exposure (Elexpuru-Zabaleta et al., 2022).

1.8.2.6 Hepatoblastoma (HepG2) cell line

HepG2 is a cancer cell line that was derived in 1975 from the liver tissue of a 15-year-old Caucasian male with well-differentiated hepatocellular carcinoma (Aden et al., 1979). These are epithelial in morphology and a suitable *in vitro* model system for studying polarized human hepatocytes (Moscato et al., 2015). Moreover, HepG2 and its derivatives are also used as a model system for studies of liver metabolism and toxicity assessment (Arzumanian et al., 2021).

1.8.3 *In Vivo* studies on exposure to EM fields

1.8.3.1 Toxicological assessment of ELF-EMF

The ELF-PEMFs are widely utilized for determination of toxicological after effects of short and long duration exposure studies and it has been vital to decipher the biological changes associated with occupational/household MF exposure. Tian et al. found mild changes in total bilirubin (TBIL), white blood cells (WBC), platelet, and lymphocytes but no severe long-term static magnetic field (SMF) exposure (3.5-23 T, 2 h) effects on 112C57BL/6 mice (Tian et al., 2019) . Lai et al. observed that 50 Hz EMF (100 μT) did not induce significant changes in aspartate aminotransferases (AST), alanine aminotransferases (ALT), creatinine, or structural changes in kidney and liver tissues (Lai et al., 2016). Santini et al. studied the 50 Hz EMF exposure (1000 μT, 2000 μT, 3000 μT) and observed the alterations in the liver's antioxidant levels (Santini et al., 2009, 2018). Based on the above-mentioned studies, we can conclude that toxicological effects are mostly dependent on field intensity, frequency and duration of MFs.

1.8.3.2 Effects on neurodegenerative (ND) diseases

The ELF-PEMF has been found to benefit brain functions depending on frequency and exposure duration. Moreover, it can also be used to supplement and enhance currently existing healthcare modalities. Numerous studies proposed that ELF-PEMF exposure is also able to reduce the amyloid-β peptide levels, modulate microRNA (miRNA) in Alzheimer's disease, and support better absorption of nutrients (Capelli et al., 2017; Mohammad Alizadeh et al., 2019). Perez et al. exposed primary human brain (PHB) cells culture with repeated electromagnetic field stimulation (REMFS) and observed a reduction in β-amyloid 40 (Aβ40) and β-amyloid 42 (Aβ42) levels (Perez et al., 2021). Akdag et al. investigated ELF-MF exposure effects on rat brains and observed significant changes in amyloid-β protein (BAP), protein carbonyl (PC), and malondialdehyde (MDA) levels (Akdag et al., 2013). ELF fields are also reported to influence blood glucose, fat metabolism, sperm count, central nervous system, and cardiovascular system (Akdag et al., 2010; Arash and Farhad, 2012; Nafisi et al., 2012; Nichols, 2012). However, the overall scientific evidence is mixed, and more research is needed to establish conclusive findings.

1.8.4 Effects of EM fields on cancer cells

MFs can disrupt cellular connections between molecules and electrons, potentially harming cellular functions like DNA synthesis and slowing cancer cell division and growth (Ghodbane et al., 2013; Nie et al., 2013; Spyridopoulou et al., 2018; Zhou et al., 2017). Based on the experimental conditions, we divided the literature into the following categories:

1.8.4.1 *In Vivo* studies

Nuccitelli et al. observed the effects of a pulsed electric field (PEF) (>20 kV/cm) on melanoma cells under *in vivo* conditions. The results showed significant shrinkage of tumour cells (90%) and blood flow reduction following PEMF exposure (Nuccitelli et al., 2010). Tatarov et al. studied the effects of a magnetic field (100 mT) on tumour growth and viability in mice (3 groups) with exposure duration (60, 180, 360 min daily for 4 weeks) injected with breast cancer cells. The *in vivo* imaging for tumour growth with whole-body bioluminescence imaging showed that a magnetic field of 100 mT for a duration of 360 min/day for 4 weeks caused extensive necrosis in the tumour (Tatarov et al., 2011). Emara et al. studied the therapeutic effectiveness of LF-PEMF on rat liver cancer. The results showed a significant decrease in alpha-fetoprotein (AFP) levels and a mild increase in the dielectric properties of the liver (Emara et al., 2013). Ren et al. observed upregulation of miR-34a, inhibiting iron metabolism and suppressing lung cancer after RMF (7.5 Hz, 0.4 T (2 h/day for 6 days)) exposure (Ren et al., 2017). Chen et al. conducted osteogenic PMF (0.68 at 3.846 Hz & 1.19 mT at 40.85 Hz) exposure with chemotherapy (cisplatin & pemetrexed) and observed change in cell membrane permeability followed by suppressed cell growth in A549 and MCF-7 (Chen et al., 2022).

1.8.4.2 *In Vitro* studies

Xu et al. observed upregulation in miR-486 and inhibition of AKT/mTOR signalling pathway after low-frequency (LF)-MF (0.4T,7.5 Hz, 4 h/day) exposure on human embryonic kidney cells (293T) and A549 cells (Xu et al., 2017). Ashdown et al. observed intracellular protease release and altered membrane integrity after exposure to PEMF (20 mT, 50/385 Hz, 10 min) (Ashdown et al., 2020). Tian et al. observed that the MF direction (upward) affected the growth of the human gastrointestinal stromal cancer cell line (GIST-T1), A549, human colon cancer cell (HCT116), and human lung cancer cell line (PC9) (Tian et al., 2018). Bisceglia et al. observed a noted increase in alkaline phosphate (ALP) enzymatic activity of 35% and 80% in human osteosarcoma (SaOS-2) cells and HepG2 cells, respectively (Bisceglia et al., 2011). Nuccitelli et al. investigated nanosecond pulsed electric field (nsPEF) (> 20 kV/cm) exposure effect and observed cell shrinkage and cell death in murine B16-F10 cells (Nuccitelli et al., 2006).

Based on the studies mentioned above, 50 Hz ELF-PEMF exposure as a non-invasive therapy has immense potential. Still, we need more studies to understand better the exact intensity range, frequency, and exposure duration suitable for diagnostic or therapeutic applications. Hence, this thesis attempts to develop an ELF-PEMF chamber for biomedical applications by exploring the magnetic field-induced biological effects under *in vitro* and *in vivo* conditions.

Table 1.3 The experimental studies to assess the effectiveness of ELF-PEMF exposure as an alternative diagnostic or therapeutic method.

Name of the authors	Experimental setup/modality	Results & Observation
***In vitro* studies**		
Xu et al., 2017	low-frequency magnetic fields (LF-MF): 0.4T @ 7.5 Hz Duration: 4 h/day	• Upregulation in miR-486 inhibits the AKT/mTOR signalling pathway.

