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Perspectives in Environmental Toxicology

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Perspectives in Environmental Toxicology

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Foreword

The present volume is being brought out by Dr. Kavindra K. Kesari which explores in detail multidisciplinary approaches to environmental toxicology, with a focus on the following aspects:

- The effects of man-made electromagnetic fields (RF-EMF) on human health proposed mechanisms and biological effects and measures;
- An overview of nanotoxicity, nanomedicine and cancer research.
- A bio-computational approach to the molecular interaction of environmental carcinogens with DNA.
- The toxicology of environmental pollutants in the air, dust, soil, water and natural toxins in the environment: exposure and health.
- Social insects as environmental indicators of ecotoxicological effects in different ecosystems.

Environmental toxicology deals with the effects of chemicals on human health and the environment. It is an interdisciplinary science integrating biology, microbiology, chemistry, engineering, environmental sciences, ecology and even physical sciences. It pertains to innovative insights into toxic pollutants in the environment and their impacts on natural ecosystems; both freshwater and marine aquatic ecosystems in addition to terrestrial habitats. Evaluation of the environmental effects of chemicals is intricate because it depends on the organisms tested and deals with the toxicity of individual chemicals; their interactive effects, (genotoxicity, mutagenicity and immunotoxicity tests). These chemicals and factors may exhibit synergetic effects on environments which are tricky to quantify or envisage. Subjects covered are anthropogenic and natural pollution as well as feedback mechanisms and multiple stress or response to variable factors including alterations in temperature, pH and radiations.

In the opening Chapters "Neurophysiological and Behavioral Dysfunctions After Electromagnetic Field Exposure: A Dose Response Relationship" and "Induction of LPO and ROS Production in Rat Brain Exposed to Microwaves: Computational Elucidation of Melatonin in Repair System" Sharma et al. and

Kesari et al. discuss the Neurophysiological and behavioral dysfunctions after electromagnetic field exposure: A dose response relationship. In Chapter "Nanoparticles: Applications, Toxicology and Safety Aspects" Anupam Dhasmana discusses the applications and toxicological aspects of nanoparticles and recommendations of safety aspects. In Chapter "Cadmium Toxicity Showing Organ Specific Signature of Responsiveness" Sandeep Agnihotri emphasizes the signature of cadmium toxicity showing organ specific responsiveness.

There is a total of 10 chapters which discuss: biomarkers of ecotoxicological effects in social insects; environmental Toxicology of wastewater, novel treatment techniques and its irrigation reuse potential; antibiotic resistance genes: an emerging environmental pollutant; carcinogenic toxicity of cigarette smoke: a computational enzymatic interaction and DNA repair pathways; determination of *murG* transferase as a potential drug target in *Neisseria meningitides* by spectral graph theory approach; nanotoxicity: current progress and future perspectives; nanoparticles: application, safety and toxicology; nanomedicines in cancer research: an overview and toxicity of synthesized nanomaterial in natural environment.

These discussions highlight experimental and theoretical approaches to the field of environmental toxicology. In a way goad the environmentalists to make the public aware of these maladies. The present volume is a welcome approach with an intent to monitor and analyze levels of pollutants and predict future trends. The excessive use of mobile and its adverse effects call for a wide public awareness. Further topics such as transport of toxic substances, chemical and physical processes, their mitigation to prevent pollution by toxic substances should attract further discussion. The book provides recent topics for individuals interested in the field of toxicology. Overall, the book should be recommended for undergraduate or graduate students as introductory or exploratory text which endeavors the researchers on topical issues.

The present volume is intended for scientists, professionals, and graduate students interested in improving the environment. The book will be extremely useful for biotechnologists, geneticists, molecular biologists, nanotechnologists, nanobiotechnologists, and physiologists. Postgraduate students, honors students, in these disciplines having adequate background in environmental toxicology and spectrum of other researchers interested in biology and agriculture will also find the book a worthwhile reference text. We sincerely hope that the information embodied in the book will enthuse environmentalists and ameliorate upcoming new information.

Dr. Kavindra K. Kesari must be congratulated to undertake this very important topical issue.

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Preface and Acknowledgements

Perspectives in Environmental Toxicology is a comprehensive textbook deciphers the phenomena and highlights the latest developments in environmental toxicology. The fundamental information on the effect of environmental toxicants or pollutants focuses on the multidisciplinary field of science by applying the principles of biology, physics, and chemistry. The *biological* (bacteria, viruses, parasites, fungi, enzymes, biological toxicants) and *chemical* contaminations (metal contamination, pesticides, toxic chemicals, compounds, tobacco smoke, nanoparticles), and *physical* exposures (high power tension wire, electromagnetic field (EMF), electronic gadgets, medical devices) have been discussed in this book. This chemical, physical, and biological contaminants are all around us and pose a problem in the onset of various diseases or physiological disorders to human beings due to man-made substances and compounds. There are a number of different ways to affect the human health by toxic substances such as air, water, soil, and noise. Man-made EMF has been considered as an "electro-pollution" or "electrosmog" in the list of air, water, or soil pollution. The overall objectives of this book are to cover the effects of environmental toxicants in animals, plants and humans. Complementary chapters examine the environmental causes of cancer, classification of carcinogens, metabolism of chemical carcinogens, and DNA damage and repair system. This highlights the latest developments in agriculture solid waste management and ecotoxicological effects. This book has value-added collections of 10 different papers (chapters) and links to multidisciplinary approaches of environmental toxicology with a focus on the following aspects.