Ashdown et al., 2020	PEMF: 20 mT @ 50/385 Hz Duration: 10 min	• Intracellular protease release, suggesting altered membrane integrity.
(Tian et al., 2018)	SMF: 3.5-23 T Duration: 2 h	• Magnetic field direction can affect the growth of selected cell lines (GIST-T1, A549, HCT116, PC9).
(Nuccitelli et al., 2006)	PEF: >20 kV/cm Rise time: 30 ns Duration: 300 ns	• Induced shrinkage of murine B16-F10 cell nuclei and blood flow to stop.
(Yoshizawa et al., 2002)	Rotating ELF-MF (2, 20, 100, 500 µT) Duration: 3 days	• No changes in cell growth or initial response to cell proliferation.
***In vivo* studies**		
(Tatarov et al., 2011)	PEMF: 100 mT Duration: 60, 80, 360 min/daily for 4 weeks	• Suppressed tumour growth and viability • PEMF exposure caused necrosis in tumour
(Chen et al., 2022)	PMF1: 0.68 mT @ 3.846 kHz PMF2: 1.19 mT @ 40.85 kHz (both are variations of FDA approved signals of Spinal-Stim®, Orthofix Inc. (Lewisville, TX)) Duration: 0, 4, 6, 8, 24 h (daily) Chemotherapy drugs: Cisplatin (4.0 or 8.0 µM) or Pemetrexed (5.0 or 50.0 µM)	• Suppressed cancer cell growth in A549 and MCF-7 • Apoptosis was observed when PEMF combined with pemetrexed • Perturbances in cell cycling and gene expression, as well as increased cell membrane permeability and changes in morphology • PEMF moderately inhibited tumour growth *in vitro*.
(Emara et al., 2013)	Coil A: 13-42 Gauss @ 2-3 Hz Coil B: 0.6 Tesla @ f< 1 Hz Duration: Coil A (30 min/day/rat), Coil B (5 min/day/rat)	• Significant decrease in α-feto protein (AFP). • Mild increase in dielectric properties of the liver. • LF-PEMF is therapeutically effective on rat liver cancer.

(Lai et al., 2016)	ELF-PEMF: 100 µT @ 50 Hz Duration: 24 weeks	• There were no significant changes in AST, ALT, and creatinine. • No structural changes in kidney and liver tissues.
(Lai et al., 2016)	ELF-EMF: 100 µT @ 50 Hz Duration: 20 h/day for 3 months	• No change in blood chemistry (including lipid profile, blood glucose, liver function, and renal function of rats).
(Akdag et al., 2013)	ELF-MF: 100- 500 µT @ 50 Hz Duration: 2 h/day for 10 months	• Significant changes in BAP, P.C., and MDA levels in rat brains were observed.
(Perez et al., 2021)	Repeated electromagnetic field stimulation (REMFS): 1-3 T @ 64 MHz, duration:1 h/day for 14 days	• REMFS lowered Aβ40 and Aβ42 levels in primary human brain cell (PHB) cultures. • Daily REMFS for 14 days at different lengths of exposure was non-toxic to cells and reduced Aβ40 and Aβ42 levels.
(Tian et al., 2019)	SMF: 3.5-23 T Duration: 2 h	• Food consumption and body weight decreased in the 23 T exposed group. • TBIL, WBC, platelet, and lymphocytes were affected but still in the reference range. • No severe long-term effects on 112C57BL/6 mice.
(Ren et al., 2017)	LF-MF: 0.4 T @ 7.5 Hz Duration: 35 days	• Cell growth arrest. • Inhibiting cell iron metabolism. • Stabilized p53 protein. • It enhanced miR-34a transcription induced cell proliferation.
(Nuccitelli et al., 2010)	nsPEF generator rise time & fall time: 15 ns	• Reduction in skin tumour volume. • nsPEF effects are highly localized in Charles River skin tumours.
Clinical studies		

(Zhu et al., 2020)	Low-frequency rotating static magnetic field (LFRSMF) and chemotherapy Duration: 2 h/day for 21 days	• Significant alternation in blood cytokine concentration. • It can be used as adjuvant therapy along with chemotherapy.
(Capelli et al., 2017)	EMF: 3 mT @75 Hz Duration: 15, 30,60 min	• LF-PEMF modulated the expression of all miRNAs (miR-107, miR-335, and miR-26b). • LF-PEMF can alter A.D.-related pathways.
Diagnostic applications		
(Pearlman et al., 2011)	Magnetoencephalography (WH3600 whole-head neuromagnetometer) Signal sampling: 500 Hz Bandpass: 0.01-50 Hz	• The non-invasive modality for differentiating among neoplastic brain tissues is designed to be combined with C.T. and MRI.
(Vannelli et al., 2010)	Tissue Resonance Interaction method (TRIMprob) Freq.: 465, 930 and 1395 MHz	• The analysis of resonance values showed that only the 465-MHz frequency differentiated patients with rectal cancer.
(Barbault et al., 2009)	TheraBionic Freq.: 0.1-11.4 Hz	• Successfully identified a tumour-specific frequency signature in patients diagnosed with cancer.
Therapeutic applications		
(Aaron et al., 2004)	Electric field: 1-100 mV/cm Voltage: 1-10 volts Freq.: 20-200 kHz	• EMF has efficacy similar to a graft in treating non-union fractures and spinal fusions.
(Pasche et al., 1996)	Low Energy Emission Therapy (LEET) Freq.: 27.12 MHz Bandwidth: 0.1 Hz-10 kHz	• A double-blind cross-over study demonstrated decreased sleep latency and increased sleep duration in patients treated with LEET.
(Stupp et al., 2012)	Novo Tumour Treatment Fields (TTF)-100A Electric fields: > 0.7 V/cm Freq.: 200 kHz	• Delivery of electric fields demonstrated efficacy comparable to chemotherapy regimens.

(Costa et al., 2011)	TheraBionic Freq.: 27.2 MHz Modulation depth: 85±5% R.F. output: 100 mW	• Amplitude-modulated RF-EMF demonstrated safety and antitumour effects in patients with unresectable hepatocellular carcinoma.

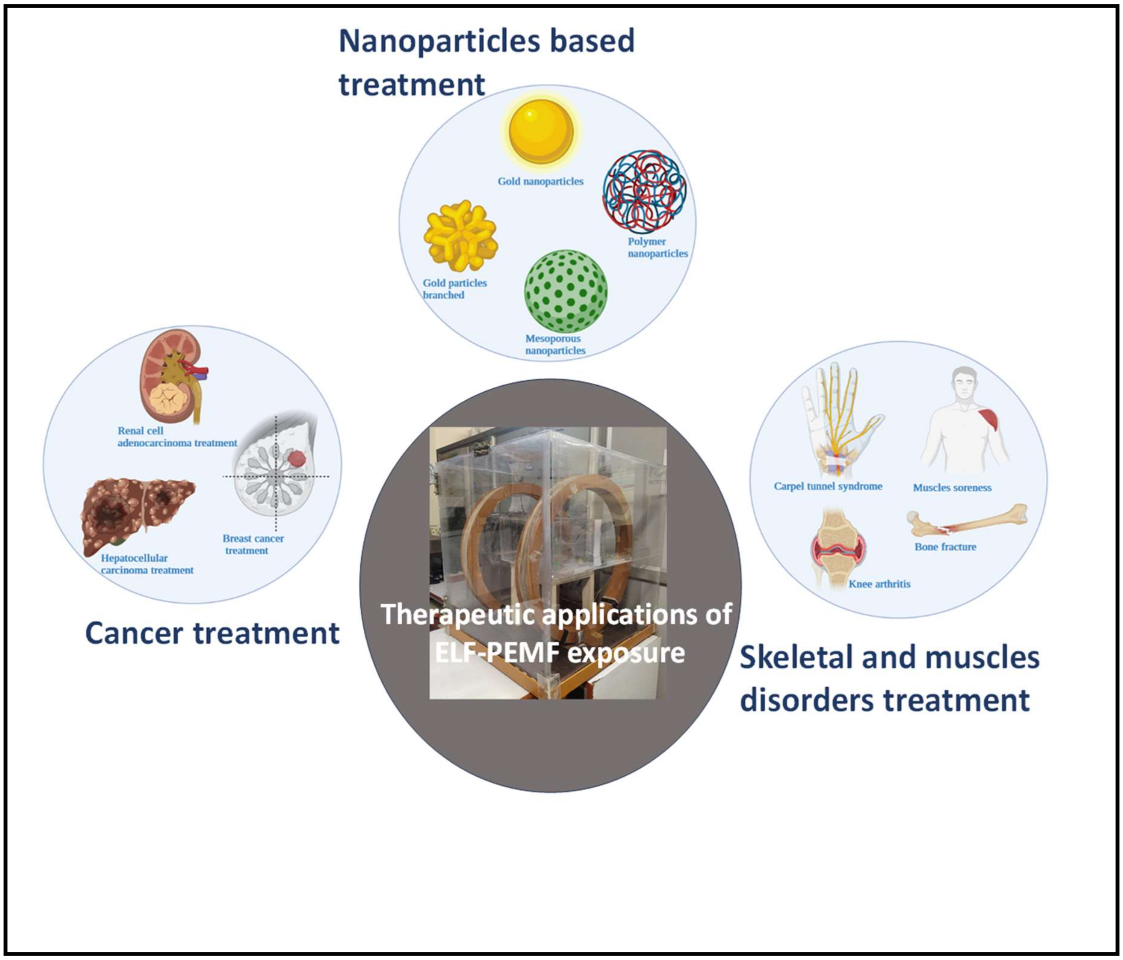

Figure 1.6 50 Hz ELF-PEMF exposure for treatment of various diseases, including cancer and skeletal muscle disorders (Goya et al., 2013; Yang et al., 2020).

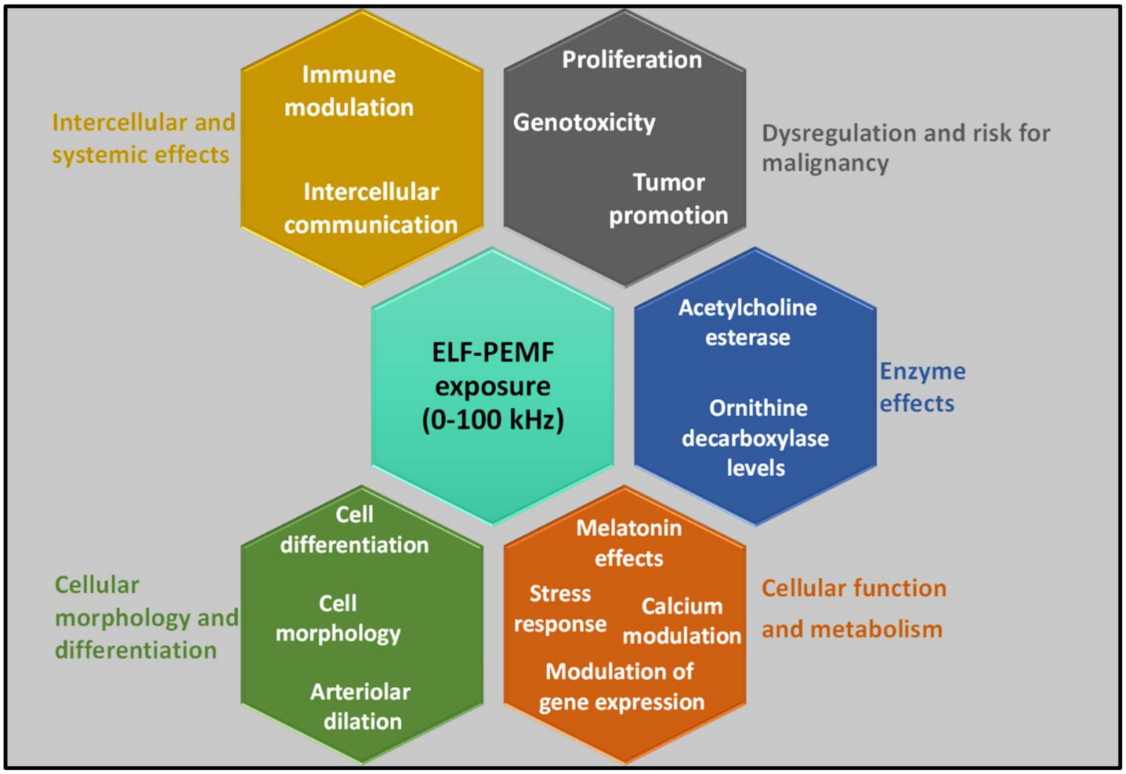

Figure 1.7 State of the art of magnetic field exposure (Xu et al., 2022).

1.9 Research objectives

The primary aim of this thesis is to design and develop an ELF-PEMF chamber for biomedical applications. Several sub-goals must be met to achieve this. As a result, the objectives have been divided into the following sections.

1. Design and development of a 50 Hz ELF-PEMF chamber for *in vivo* and *in vitro* studies. We utilised the methodologies mentioned in the literature to generate and maintain a uniform magnetic field inside chamber.

1.1 Computational and simulation studies are conducted in ANSYS 18.0 to determine the MF behaviour and homogeneity of MF.

1.2 Fabrication and magnetic field characterization of monoaxial Helmholtz coil for studying the effects of 50 Hz ELF-PEMF exposure under *in vivo* and *in vitro* conditions.

2. Effects of 50 Hz ELF-PEMF exposure on spontaneous alternation, anxiety, motor coordination and locomotor activity of adult Wistar rats and viability of C6 (Glial) cells in culture.

2.1 Assessment of 50 Hz ELF-PEMF exposure effects on C6 cell lines under *in vitro* conditions.

2.2 Assessment of 50 Hz ELF-PEMF exposure effects on behavioural and histological parameters of adult Wistar rats under *in vivo* conditions.

3. Effects of extremely low frequency 50 Hz ELF-PEMF on vital organs of adult Wistar rats and viability of mouse fibroblast cells.

3.1 Assessment of 50 Hz ELF-PEMF exposure effects on RFP-L929 cell lines under *in vitro* conditions.

3.2 Assessment of 50 Hz ELF-PEMF exposure effects on biochemical and histological parameters of adult Wistar rats under *in vivo* conditions.

3.3 Extremely low-frequency magnetic field exposure induced antiproliferative activity against selective cancer cells: an *in vitro* study

4.1 Assessment of 50 Hz ELF-PEMF exposure effects on cell proliferation of lung adenocarcinoma (A549) cells and induced cytotoxicity under *in vitro* conditions.

4.2 Assessment of 50 Hz ELF-PEMF exposure effects on cell proliferation of breast cancer (MCF-7) cells and induced cytotoxicity under *in vitro* conditions.

4.3 Assessment of 50 Hz ELF-PEMF exposure affects cell proliferation of hepatoblastoma (HepG2) cells and induced cytotoxicity under *in vitro* conditions.

1.10 Thesis outline

This thesis is organized into five chapters. **Chapter 1** (this chapter) provides a general overview of the electromagnetic spectrum, characteristics, and applications of the EM field. This chapter also presents a detailed literature review for applications of 50 Hz ELF-PEMF exposure under *in vitro* and *in vivo* conditions.