Chapter "Neurophysiological and Behavioral Dysfunctions After Electromagnetic Field Exposure: A Dose Response Relationship" represents the introduction of radiofrequency EMF effects on neurophysiology, brain behavior, and dose response relationship. Interestingly, this chapter not only is limited to theoretical or mechanistic view but also explores the experimental examinations. This chapter shows evidence of the effect of EMF on Alzheimer disease and neurodegeneration. Chapter "Induction of LPO and ROS Production in Rat Brain Exposed to Microwaves: Computational Elucidation of Melatonin in Repair System" investigates the effect of microwave radiations on brain antioxidative levels. The administration of melatonin against microwave radiations and computational elucidation of melatonin in repair system are the main observations. Therefore, Chapters "Neurophysiological and Behavioral Dysfunctions After Electromagnetic Field Exposure: A Dose Response Relationship" and "Induction of LPO and ROS Production in Rat Brain Exposed to Microwaves: Computational Elucidation of Melatonin in Repair System" mainly focus to explore the dose response relationship between EMF exposure and the effect on brain, and also in repair system by introducing melatonin. Chapter "Nanoparticles: Applications, Toxicology and Safety Aspects" discusses good and bad science of nanoparticles. Twenty-first century is known for both technological prosperity and environmental toxicity. This chapter mainly focuses on the applications of nanoparticle in the environmental and biomedical sciences. Also the causative factors come through environmental contaminations and recommended safety aspects have been discussed. Chapter "Cadmium Toxicity Showing Organ Specific Signature of Responsiveness" is in continuation of Chapter "Nanoparticles: Applications, Toxicology and Safety Aspects". The environmental exposures are of several types such as nanoparticle dust, metals or chemical toxicity. Toxic heavy metals like cadmium are found to be more hazardous for the biological system. This chapter mainly explores the toxic effect of cadmium, source of exposure and possible mechanism of health effects. The environmental toxicants that cause severe neurodegenerative diseases are also discussed in Chapter "Toxicity of Protein and DNA-AGEs in Neurodegenerative Diseases (NDDs) with Decisive Approaches to Stop the Deadly Consequences". This chapter's focus is to measure the toxicity of protein and DNA-AGEs in neurodegenerative diseases and to discuss approaches to stop the deadly or severe consequences, which has been associated with toxicity of glycation intermediate (dicarbonyl compounds and ketoamine moieties) and their end products. The measurement and the interaction of enzymes, proteins, and DNA repair pathways suggested to introduce by applying computational approach. Somehow, it is a problem-solving tool of experimental research. Therefore, Chapter "Carcinogenic Toxicity of Cigarette Smoke: A Computational Enzymatic Interaction and DNA Repair Pathways" first time introduces *in silico* approach to find molecular interaction of cigarette smoke carcinogens with enzymes involved in DNA repair pathways. In this continuation, Chapter "Determination of *murG* Transferase as a Potential Drug Target in *Neisseria meningitides* by Spectral Graph Theory Approach" deciphering the fundamentals for the determination of *murG* transferase as a potential drug target in *Neisseria meningitides* by spectral graph theory. Interestingly 3D structure of *murG* transferase has been suggested for further use in *in silico* drug designing by docking methods with suitable inhibitors. This is growing area of research, which has fruitful and novel use in wet laboratory and cancer research. Cancer or associated health concerns are becoming severe nowadays due to an increasing environmental exposure or toxicity. This exposure has a big source of agricultural solid wastes. Chapter "Review processing, Properties and Applications of Agricultural Solid Waste: Effect of an Open Burning in Environmental Toxicology" shows the pros and cons of solid wastes. The wastes such as rice straw, husk, sugarcane bagasse, leaves or other biomass found good source of bioenergy or biofuel in this chapter, where as the open burning of these agricultural wastes has reported hazardous effect on human health and the environment. This article provides the pathway of mechanism and future recommendations for the use of agriculture wastes as a bioresource for the production of biofuel or bioenergy. Some of the waste has also use in biomedical science like silica nanoparticles, which could be synthesized from rice husk. Concerning medical sciences, Chapter "Antibiotic Resistance Genes: An Emerging Environmental Pollutant" gives an overview on the impact of antibiotics resistance bacteria (ARB) and antibiotic resistance genes (ARGs) as an environmental pollutant into different form of the environment. ARB and ARGs have been extensively detected in wastewater, agricultural soil, animal manure and hospital waste. This type of environmental pollution found more dangerous and causative for human health and need to be exploring by providing the experimental data. Now from Chapter "Neurophysiological and Behavioral Dysfunctions After Electromagnetic Field Exposure: A Dose Response Relationship"–"Antibiotic Resistance Genes: An Emerging Environmental Pollutant" it is very clear that day by day, our environment is getting highly polluted due to man-made sources. The above-reported types of environmental toxicants or pollutants are very dangerous for climate change and ecosystem, insects, soil organisms, and human beings. Chapter "Biomarkers of Ecotoxicological Effects in Social Insects" explores the biomarkers of ecotoxicological effects in social insects. For the ecotoxicity testing, biochemical, morphological, or behavioral parameters of living organisms have been set to biomarkers of exposure, effect or susceptibility or biomarkers of defense and damage. Social insects such as ants, drosophila are well indicators of the lifespan and healthy environment.