Chapter 2 describes the design and development stages of a monoaxial Helmholtz coil system. This chapter discusses the theoretical basis of uniform MF generation inside the Helmholtz coil system. Additionally, computational simulation is performed on ANSYS 18.0 to determine the MF distribution and intensity under different loading voltages. This chapter also includes the fabrication process of two 0.5-inch thick plywood circular frames of a circumference ($2\pi r = 1.66\ m$), wire length ($L_w = 898.668$ m), coil radius ($R_c = 0.265\ m$) and coil separation distance ($0.265\ m$). Moreover, we also discussed the fabrication of an acrylic sheet chamber utilized in the *in vitro* studies of different cell lines.

Chapter 3 discusses the effects of 50 Hz ELF-PEMF exposure on spontaneous alternation, anxiety, motor coordination abilities, and locomotor activities on adult Wistar rats and C6 (Glial) cell viability under *in vivo* and *in vitro* conditions, respectively. Moreover, we also conducted histological examination of rat brain tissues to assess the changes in tissue structure and morphology.

Chapter 4 discusses the utilization of 50 Hz ELF-PEMF magnetic exposure for assessment of the effects on biochemical parameters (AST, ALT, TBIL, serum creatinine, and CK-MB) and histological examination of liver, kidney, and heart of adult Wistar rats and cell viability of RFP-L929 (mouse fibroblast) cells under *in vivo* and *in vitro* conditions, respectively.

From **Chapter 5** onwards, the thesis focuses on exploring the impact of 50 Hz ELF-PEMF exposure on different cancer cell lines. The primary objective of this chapter is to compare the effects of ELF-PEMF exposure (1-3 mT, 20 min (twice) with 4 h gap) on cell proliferation of lung adenocarcinoma (A549), breast cancer (MCF-7), and hepatoblastoma (HepG2) cell lines. Moreover, we also determined the 50 Hz ELF-PEMF exposure induced cytotoxicity with MTT assay, supporting its potential for biomedical applications.

Finally, the key conclusions and future scope of work of the thesis are summarized in **Chapter 6**.

1.11 References

Aaron, R.K., Ciombor, D.M., Simon, B.J., 2004. Treatment of Nonunions With Electric and Electromagnetic Fields. Clin. Orthop. Relat. Res. 419, 21.

Aden, D.P., Fogel, A., Plotkin, S., Damjanov, I., Knowles, B.B., 1979. Controlled synthesis of HBsAg in a differentiated human liver carcinoma-derived cell line. Nature 282, 615–616. https://doi.org/10.1038/282615a0

Ahlbom, A., Bridges, J., De Seze, R., Hillert, L., Juutilainen, J., Mattsson, M.-O., Neubauer, G., Schüz, J., Simko, M., Bromen, K., 2008. Possible effects of electromagnetic fields (EMF) on human health–opinion of the scientific committee on emerging and newly identified health risks (SCENIHR). Toxicology 246, 248–50.

Akdag, M.Z., Dasdag, S., Cakir, D.U., Yokus, B., Kizil, G., Kizil, M., 2013. Do 100- and 500-μT ELF magnetic fields alter beta-amyloid protein, protein carbonyl and malondialdehyde in rat brains? Electromagn. Biol. Med. 32, 363–372. https://doi.org/10.3109/15368378.2012.721848

Akdag, M.Z., Dasdag, S., Ulukaya, E., Uzunlar, A.K., Kurt, M.A., Taşkın, A., 2010. Effects of Extremely Low-Frequency Magnetic Field on Caspase Activities and Oxidative Stress Values in Rat Brain. Biol. Trace Elem. Res. 138, 238–249. https://doi.org/10.1007/s12011-010-8615-3

Anita, Yadav, A., 2019. AEFA: Artificial electric field algorithm for global optimization. Swarm Evol. Comput. 48, 93–108. https://doi.org/10.1016/j.swevo.2019.03.013

Arash, K., Farhad, S.G., 2012. Effects of rosmarinic acid on male sex hormones (testosterone-FSH-LH) and testis tissue apoptosis after exposure to electromagnetic field (EMF) in rats. Afr. J. Pharm. Pharmacol. 6, 248–252.

Arzumanian, V.A., Kiseleva, O.I., Poverennaya, E.V., 2021. The Curious Case of the HepG2 Cell Line: 40 Years of Expertise. Int. J. Mol. Sci. 22, 13135. https://doi.org/10.3390/ijms222313135

Ashdown, C.P., Johns, S.C., Aminov, E., Unanian, M., Connacher, W., Friend, J., Fuster, M.M., 2020. Pulsed Low-Frequency Magnetic Fields Induce Tumor Membrane Disruption and Altered Cell Viability. Biophys. J. 118, 1552–1563. https://doi.org/10.1016/j.bpj.2020.02.013

Auer, R.N., Maestro, R.F.D., Anderson, R., 1981. A Simple and Reproducible Experimental in Vivo Glioma Model. Can. J. Neurol. Sci. 8, 325–331. https://doi.org/10.1017/S0317167100043468

Azadniv, M., Klinge, C.M., Gelein, R., Carstensen, E.L., Cox, C., Brayman, A.A., Miller, M.W., 1995. A Test of the Hypothesis That a 60-Hz Magnetic Field Affects Ornithine Decarboxylase Activity in Mouse L929 Cells in vitro. Biochem. Biophys. Res. Commun. 214, 627–631. https://doi.org/10.1006/bbrc.1995.2332

Baaken, D., Wollschläger, D., Samaras, T., Schüz, J., Deltour, I., 2020. EXPOSURE TO EXTREMELY LOW-FREQUENCY MAGNETIC FIELDS IN LOW- AND MIDDLE-INCOME COUNTRIES: AN OVERVIEW. Radiat. Prot. Dosimetry 191, 487–500. https://doi.org/10.1093/rpd/ncaa172

Bagheri, L., Pellati, A., Rizzo, P., Aquila, G., Massari, L., De Mattei, M., Ongaro, A., 2018. Notch pathway is active during osteogenic differentiation of human bone marrow mesenchymal stem cells induced by pulsed electromagnetic fields. J. Tissue Eng. Regen. Med. 12, 304–315. https://doi.org/10.1002/term.2455

Baliah, J., Subramanian, B., Livingstone, D., Kanwal, B., Zaman, M.U., Srivastava, K.C., Abutayyem, H., Al-Johani, K., David, A.P., Shrivastava, D., Alam, M.K., 2022. Comparative Analysis of Electric Field Strength, Magnetic Field Strength and Power Density around the Cell Phone Towers of Varying Characteristics with a Proposed Classification Facilitating Research on Human Population. Int. J. Environ. Res. Public. Health 19, 14157. https://doi.org/10.3390/ijerph192114157

Banks, R.S., Thomas, W., Mandel, J.S., Kaune, W.T., Wacholder, S., Tarone, R.E., Linet, M.S., 2002. Temporal trends and misclassification in residential 60 Hz magnetic field measurements. Bioelectromagnetics 23, 196–205.