This is the first book ever providing comprehensive evidence on multidisciplinary approach of total environmental toxicity for students, research scholars, academicians, scientists, and layman. This book is fundamentally, theoretically, and principally strong to present the mechanisms of interaction of environmental toxicity and human health by flow diagrams. This book analyzes the carcinogenic, mutagenic, genotoxic, and neurotoxic effects of both anthropogenic and natural toxins present in water, soil, air, and our surroundings in the form of electropollution or electrosmog. All Chapters "Neurophysiological and Behavioral Dysfunctions After Electromagnetic Field Exposure: A Dose Response Relationship"–"Toxicity of Protein and DNA-AGEs in Neurodegenerative Diseases (NDDs) with Decisive Approaches to Stop the Deadly Consequences" have followup links from each other, and conclude that reactive oxygen species (ROS) is the responsible factor for all types of induced environmental toxicity and human health. I hope this book will serve as both an excellent review and a valuable reference for formulating suitable measures against environmental toxicology and for promoting the science involved in this area of research.

Finally, I would like to dedicate this book to my mother, late Parwati Devi. She passed away on 31 January 2016, and left her infinite blessings for all my success. I would like to thank my father, Dr. Arjundas Kesari, who has given me much encouragement and support. I would like to thank all authors who have contributed to this book. Last but not least, my special thanks go to series editor, publisher, and entire Springer team for their sincere assistance and support.

Kuopio, Finland Kavindra Kumar Kesari, Ph.D.

Contents

Neurophysiological and Behavioral Dysfunctions After Electromagnetic Field Exposure: A Dose Response Relationship

Archana Sharma, Kavindra Kumar Kesari, H.N. Verma and Rashmi Sisodia

Abstract For decades, there has been an increasing concern about the potential hazards of ionizing and non-ionizing radiations on human health. This chapter provides several evidences related to pathophysiology of electromagnetic field (EMF) and its effects on different tissues and organs with special reference to neurophysiological and behavioral dysfunctions. Developing central nervous system (CNS) is extremely sensitive to EMF due to various factors especially due to presence of the high amount of water content, lipids and low amount of antioxidant enzymes. Therefore, the study is focused on the effects of radio frequency (RF) EMF and extremely low frequency magnetic field (ELF MF) on neurological disorders. The severity of effects always depends on exposure doses like, exposure duration, position of subjects, power density and field intensity, which could be measured in terms of specific absorption rate (SAR). There are several biomarkers, which are very useful to measure the radiation effects in both in vitro and in vivo model. The most intensely studied biomarkers by various researchers in CNS are protein kinase C, micronuclei, mitochondrial pathways, melatonin, calcium ion concentration, antioxidant enzymes like glutathione, superoxide dismutase, catalase etc. EMF may also lead to alterations in neurotransmission and consequently in cognitive and memory functions which are mainly linked to the brain hippocampus. Thus there are various histopathological aspects of hippocampus, which are studied and discussed in this chapter. Additionally, the dose response relationship between EMF and biological effects are discussed in this chapter.

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1 Introduction

Environment surrounding us, contains several type of contaminants, toxicants, pollutants and manmade exposures. These are biological, chemical or physical and could be classified under environmental toxicology. By applying the principles of biology, physics and chemistry, toxicologists can study the toxic behavior of man-made electromagnetic field (EMF) exposure. The hazards of radiofrequency electromagnetic radiation (RF-EMR) pervading the environment have now been increasingly realized and therefore, such radiations have been considered as an "electro-pollution" or "electrosmog" in the list of other environmental pollutants (air, water, soil, and noise pollution) (Behari 2009). Epidemiological evidences indicate that RF-EMF exposures are associated with adverse health effects such as tumor or cancer risk (Ahlbom et al. 2009). Not only the range of RF, but also extremely low frequency magnetic field (ELF MF) have been found to have causative effect on human health. Several epidemiological studies on RF-EMF or ELF MF exposure have investigated the health risks in populations living near cell phone towers, power lines, or who are in electrical occupations. The most common concerns include impaired sperm quality (Akdag et al. 1999; Cleary 1995; Kesari and Behari 2010), liver (Kumari et al. 2012), neurological dysfunctions (Sharma et al. 2014, 2016; Kesari et al. 2014; Kunjilwar and Behari 1993; Meena et al. 2014; Paulraj and Behari 2006) and histopathological changes such as cell injuries (Khayyat and Abou-zaid 2009; Kumari et al. 2012; Verschaeve 2009; Zare et al. 2007). Therefore, RF EMF and ELF MF were classified as a 'possibly carcinogenic to humans' (group 2B) by the International Agency for Research on Cancer (IARC 2002; Baan et al. 2011). Also at higher frequency level, International Commission on Non-Ionizing Radiation Protection reported that the specific absorption rate (*SAR*) *of* mobile phones is legally limited to 2.0 W/kg (ICNIRP 1998). In the USA, Canada and Australia, the maximum SAR level is limited to 1.6 and 2.0 W kg^{-1} in Europe (Dahal 2013), but most have an average SAR of ~1.4 W/kg (Agarwal et al. 2011).

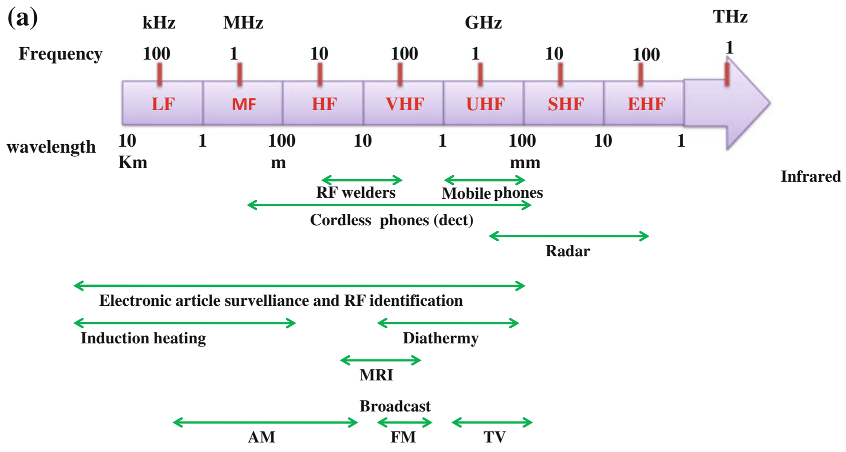
There are more than 2 billion mobile cellular phones or 4 billion people using mobile throughout the world (Stefanics et al. 2007; Roxanne 2009). These handholds mobile phones were normally started with 1G (first generation) and 2G (Second generation) and extended to 3G and 4G (third and fourth generation). With an increasing demand, now 5G (fifth generation) mobile phones are about to launch in market. With an increasing frequencies, the power density and exposure levels are also raised. Not only cell phone but also other electronic appliances like microwave oven has raised serious concern because of their frequent use in houses. The amount of RF EMF radiations absorbed by human tissue depends on the frequency, intensity, polarization and duration of exposure (Agarwal et al. 2011). It also depends on the level of doses, like for how long does a person is getting exposure? In the case of chemical exposure, what is the amount or concentration level of intake? For the monitoring of radiation exposure, SAR is an important factor to measure the absorbed radiation into the body. The SAR value varies for each type of mobile phone and particular model based on usage conditions (Agarwal and Durairajanayagam 2015) and positions of keeping it with your body. Keeping cell phone near head while talking may lead to more absorption of power in the brain. This may cause an increase of up to 2 °C in the brain temperature on continuously talking for more than 20 min on phone. Microwave radiations have potential to penetrate the cranium, and nearly 40% of these can reach deeper into the brain (Barnett et al. 2007; Kang et al. 2001), where penetration depth is assumed to be 4–5 cm deep into the brain (Dimbylow and Mann 1994; Rothman et al. 1996). An interaction of microwave radiation with tissues arise as a result of mainly three processes; deep penetration into the tissue and their propagation into the living system, then the primary interaction of the waves within tissue, and the possible secondary effects arising from the primary interaction (Rachael 2010). The deep penetration of microwaves within the tissue or living cells is the process that causes the overproduction of free radicals/reactive oxygen species (ROS), will be discussed later in this chapter. Microwave induced oxidative stress may produce ROS which are reported to be the main cause of cellular damage or tissue injury (Dasdag et al. 2008; Kesari and Behari 2010, 2012). Therefore, this chapter provides several important findings related to pathophysiology of microwave radiation and its effects on different tissues and organs. These findings are in agreement with our own previous findings (Kesari et al. 2010a, b, 2012, 2013; Sharma et al. 2014), which indicate that the biological changes could occur due to a microwave exposure induced oxidative stress as also debated by several researchers (De-Iullis et al. 2009; Oktem et al. 2005).