Barbault, A., Costa, F.P., Bottger, B., Munden, R.F., Bomholt, F., Kuster, N., Pasche, B., 2009. Amplitude-modulated electromagnetic fields for the treatment of cancer: Discovery of tumor-specific frequencies and assessment of a novel therapeutic approach. J. Exp. Clin. Cancer Res. 28, 51. https://doi.org/10.1186/1756-9966-28-51

Belpomme, D., Hardell, L., Belyaev, I., Burgio, E., Carpenter, D.O., 2018. Thermal and non-thermal health effects of low intensity non-ionizing radiation: An international perspective. Environ. Pollut. 242, 643–658. https://doi.org/10.1016/j.envpol.2018.07.019

Bisceglia, B., Zirpoli, H., Caputo, M., Chiadini, F., Scaglione, A., Tecce, M.F., 2011. Induction of alkaline phosphatase activity by exposure of human cell lines to a low-frequency electric field from apparatuses used in clinical therapies. Bioelectromagnetics 32, 113–119. https://doi.org/10.1002/bem.20630

Burdak-Rothkamm, S., Rothkamm, K., Folkard, M., Patel, G., Hone, P., Lloyd, D., Ainsbury, L., Prise, K.M., 2009. DNA and chromosomal damage in response to intermittent extremely low-frequency magnetic fields. Mutat. Res. Toxicol. Environ. Mutagen. 672, 82–89.

Campbell, W.H., 2003. Introduction to Geomagnetic Fields. Cambridge University Press.

Cannella, V., Altomare, R., Chiaramonte, G., Di Bella, S., Mira, F., Russotto, L., Pisano, P., Guercio, A., 2019. Cytotoxicity Evaluation of Endodontic Pins on L929 Cell Line. BioMed Res. Int. 2019, e3469525. https://doi.org/10.1155/2019/3469525

Capelli, E., Torrisi, F., Venturini, L., Granato, M., Fassina, L., Lupo, G.F.D., Ricevuti, G., 2017. Low-frequency pulsed electromagnetic field is able to modulate miRNAs in an experimental cell model of Alzheimer's disease. J. Healthc. Eng. 2017.

Chand, R., Israil, M., Rai, J., 2009. Schumann resonance frequency variations observed in magnetotelluric data recorded from Garhwal Himalayan region India, in: Annales Geophysicae. Copernicus GmbH, pp. 3497–3507.

Chen, M.Y., Li, J., Zhang, N., Waldorff, E.I., Ryaby, J.T., Fedor, P., Jia, Y., Wang, Y., 2022. In Vitro and in Vivo Study of the Effect of Osteogenic Pulsed Electromagnetic Fields on Breast and Lung Cancer Cells. Technol. Cancer Res. Treat. 21, 15330338221124658. https://doi.org/10.1177/15330338221124658

Costa, F.P., de Oliveira, A.C., Meirelles, R., Machado, M.C.C., Zanesco, T., Surjan, R., Chammas, M.C., de Souza Rocha, M., Morgan, D., Cantor, A., Zimmerman, J., Brezovich, I., Kuster, N., Barbault, A., Pasche, B., 2011. Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields. Br. J. Cancer 105, 640–648. https://doi.org/10.1038/bjc.2011.292

Cress, L.W., Owen, R.D., Desta, A.B., 1999. Ornithine decarboxylase activity in L929 cells following exposure to 60 Hz magnetic fields. Carcinogenesis 20, 1025–1030. https://doi.org/10.1093/carcin/20.6.1025

Diab, K.A., 2020. The Impact of the Low Frequency of the Electromagnetic Field on Human, in: Turksen, K. (Ed.), Cell Biology and Translational Medicine, Volume 7: Stem Cells and Therapy: Emerging Approaches, Advances in Experimental Medicine and Biology. Springer International Publishing, Cham, pp. 135–149. https://doi.org/10.1007/5584_2019_420

Dj, P., N, M., A, K., Al, P., Lh, M., 2000. A mechanism for action of oscillating electric fields on cells. Biochem. Biophys. Res. Commun. 272. https://doi.org/10.1006/bbrc.2000.2746

Draper, G., Vincent, T., Kroll, M.E., Swanson, J., 2005. Childhood cancer in relation to distance from high voltage power lines in England and Wales: a case-control study. Bmj 330, 1290.

Duyn, J.H., Schenck, J., 2017. Contributions to magnetic susceptibility of brain tissue. NMR Biomed. 30, e3546. https://doi.org/10.1002/nbm.3546

Elexpuru-Zabaleta, M., Lazzarini, R., Tartaglione, M.F., Piva, F., Ciarapica, V., Marinelli Busilacchi, E., Poloni, A., Valentino, M., Santarelli, L., Bracci, M., 2022. A 50 Hz magnetic field influences the viability of breast cancer cells 96 h after exposure. Mol. Biol. Rep. https://doi.org/10.1007/s11033-022-08069-7

Eliyahu, I., Hareuveny, R., Riven, M., Kandel, S., Kheifets, L., 2017. 24-h personal monitoring of exposure to Power Frequency Magnetic Fields in adolescents – Results of a National Survey. Environ. Res. 158, 295–300. https://doi.org/10.1016/j.envres.2017.06.027

Emara, S.O., EL-Kholy, S.M., Kazem, A.H., Hussein, N.A., Al-dein, R.S., 2013. Therapeutic effects of low frequency pulsed electromagnetic fields on rat liver cancer. Res Inven. Int J Eng Sci 2, 17–18.

Erdmann, W., Kmita, H., Kosicki, J.Z., Kaczmarek, Ł., 2021. How the Geomagnetic Field Influences Life on Earth – An Integrated Approach to Geomagnetobiology. Orig. Life Evol. Biospheres 51, 231–257. https://doi.org/10.1007/s11084-021-09612-5

Focke, F., Schuermann, D., Kuster, N., Schär, P., 2010. DNA fragmentation in human fibroblasts under extremely low frequency electromagnetic field exposure. Mutat. Res. Mol. Mech. Mutagen. 683, 74–83.

Gajšek, P., Ravazzani, P., Grellier, J., Samaras, T., Bakos, J., Thuróczy, G., 2016. Review of Studies Concerning Electromagnetic Field (EMF) Exposure Assessment in Europe: Low Frequency

Fields (50 Hz–100 kHz). Int. J. Environ. Res. Public. Health 13, 875. https://doi.org/10.3390/ijerph13090875

Garrido, C., Otero, A.F., Cidras, J., 2003. Low-frequency magnetic fields from electrical appliances and power lines. IEEE Trans. Power Deliv. 18, 1310–1319.

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

Gholipour Hamedani, B., Goliaei, B., Shariatpanahi, S.P., Nezamtaheri, M., 2022. An overview of the biological effects of extremely low frequency electromagnetic fields combined with ionizing radiation. Prog. Biophys. Mol. Biol. 172, 50–59. https://doi.org/10.1016/j.pbiomolbio.2022.04.008

Giakoumettis, D., Kritis, A., Foroglou, N., 2018. C6 cell line: the gold standard in glioma research. Hippokratia 22, 105–112.

Goya, G.F., Asín, L., Ibarra, M.R., 2013. Cell death induced by AC magnetic fields and magnetic nanoparticles: current state and perspectives. Int. J. Hyperthermia 29, 810–818.

Grant, I.S., Phillips, W.R., 2013. Electromagnetism. John Wiley & Sons.