1.1 History and Sources of Electromagnetic Fields

The history of research on the biological effects of microwave radiation effectively begins with the development of radar early in World War II. Prior to this time, the energy levels at which microwaves had been produced were not sufficient to cause widespread concern about harmful effects. Before the invention of radar, artificially produced microwave energy was not a general environmental problem. However, as this field of research began to take shape, it did not do so in a vacuum. Well before the invention of radar, medical researchers had been interested in the controlled effect of RF energy on living things. Once it was discovered that radio waves could be used to heat body tissue, research was undertaken to study how such heating took place and its effect on the whole organism. As a consequence, both continuity and newness characterized this field of research during its early phase of development. Between the early 1940s and 1960, research on the biological effects of microwave radiation slowly shifted from its medical context and the search for benefits to a military-industrial context and also search for hazards started. Polyashuck (1971) reported for the first time the effect of microwave radiation on the blood-brain barrier in 1971. Since the late 1970s, researches started which revealed that exposure to ELF electric and magnetic fields produces adverse health consequences. The sources of ELF MF comes from wherever electricity is generated or transmitted i.e. power lines, electric wiring etc. However, in many houses and office environments, individuals can experience perpetual exposure to "electromagnetic smog", with occasional peaks of relatively high EMF intensity. This has led to concerns that such radiation can affect health.

The classical example for natural source of non-ionizing radiation (NIR) is the sun and it is emitting ultraviolet radiation continuously. The most common source for NIR is transmission lines (50–60 Hz), computer monitor (60–90 Hz), AM radio transmissions (530–1600 kHz), thunderstorms (30–300 MHz), FM radio transmission (88–108 MHz), television transmissions (50–700 MHz), hand phones (850 MHz–2.4 GHz), wireless data and microwave ovens (2.45 GHz). In the last few decades, many places wireless technology has been introduced for telecommunication, but the long-term health effects of those waves are unpredictable and these emissions may affect human health. The term RF refers to the part of the electromagnetic spectrum that can be readily used for radio communication purposes which lie below the infrared region: specifically, frequencies in the range of 100 kHz to 300 GHz. Frequency bands within this range have been named more formally by the International Telecommunications Union (ITU). Figure 1a, shows these bands together with the ranges of frequencies commonly used for various applications, including those for telecommunications, in medicine, and in industry. Figure 1b, showing the several electromagnetic field exposure sources and effect on whole brain. Human exposure to RF field may arise from their deliberate use- for example, as a part of the global communication networks- or adventitiously, as a part of industrial and other processes utilizing RF energy. The term radio wave is used to denote a RFEMF that is transmitted from a source for communication purposes.

The microwave frequency spectrum ranges from 300 MHz to 300 GHz and RF radiation from 0.5 to 300 MHz. The sources of microwave and RF radiation are air traffic control systems, police and military radar, earth to satellite television broadcast systems, long distance telephone equipment, medical diathermy devices, cancer diagnostic and therapeutic (hyperthermia) equipment, microwave ovens, industrial applications and microwave generators. Among these, mobile phones have been available since the end of the 1980s and have become common in the general population in recent years. In most of the countries, today more than 80% of the population uses mobile phones (Feychting et al. 2005). This worldwide expansion of the use of mobile phones has made EMF exposure ubiquitous in modern society. Additional sources of exposure to RF fields are appearing from new technologies such as domestic meters and airport security scanners. As a consequence, intermediate frequency (IF) has been identified as newest source of exposure. It falls between the low frequency (Low frequency—0.1 Hz–1 kHz) and the RF (10 MHz–300 GHz). The major source of IF are some anti-theft devices


(a)
kHz
MHz
GHz
THz
Frequency
100
1
10
100
1
10
100
1
LF
MF
HF
VHF
UHF
SHF
EHF
wavelength
10 Km
1
100 m
10
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1
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MRI
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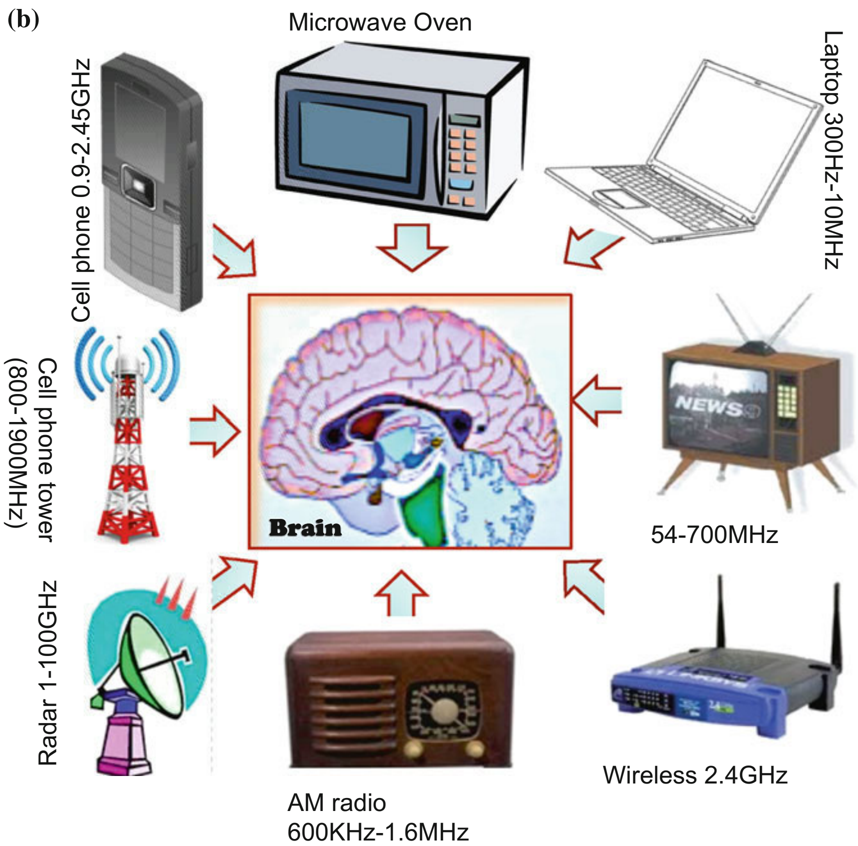
(b)
Microwave Oven
Cell phone 0.9-2.45GHz
Laptop 300Hz-10MHz
Cell phone tower (800-1900MHz)
Brain
NEWS
54-700MHz
Radar 1-100GHz
Wireless 2.4GHz
AM radio
600KHz-1.6MHz

◀**Fig. 1** **a** The electromagnetic field spectrum. Abbreviations according to the International Telecommunications Union (ITU) band are given as LF: low frequency, MF: medium frequency, HF: high frequency, VHF: very high frequency, UHF: ultra-high frequency, SHF: super high frequency and EHF: extremely high frequency. **b** Effects of electromagnetic device usage on the CNS or whole brain. Usage of electromagnetic gadgets is associated with alterations in various neurological functions from the central nervous system. Figure shows the various sources of electromagnetic field exposure with their frequency range

operated at the exits of shops, induction hotplates, computers, compact fluorescent lamps, as well as some radio antennas.

1.2 EMF Exposure and Dosimetry

Recently, the National Toxicology Program (NTP) under the National Institutes of Health (NIH) in USA (Wyde et al. 2016) has released animal studies conducted on RF (cell phone) radiation exposure effect and cancer (glioma and malignant Schwannoma in heart). This is the largest ever-animal study reported tumor in the heart. Now the question is, how such a low frequency RF radiation may cause tumor? However, it is not easy to answer the question but possibility to explore by deciphering the role of dosimetry and field measurement within the body can be done. Cell phone emits RF-EMW to nearby relay base stations or antennas. Our bodies act as antennas that absorb the radiation and convert it into alternating eddy currents (DWB 2007). When speaking on the cell phone, the sound wave from speaker goes through a transmitter that converts the sound into a sine wave. The transmitter then sends the signal to the antenna, which then sends it out into space in all directions. The transmitter in cell phone operates on about 0.75–1 W of power, with 2 W at peak usage. This electric sine wave current running through the transmitter circuit also creates an EMF around it. As the electric current moves back and forth, the fields continue to build and collapse, forming EMR. Thus, cell phone radiation is generated in the transmitter, and is emitted through the antenna in the form of a radio wave (Agarwal et al. 2011; TECH 2007). The impact of these RF EMW on the human body is measured via a standardized unit called the SAR value.

The rate of absorption and the distribution of RFR energy in an organism depend on many factors. These include: the dielectric composition (i.e., ability to conduct electricity) of the irradiated tissue, e.g., bones, with a lower water content, absorb less of the energy than muscles; the size of the object relative to the wavelength of the RFR (thus, the frequency); shape, geometry, and orientation of the object; and configuration of the radiation, e.g., how close is the object from the RFR source? These factors make the distribution of energy absorbed in an irradiated organism extremely complex and non-uniform, and also lead to the formation of so called 'hot spots' of concentrated energy in the tissue (Lai 2002). For example, an experiment reported by Chou et al. (1985), measuring local energy absorption rates

(SARs) in different areas of the brain in a rat exposed to RFR, has shown that two brain regions less than a millimeter apart can have more than a two-fold difference in SAR.

At lower frequencies (<100 kHz), many biological effects are quantified in terms of current density in tissue and this parameter is most often used as a dosimetric quantity. At higher frequencies, many (but not all) interactions are due to the rate of energy deposition per unit mass. This is why the SAR is used as the dosimetric measure at these frequencies. It is expressed as W kg^{-1}. The SAR is thus the absorbed power by the absorbing mass. It is always challenging to measure SAR directly inside the human body. Therefore, the most obvious approach towards dosimetric analysis is to experimentally determine the SAR distribution in phantoms simulating animal and human bodies, as well as in real cadavers. Phantoms are well known as tissue equivalent material. It means that, the physical properties existing in human body can fulfill by using phantom material for SAR measurement. Using this makes easy to know the absorbance level in the brain or other delicate organs.

In general, the simple and standard procedure can be applied to calculate SAR values; E-field value is measured with a miniature E-field probe. Indeed, E-field probes/monopole antenna is the most appropriate sensor to measure the SAR, due to their sensitivity and fast response. E-field maybe calculated as-

$$\mathrm{SAR(W/Kg)} = \sigma E^2 \big/ \rho$$

where sigma (σ) is conductivity of the liquid and rho (ρ) is the density of liquid. The measured E-field values and SAR distribution are 1 and 10 g mass averaged SAR values.