Halgamuge, M.N., McLean, L., 2018. Measurement and analysis of power-frequency magnetic fields in residences: Results from a pilot study. Measurement 125, 415–424. https://doi.org/10.1016/j.measurement.2018.05.007

Hu, H., Yang, W., Zeng, Q., Chen, W., Zhu, Y., Liu, W., Wang, S., Wang, B., Shao, Z., Zhang, Y., 2020. Promising application of Pulsed Electromagnetic Fields (PEMFs) in musculoskeletal disorders. Biomed. Pharmacother. 131, 110767. https://doi.org/10.1016/j.biopha.2020.110767

Ishimaru, A., 2017. Electromagnetic Wave Propagation, Radiation, and Scattering: From Fundamentals to Applications. John Wiley & Sons.

Jedrzejczak-Silicka, M., Kordas, M., Konopacki, M., Rakoczy, R., 2021. Modulation of Cellular Response to Different Parameters of the Rotating Magnetic Field (RMF)—An In Vitro Wound Healing Study. Int. J. Mol. Sci. 22, 5785. https://doi.org/10.3390/ijms22115785

Jones, D.S., 2013. The theory of electromagnetism. Elsevier.

Karipidis, K.K., 2015. Survey of residential power-frequency magnetic fields in Melbourne, Australia. Radiat. Prot. Dosimetry 163, 81–91.

Kheifets, L., Oksuzyan, S., 2008. Exposure assessment and other challenges in non-ionizing radiation studies of childhood leukaemia. Radiat. Prot. Dosimetry 132, 139–147.

Kleinerman, R.A., Kaune, W.T., Hatch, E.E., Wacholder, S., Linet, M.S., Robison, L.L., Niwa, S., Tarone, R.E., 2000. Are children living near high-voltage power lines at increased risk of acute lymphoblastic leukemia? Am. J. Epidemiol. 151, 512–515.

Kletetschka, G., Bazala, R., Takáč, M., Svecova, E., 2021. Magnetic domains oscillation in the brain with neurodegenerative disease. Sci. Rep. 11, 714. https://doi.org/10.1038/s41598-020-80212-5

Klohs, J., Deistung, A., Schweser, F., Grandjean, J., Dominietto, M., Waschkies, C., Nitsch, R.M., Knuesel, I., Reichenbach, J.R., Rudin, M., 2011. Detection of Cerebral Microbleeds with Quantitative Susceptibility Mapping in the Arcabeta Mouse Model of Cerebral Amyloidosis. J. Cereb. Blood Flow Metab. 31, 2282–2292. https://doi.org/10.1038/jcbfm.2011.118

Klohs, J., Hirt, A.M., 2021. Investigation of the magnetic susceptibility properties of fresh and fixed mouse heart, liver, skeletal muscle and brain tissue. Phys. Med. 88, 37–44. https://doi.org/10.1016/j.ejmp.2021.06.014

Kroll, M.E., Swanson, J., Vincent, T.J., Draper, G.J., 2010. Childhood cancer and magnetic fields from high-voltage power lines in England and Wales: a case–control study. Br. J. Cancer 103, 1122–1127.

Lai, J., Zhang, Y., Zhang, J., Liu, X., Ruan, G., Chaugai, S., Tang, J., Wang, H., Chen, C., Wang, D.W., 2016. Effects of 100-μT extremely low frequency electromagnetic fields exposure on hematograms and blood chemistry in rats. J. Radiat. Res. (Tokyo) 57, 16–24. https://doi.org/10.1093/jrr/rrv059

Lee, A.V., Oesterreich, S., Davidson, N.E., 2015. MCF-7 cells--changing the course of breast cancer research and care for 45 years. J. Natl. Cancer Inst. 107, djv073. https://doi.org/10.1093/jnci/djv073

Levitt, B.B., Lai, H.C., Manville, A.M., 2022. Effects of non-ionizing electromagnetic fields on flora and fauna, Part 2 impacts: how species interact with natural and man-made EMF. Rev. Environ. Health 37, 327–406. https://doi.org/10.1515/reveh-2021-0050

Magne, I., Souques, M., Bureau, I., Duburcq, A., Remy, E., Lambrozo, J., 2017. Exposure of children to extremely low frequency magnetic fields in France: Results of the EXPERS study. J. Expo. Sci. Environ. Epidemiol. 27, 505–512. https://doi.org/10.1038/jes.2016.59

Magnetic field | Definition & Facts | Britannica [WWW Document], 2023. URL https://www.britannica.com/science/magnetic-field (accessed 6.24.23).

Misek, J., Jakus, J., Hamza Sladicekova, K., Zastko, L., Veternik, M., Jakusova, V., Belyaev, I., 2023. Extremely low frequency magnetic fields emitted by cell phones. Front. Phys. 11.

Mohammad Alizadeh, M.A., Abrari, K., Lashkar Blouki, T., Ghorbanian, M. taghi, Jadidi, M., 2019. Pulsed electromagnetic field attenuated PTSD-induced failure of conditioned fear extinction. Iran. J. Basic Med. Sci. 22, 650–659. https://doi.org/10.22038/ijbms.2019.32576.7797

Moscato, S., Ronca, F., Campani, D., Danti, S., 2015. Poly(vinyl alcohol)/gelatin Hydrogels Cultured with HepG2 Cells as a 3D Model of Hepatocellular Carcinoma: A Morphological Study. J. Funct. Biomater. 6, 16–32. https://doi.org/10.3390/jfb6010016

Mumtaz, S., Rana, J.N., Choi, E.H., Han, I., 2022. Microwave Radiation and the Brain: Mechanisms, Current Status, and Future Prospects. Int. J. Mol. Sci. 23, 9288. https://doi.org/10.3390/ijms23169288

Nafisi, S., Nezhady, M.A.M., Asghari, M.H., 2012. Comparative and Mixture Effect of Cynodon Dactylon, ElectroMagnetic Field and Insulin on Diabetic Mouse. Balk. Med. J. 2012, 345–348. https://doi.org/10.5152/balkanmedj.2012.091

Nichols, T.W., 2012. Mitochondria of mice and men: Moderate magnetic fields in obesity and fatty liver. Med. Hypotheses 79, 287–293. https://doi.org/10.1016/j.mehy.2012.05.006

Nie, Y., Du, L., Mou, Y., Xu, Z., Weng, L., Du, Y., Zhu, Y., Hou, Y., Wang, T., 2013. Effect of low frequency magnetic fields on melanoma: tumor inhibition and immune modulation. BMC Cancer 13, 1–11.

Nuccitelli, R., Pliquett, U., Chen, X., Ford, W., James Swanson, R., Beebe, S.J., Kolb, J.F., Schoenbach, K.H., 2006. Nanosecond pulsed electric fields cause melanomas to self-destruct. Biochem. Biophys. Res. Commun. 343, 351–360. https://doi.org/10.1016/j.bbrc.2006.02.181

Nuccitelli, R., Tran, K., Sheikh, S., Athos, B., Kreis, M., Nuccitelli, P., 2010. Optimized nanosecond pulsed electric field therapy can cause murine malignant melanomas to self-destruct with a single treatment. Int. J. Cancer 127, 1727–1736. https://doi.org/10.1002/ijc.25364

Panagopoulos, D.J., 2013. Electromagnetic interaction between environmental fields and living systems determines health and well-being. Electromagn. Fields Princ. Eng. Appl. Biophys. Eff.