2 Biomarkers of Neurological Dysfunction

Central nervous system (CNS) or brain is a very complicated part of our body and also a carrier for all other organs and metabolisms. Any damage or changes due to environmental exposure in brain may lead to serious health concerns. Biomarkers are often measured and evaluated to examine such changes in various part of human body, especially in brain. The brain is very sensitive and delicate part of human body on which any direct experiments are not possible. Though in vitro and in vivo methods are implemented to measure the neurological dysfunctions. Therefore, several biomarkers like, protein kinases, micronuclei, mitochondrial pathways, DNA damage etc. are very useful to measure the causative factors. An overview of EMF exposure effect on biomarkers, its mechanism and possible diseases are presented in Fig. 2.

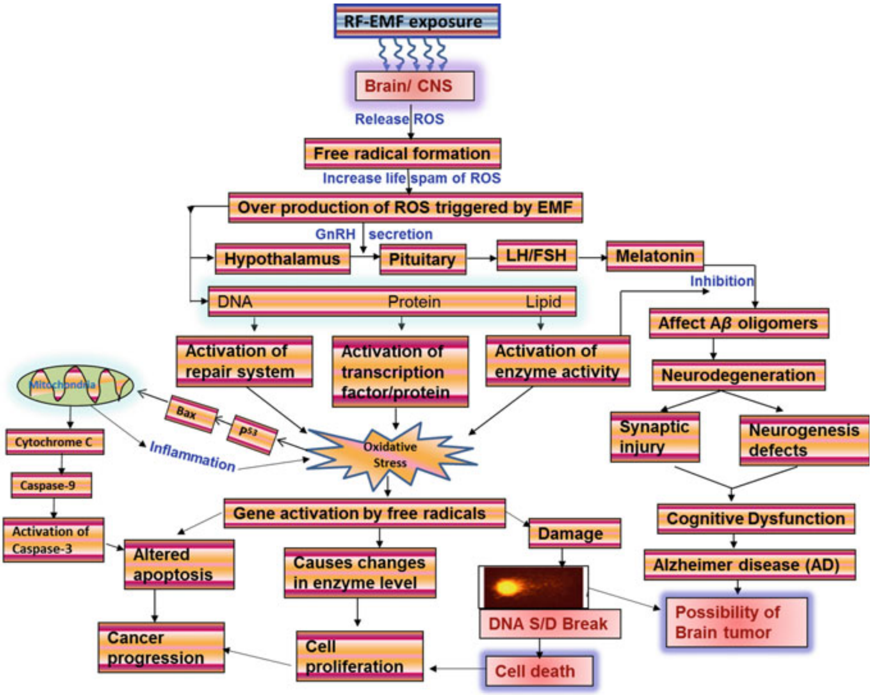

Fig. 2 Summary of the biological effects of RF-EMR exposure on central nervous system. This figure indicates enhanced ROS due to RF-EMR radiation can cause several changes at enzymatic and hormonal level, which may result Alzheimer disease and brain tumor. The activation of transcription and enzyme activity produce oxidative stress due to RF-EMF induced ROS formation. This results apoptosis by release of cytochrome c from mitochondria. The changes due to RF-EMF may enhance the DNA strand break by ROS formation and cause finally cell death

2.1 Protein Kinase C (PKC)

PKC is an isozyme and reported at least twelve in number. It differs in structure, biochemical properties, tissue distribution, subcellular localization, and substrate specificity. The first isoform that were Ca^{++}-activated, phospholipid-dependent protein kinases are ubiquitous enzymes that are highly enriched in the brain (Huang et al. 1986). Ca^{2+}-dependent PKC has been classified as conventional isozymes with α, β and γ. In late 1970s, it was first recognized as proteolytically activated serine/threonine kinase (Takai et al. 1977). PKC plays a major role in brain by regulating both pre and postsynaptic aspects of neurotransmission (Newton 1995; Nishizuka 1992; Stabel and Parker 1991). Any changes in the level of PKC and activation of various isozymes have resulted in brain tumor or neurodegeneration, like Alzheimer disease (Fig. 2). Therefore, researchers reported the structural basis for enhancement of long-term associated memory in single dendritic spines regulated by PKC (Hongpaisan and Alkon 2007). PKC play an important role in neurological functions, which could be functional in mitochondria. Mitochondria are crucial regulators of energy metabolism and apoptotic pathways that have been closely linked to the pathogenesis of neurodegenerative disorders or malignancies. A malignancy like tumor promoter is well known receptor of PKC (Parker et al. 1984). Figure 2 shows the exposure pathway, that how the EMF interacts with skin and organs and producing free radicals in the cells. Free radicals generation enhance the ROS formation, which may effect several metabolic, enzymatic, transcriptional activity and lead to cell death.