Panagopoulos, D.J., Karabarbounis, A., Yakymenko, I., Chrousos, G.P., 2021. Human-made electromagnetic fields: Ion forced-oscillation and voltage-gated ion channel dysfunction, oxidative stress and DNA damage (Review). Int. J. Oncol. 59, 1–16. https://doi.org/10.3892/ijo.2021.5272

Pasche, B., Erman, M., Hayduk, R., Mitler, M.M., Reite, M., Higgs, L., Kuster, N., Rossel, C., Dafni, U., Amato, D., Barbault, A., Lebet, J.-P., 1996. Effects of Low Energy Emission Therapy in

Chronic Psychophysiological Insomnia. Sleep 19, 327–336. https://doi.org/10.1093/sleep/19.4.327

Pearlman, M., Frye, R., Butler, I., Papanicolaou, A.C., Castillo, E., Slopis, J., 2011. Patterns of electromagnetic activity recorded from neoplastic tissue. J. Neurooncol. 105, 445–449. https://doi.org/10.1007/s11060-011-0600-y

Pedersen, C., Raaschou-Nielsen, O., Rod, N.H., Frei, P., Poulsen, A.H., Johansen, C., Schüz, J., 2014. Distance from residence to power line and risk of childhood leukemia: a population-based case–control study in Denmark. Cancer Causes Control 25, 171–177.

Penafiel, L.M., Litovitz, T., Krause, D., Desta, A., Mullins, J.M., 1997. Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929 cells. Bioelectromagnetics 18, 132–141. https://doi.org/10.1002/(SICI)1521-186X(1997)18:2<132::AID-BEM6>3.0.CO;2-3

Peprah, M.K., Astary, G.W., Mareci, T.H., Meisel, M.W., 2014. Absolute magnetic susceptibility of rat brain tissue. Magn. Reson. Med. 72, 876–879. https://doi.org/10.1002/mrm.24965

Perez, F.P., Maloney, B., Chopra, N., Morisaki, J.J., Lahiri, D.K., 2021. Repeated electromagnetic field stimulation lowers amyloid-β peptide levels in primary human mixed brain tissue cultures. Sci. Rep. 11, 621. https://doi.org/10.1038/s41598-020-77808-2

Pooam, M., Jourdan, N., Esawi, M.E., Sherrard, R.M., Ahmad, M., 2020. HEK293 cell response to static magnetic fields via the radical pair mechanism may explain therapeutic effects of pulsed electromagnetic fields. PLOS ONE 15, e0243038. https://doi.org/10.1371/journal.pone.0243038

Powell, S., McMillan, T.J., 1990. DNA damage and repair following treatment with ionizing radiation. Radiother. Oncol. 19, 95–108.

Ray, R.S., Agrawal, N., Sharma, A., Hans, R.K., 2008. Use of L-929 cell line for phototoxicity assessment. Toxicol. Vitro Int. J. Publ. Assoc. BIBRA 22, 1775–1781. https://doi.org/10.1016/j.tiv.2008.06.015

Ren, J., Ding, L., Xu, Q., Shi, G., Li, Xiaojing, Li, Xiujun, Ji, J., Zhang, D., Wang, Y., Wang, T., Hou, Y., 2017. LF-MF inhibits iron metabolism and suppresses lung cancer through activation of P53-miR-34a-E2F1/E2F3 pathway. Sci. Rep. 7, 749. https://doi.org/10.1038/s41598-017-00913-2

Ryan, J.L., 2012. Ionizing Radiation: The Good, the Bad, and the Ugly. J. Invest. Dermatol. 132, 985–993. https://doi.org/10.1038/jid.2011.411

Sackeim, H.A., Aaronson, S.T., Carpenter, L.L., Hutton, T.M., Mina, M., Pages, K., Verdoliva, S., West, W.S., 2020. Clinical outcomes in a large registry of patients with major depressive disorder treated with Transcranial Magnetic Stimulation. J. Affect. Disord. 277, 65–74. https://doi.org/10.1016/j.jad.2020.08.005

Salceanu, A., Paulet, M.V., Neagu, C.D., Bordeianu, D.F., 2020. On the coupling influence of the relative position of human trunk with respect to the overhead high-voltage power line. Acta IMEKO 9, 53–58. https://doi.org/10.21014/acta_imeko.v9i3.790

Saliev, T., Begimbetova, D., Masoud, A.-R., Matkarimov, B., 2019. Biological effects of non-ionizing electromagnetic fields: Two sides of a coin. Prog. Biophys. Mol. Biol. 141, 25–36. https://doi.org/10.1016/j.pbiomolbio.2018.07.009

Saliev, T., Mustapova, Z., Kulsharova, G., Bulanin, D., Mikhalovsky, S., 2014. Therapeutic potential of electromagnetic fields for tissue engineering and wound healing. Cell Prolif. 47, 485–493. https://doi.org/10.1111/cpr.12142

Santini, M.T., Rainaldi, G., Indovina, P.L., 2009. Cellular effects of extremely low frequency (ELF) electromagnetic fields. Int. J. Radiat. Biol. 85, 294–313. https://doi.org/10.1080/09553000902781097

Santini, S.J., Cordone, V., Falone, S., Mijit, M., Tatone, C., Amicarelli, F., Di Emidio, G., 2018. Role of Mitochondria in the Oxidative Stress Induced by Electromagnetic Fields: Focus on Reproductive Systems. Oxid. Med. Cell. Longev. 2018, e5076271. https://doi.org/10.1155/2018/5076271

Schenck, J.F., 1996. The role of magnetic susceptibility in magnetic resonance imaging: MRI magnetic compatibility of the first and second kinds. Med. Phys. 23, 815–850. https://doi.org/10.1118/1.597854

Schuetz, P.W., Barbenel, J.C., Paul, J.P., 1985. Effects of time-varying magnetic fields on fibroblast growth. Clin. Phys. Physiol. Meas. 6, 155. https://doi.org/10.1088/0143-0815/6/2/007

Schüz, J., 2011. Exposure to extremely low-frequency magnetic fields and the risk of childhood cancer: Update of the epidemiological evidence. Prog. Biophys. Mol. Biol., Non-Ionizing Radiation (NIR) and Children's Health 107, 339–342. https://doi.org/10.1016/j.pbiomolbio.2011.09.008

Serafini, G., Pompili, M., Murri, M.B., Respino, M., Ghio, L., Girardi, P., Fitzgerald, P.B., Amore, M., 2015. The Effects of Repetitive Transcranial Magnetic Stimulation on Cognitive Performance in Treatment-Resistant Depression. A Systematic Review. Neuropsychobiology 71, 125–139. https://doi.org/10.1159/000381351

Sharma, S.D., Fischer, R., Schoennagel, B.P., Nielsen, P., Kooijman, H., Yamamura, J., Adam, G., Bannas, P., Hernando, D., Reeder, S.B., 2017. MRI-based quantitative susceptibility mapping (QSM) and R2* mapping of liver iron overload: Comparison with SQUID-based biomagnetic liver susceptometry. Magn. Reson. Med. 78, 264–270. https://doi.org/10.1002/mrm.26358

Sherman, R.A., Robson, L., Marden, L.A., 1998. Initial exploration of pulsing electromagnetic fields for treatment of migraine. Headache J. Head Face Pain 38, 208–213.

Shirazi, F.H., Zarghi, A., Kobarfard, F., Zendehdel, R., Nakhjavani, M., Arfaiee, S., Zebardast, T., Mohebi, S., Anjidani, N., Ashtarinezhad, A., Shoeibi, S., Shirazi, F.H., Zarghi, A., Kobarfard, F., Zendehdel, R., Nakhjavani, M., Arfaiee, S., Zebardast, T., Mohebi, S., Anjidani, N., Ashtarinezhad, A., Shoeibi, S., 2011. Remarks in Successful Cellular Investigations for Fighting Breast Cancer Using Novel Synthetic Compounds, in: Breast Cancer - Focusing Tumor Microenvironment, Stem Cells and Metastasis. IntechOpen. https://doi.org/10.5772/23005

Skiles, D.D., 1985. The Geomagnetic Field Its Nature, History, and Biological Relevance, in: Kirschvink, J.L., Jones, D.S., MacFadden, B.J. (Eds.), Magnetite Biomineralization and Magnetoreception in Organisms: A New Biomagnetism, Topics in Geobiology. Springer US, Boston, MA, pp. 43–102. https://doi.org/10.1007/978-1-4613-0313-8_3

Smith, B.T., 1977. Cell line A549: a model system for the study of alveolar type II cell function. Am. Rev. Respir. Dis. 115, 285–293. https://doi.org/10.1164/arrd.1977.115.2.285

Sobiś, J., Jarząb, M., Hese, R.T., Sieroń, A., Zyss, T., Gorczyca, P., Gierlotka, Z., Pudlo, R., Matysiakiewicz, J., 2010. Therapeutic efficacy assessment of weak variable magnetic fields with low value of induction in patients with drug-resistant depression. J. Affect. Disord. 123, 321–326. https://doi.org/10.1016/j.jad.2009.09.016

Spyridopoulou, K., Aindelis, G., Lampri, E., Giorgalli, M., Lamprianidou, E., Kotsianidis, I., Tsingotjidou, A., Pappa, A., Kalogirou, O., Chlichlia, K., 2018. Improving the subcutaneous mouse tumor model by effective manipulation of magnetic nanoparticles-treated implanted cancer cells. Ann. Biomed. Eng. 46, 1975–1987.

Straub, S., Schneider, T.M., Emmerich, J., Freitag, M.T., Ziener, C.H., Schlemmer, H.-P., Ladd, M.E., Laun, F.B., 2017. Suitable reference tissues for quantitative susceptibility mapping of the brain. Magn. Reson. Med. 78, 204–214. https://doi.org/10.1002/mrm.26369

Stupp, R., Wong, E.T., Kanner, A.A., Steinberg, D., Engelhard, H., Heidecke, V., Kirson, E.D., Taillibert, S., Liebermann, F., Dbalỳ, V., 2012. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur. J. Cancer 48, 2192–2202.

Swanson, J., Kheifets, L., Vergara, X., 2019. Changes over time in the reported risk for childhood leukaemia and magnetic fields. J. Radiol. Prot. 39, 470. https://doi.org/10.1088/1361-6498/ab0586

Tatarov, I., Panda, A., Petkov, D., Kolappaswamy, K., Thompson, K., Kavirayani, A., Lipsky, M.M., Elson, E., Davis, C.C., Martin, S.S., DeTolla, L.J., 2011. Effect of magnetic fields on tumor growth and viability. Comp. Med. 61, 339–345.

Tian, X., Wang, D., Feng, S., Zhang, L., Ji, X., Wang, Z., Lu, Q., Xi, C., Pi, L., Zhang, X., 2019. Effects of 3.5–23.0 T static magnetic fields on mice: A safety study. NeuroImage 199, 273–280. https://doi.org/10.1016/j.neuroimage.2019.05.070

Tian, X., Wang, D., Zha, M., Yang, X., Ji, X., Zhang, L., Zhang, X., 2018. Magnetic field direction differentially impacts the growth of different cell types. Electromagn. Biol. Med. 37, 114–125.

Torricelli, P., Fini, M., Giavaresi, G., Canè, V., Giardino, R., 1998. In Vitro Evaluation of the Effects of Electromagnetic Fields used for Bone Healing. Electro- Magnetobiology 17, 335–342. https://doi.org/10.3109/15368379809030733

Trock, D.H., Bollet, A.J., Dyer Jr, R.H., Fielding, L.P., Miner, W.K., Markoll, R., 1993. A double-blind trial of the clinical effects of pulsed electromagnetic fields in osteoarthritis. J. Rheumatol. 20, 456–460.

Vannelli, A., Battaglia, L., Poiasina, E., Leo, E., 2010. Diagnosis of rectal cancer by Tissue Resonance Interaction Method. BMC Gastroenterol. 10, 45. https://doi.org/10.1186/1471-230X-10-45

Vu-Dinh, H., Feng, H., Jen, C.-P., 2021. Effective Isolation for Lung Carcinoma Cells Based on Immunomagnetic Separation in a Microfluidic Channel. Biosensors 11, 23. https://doi.org/10.3390/bios11010023

Watts, B.V., Landon, B., Groft, A., Young-Xu, Y., 2012. A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. Brain Stimulat. 5, 38–43. https://doi.org/10.1016/j.brs.2011.02.002

Xu, W., Sun, J., Le, Y., Chen, J., Lu, X., Yao, X., 2019. Effect of pulsed millisecond current magnetic field on the proliferation of C6 rat glioma cells. Electromagn. Biol. Med. 38, 185–197. https://doi.org/10.1080/15368378.2019.1608233

Xu, W., Xie, X., Wu, H., Wang, X., Cai, J., Xu, Z., E, S., 2022. Pulsed electromagnetic therapy in cancer treatment: Progress and outlook. View 20220029.

Xu, Y., Wang, Y., Yao, A., Xu, Z., Dou, H., Shen, S., Hou, Y., Wang, T., 2017. Low frequency magnetic fields induce autophagy-associated cell death in lung cancer through miR-486-mediated inhibition of Akt/mTOR signaling pathway. Sci. Rep. 7, 1–14.

Yang, X., He, H., Ye, W., Perry, T.A., He, C., 2020. Effects of Pulsed Electromagnetic Field Therapy on Pain, Stiffness, Physical Function, and Quality of Life in Patients With Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials. Phys. Ther. 100, 1118–1131. https://doi.org/10.1093/ptj/pzaa054

Yoshizawa, H., Tsuchiya, T., Mizoe, H., Ozeki, H., Kanao, S., Yomori, H., Sakane, C., Hasebe, S., Motomura, T., Yamakawa, T., Mizuno, F., Hirose, H., Otaka, Y., 2002. No effect of extremely low-frequency magnetic field observed on cell growth or initial response of cell proliferation in human cancer cell lines. Bioelectromagnetics 23, 355–368. https://doi.org/10.1002/bem.10006

Zhou, Z., Tian, R., Wang, Z., Yang, Z., Liu, Y., Liu, G., Wang, R., Gao, J., Song, J., Nie, L., 2017. Artificial local magnetic field inhomogeneity enhances T2 relaxivity. Nat. Commun. 8, 1–10.

Zhu, M., Yang, Z., Yu, H., Zhu, Q., Xu, Y., Li, Y., Li, C., Zhao, W., Liang, Z., Chen, L., 2020. The efficacy and safety of low-frequency rotating static magnetic field therapy combined with chemotherapy on advanced lung cancer patients: a randomized, double-blinded, controlled clinical trial. Int. J. Radiat. Biol. 96, 943–950. https://doi.org/10.1080/09553002.2020.1748737