Maximum quantity of PKC is found in the brain hippocampus, which is an integral part of the brain's limbic system. PKC also play an important role in behavior and learning memory—the cellular mechanism believed to underlie learning and memory. Damage to neurons in the hippocampus may therefore lead to impaired learning, memory and behavioral dysfunctions. PKC is known to exist as a family of closely related subspecies, has a heterogenous distribution in brain (with particularly high levels in presynaptic nerve terminals), and together with other kinases, appears to play a crucial role in the regulation of synaptic plasticity and various forms of learning and memory (discussed later in this chapter). Studies from our group have reported the PKC activity (in whole brain of Wistar rat) is reduced significantly ($P = 0.0483$) in EMF exposed group, as compared to sham exposed. Similarly, a significant decrease in the activity of PKC in developing rat brain was recorded more in hippocampus in comparison with whole brain data (Kesari et al. 2011b; Paulraj et al. 1999). PKC activity may play an important role in EMF-induced genotoxicity, and formation of micronuclei may lead to genomic instability.

2.2 Micronuclei: Genomic Instability

Micronuclei (MN) are small, nucleus-like structures present in the cell, especially relevant in the assessment of genotoxic effect. In cell culture studies, the elevated level of micronuclei in neuronal cell (SH-SY5Y) indicates that exposure to ELF MFs may induce genomic instability (GI) (Luukkonen et al. 2014), as also reported by Kesari et al. (2015). Micronuclei are a good biomarker for the detection of GI. Kesari et al. (2015) reported MF induced genomic instability in follow-up study of 15 and 30 days after 24 h of MF exposure. Any late effects due to environmental or chemical exposure may induce GI. Moreover, induced genomic instability (IGI) has also been investigated after exposure to a non-genotoxic agent (Korkalainen et al. 2012). Therefore, genomic instability or genotoxic effect is not only caused due to induced non-ionizing radiation but also non-genotoxic agents and ionizing radiation (well-known inducer of genomic instability) (Baverstock 2000). In the animal study, micronuclei in bone marrow or peripheral blood erythrocytes are widely accepted as a sensitive predictor of the clastogenic potential of chemical and radiation exposure (Criswell et al. 1998). Markers such as micronuclei, which are biomarkers of chromosome malsegregation and/or breakage, have been investigated in patients affected by one of several neurodegenerative disorders and in groups of subjects at increased risk of neurodegeneration (Kesari et al. 2015, 2016: Trippi et al. 2001; Thomas et al. 2007; Jaworska et al. 2002; Scott et al. 1996; Vral et al. 1996; Migliore et al. 2011). Earlier, Kesari et al. (2011a) showed a significant decrease ($P < 0.002$) in micronuclei of mobile phone exposed group as compared with control group, where a decrease was recorded by comparing the ratio of PCE (polychromatic erythrocyte) and NCE (normochromatic erythrocyte) in animal blood cells. Kumar et al. (2010a, b) also showed the causative effect by lowered percentage of PCE/NCE at two frequency level of 10 and 50 GHz of exposure. The basic phenomenon of micronuclei shows that during RBC formation, erythroblasts expel their nucleus and may also damage the chromosome in the cytoplasm of young erythrocyte (in the form of micronuclei). Due to their relatively small size, the RF-induced MN is likely to change via a clastogenic effect. Therefore, during proliferation, the cells continue to divide and cause chromosomal damage such as breaks and exchanges, which eventually lead to formation of micronuclei. The significant changes in the frequency of micronucleated PCE in the experimental group is an indication of induced chromosomal damage. MN formation occurred with the loss of chromosome fragments due to microwave radiation. Such changes are responsible for the neurodegeneration or neurological diseases in developing brain, which may also cause Alzheimer's disease (Fig. 6).

2.3 The Mitochondrial Pathway: Role in Apoptosis

Mitochondria, which is well known powerhouse of the cell has the main site of oxygen metabolism, where cell consumed approximately 85–90% of the oxygen (Chance et al. 1979; Shigenaga et al. 1994). Oxygen takes part in glucose break down in mitochondria through oxidative phosphorylation and generates energy currency of cells i.e. ATP (Harvey et al. 1999). Mitochondria are vital cell organelles that capture the chemical energy of food to form ATP in the mitochondrial respiratory chain (MRC) (Schapira et al. 2006). Any mutation in mtDNA leads to impaired ATP generation and perturbed oxidative phosphorylation cascade that may further lock the neuronal function (Guido and John 2000). Therefore, a moderate increase in ROS levels can stimulate cell growth, proliferation or apoptosis and also cause cellular injury (e.g., damage to DNA, lipid membranes, and proteins) due to which it may lead to neuronal dementia. Mitochondrial dysfunctions and finally apoptosis have been reported as pathological cause for aging and neurodegenerative diseases in many dementias such as Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS) and amyolotrophic lateral sclerosis (ALS) (Uttara et al. 2009). Not only neuronal dysfunction, but also it is associated with a number of diseases for example including inherited mitochondrial disorders and lifestyle–related metabolic diseases, such as obesity. Obesity increases a risk of many diseases such as type 2 diabetes, cardiovascular diseases, cancers, inflammation, osteoarthritis, breathing disorders and depression, and significantly reduces the life