Chapter 4
Modified Health Effects of Non-ionizing Electromagnetic Radiation Combined with Other Agents Reported in the Biomedical Literature

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Abstract Ionizing and non-ionizing electromagnetic field (EMF) radiation, either stand-alone or in combination with other agents, exert health effects on biological systems. The present chapter examines the scope of non-ionizing EMF radiation combined effects; i.e., identifies effects on biological systems from combined exposure to non-ionizing electromagnetic fields/radiation and at least one other agent. Only articles in which the presence of non-ionizing EMF radiation had some effect (beneficial or adverse) on the biological system were selected. A comprehensive and novel query was developed using an iterative hybrid approach, whereby articles related by common text and by citation linkages were retrieved. This retrieved literature was: (1) clustered algorithmically into 32 biomedical sub-themes (assigned by the authors); (2) grouped through factor analysis into 32 factors; and (3) subsequently grouped manually (by the authors) into an effects-based taxonomy. The common principles within each thematic cluster/group that accounted for the combined effects were identified.

Non-ionizing EMF radiation plays a supportive role in a wide range of beneficial and adverse effects. Major beneficial effects include (1) accelerated healing of wounds and injuries in concert with other agents and (2) treatment of cancer by combining chemotherapy with radiation. Major adverse effects, on the other hand, include (1) enhanced carcinogenesis, (2) enhanced cellular or genetic mutations, and (3) teratogenicity. It should be noted that community consensus (unanimity among papers published in peer-reviewed journals) does not exist on these potential effects, either beneficial or adverse, although there is substantial credible scientific evidence supporting the above effects (as described in this chapter).

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In daily living, the body is exposed to multiple external agents simultaneously, e.g., myriad non-ionizing EMF radiations, pesticides, food additives, heavy metal, legal and illegal drugs, ionizing radiation, and air pollution. The number of combinations of potential external agents is large. Each combination could potentially have synergistic or antagonistic, and beneficial or adverse, effects. However, non-ionizing EMF radiation exposure safety standards are based primarily on stand-alone radiation exposures. When combined with other agents, the adverse effects of non-ionizing EMF radiation on biological systems may be more severe. Much work remains to be done before definitive statements about non-ionizing EMF radiation exposure safety can be made.

Keywords EMF • Electromagnetic fields • Magnetic fields • Radio frequency radiation • Microwave radiation • Interactive effects • Combined effects • Synergistic effects • Additive effects • Antagonist effects • Potentiative effects • Co-promotion • Co-mutagenic • Co-carcinogenic • Combined exposure • Combined treatment • DMBA • TPA • Text mining • Document clustering

4.1 Introduction

4.1.1 Electromagnetic Spectrum Definitions (See Table 4.1)

The electromagnetic spectrum encompasses the entire span of electromagnetic radiation. The spectrum includes: ionizing radiation (gamma rays, x-rays, and the extreme ultraviolet, with wavelengths below ~10^{-7} m and frequencies above ~3×10^{15} Hz); non-ionizing visible radiation (wavelengths from ~4×10^{-7} m to ~7×10^{-7} m and frequencies between ~4.2×10^{14} Hz and ~7.7×10^{14} Hz); non-ionizing non-visible radiation (short wavelength radio waves and microwaves, with wavelengths between ~10^{-3} m and ~10^{5} m and frequencies between ~3×10^{11} to ~3×10^{3} Hz; long wavelengths, ranging between ~10^{5} m and ~10^{8} m and frequencies ranging between 3×10^{3} and 3 Hz).

In the present study of non-ionizing EMF radiation health effects, interest is focused on the frequency spectrum ranging from 3 Hz to 3000 GHz. The low frequencies (3 Hz–300 KHz) are used for electrical power line transmission (60 Hz in the U.S.) as well as maritime and submarine navigation and communications. Medium frequencies (300 KHz–900 MHz) are used for AM/FM/TV broadcasts in North America. Lower microwave frequencies (900 MHz–5 GHz) are used for telecommunications such as microwave devices/communications, radio astronomy, mobile/cell phones, and wireless LANs. Higher microwave frequencies (5 MHz–300GHz) are used for radar and proposed for microwave WiFi. Terahertz frequencies (300 GHz–3000 GHz) are used increasingly for imaging to supplement X-rays in some medical and security scanning applications.

Table 4.1 Electromagnetic spectrum

Region of EMF spectrum	Wavelength range (Meters)	Frequency range (Hz)
Ionizing	$<10^{-7}$	$>3 \times 10^{15}$
Non-ionizing visible	4×10^{-7}--->7×10^{-7}	4.2×10^{14}--->7.7×10^{14}
Non-ionizing non-visible shortwave	10^{-3}--->10^{5}	3×10^{11}--->3×10^{3}
Non-ionizing non-visible longwave	10^{5}--->10^{8}	3×10^{3}--->3×10^{0}

4.1.2 Modern Non-ionizing EMF Radiation Exposures

In ancient times, sunlight and its lunar reflections provided the bulk of the visible spectrum for human beings (with fire a distant second and lightning a more distant third). Now, many varieties of artificial light (incandescent, fluorescent, and light emitting diode) have replaced the sun as the main supplier of visible radiation during waking hours. Additionally, EMF radiation from other parts of the non-ionizing spectrum has become ubiquitous in daily life, such as from wireless computing and telecommunications. In the last two or three decades, the explosive growth in the cellular telephone industry has placed many residences in metropolitan areas within less than a mile of a cell tower. Health concerns have been raised about non-ionizing EMF radiation from (1) mobile communication devices, (2) occupational exposure, (3) residential exposure, (4) wireless networks in homes, businesses, and schools, and other non-ionizing EMF radiation sources such as 'smart meters' and 'Internet of Things'.

4.1.3 Beneficial and Harmful Effects of Non-ionizing EMF Radiation Exposure

4.1.3.1 Beneficial Effects

The effects of non-ionizing electromagnetic radiation on health can be therapeutic; e.g.,

- "ELF-EMF modulates chemokine production and keratinocyte growth through inhibition of the NF-kappa B signalling pathway and thus may inhibit inflammatory processes. ELF-EMF could represent an additional therapeutic approach in the treatment of skin injury." (Vianale et al. 2008).
- "ELF-EMF could augment the cell apoptosis effects of low doses of [radiotherapeutic] X-ray irradiation on [liver cancer cell line] BEL-7402 cells in a synergistic and cumulative way" (Jian et al. 2009).
- Treatment of cancer and other serious chronic diseases using chemotherapy combined with (typically) pulsed EMF was the largest category of combined effects from our database retrievals; e.g.,

  - "A significant synergizing antitumor effect was seen when EL4 tumor-bearing mice were simultaneously exposed to EMF-BEMER and treated with suboptimal dose of synthetic HPMA copolymer-based doxorubicin, DOXHYD-HPMA." (Rihova et al. 2011)
  - "These results demonstrated that MW radiation exposure and Gemcitabine treatment have a synergistic effect on apoptotic activity of Raji cells." (Canseven et al. 2015)

- Diathermy by low level RF radiation is used in physical therapy to deliver moderate heat directly to pathology lesions in deep tissues of the body. In surgery, extreme heat produced by diathermy (aka ablation) can be used to destroy neoplasms, warts, and infected tissues, and to cauterize blood vessels to prevent excessive bleeding. For a cutting-edge example, "This implantable magnetic nanofiber device can be exploited to apply hyperthermia with an alternating magnetic field and to achieve cancer cell-specific drug release to enable synergistic cancer therapy" (Sasikala et al. 2016)
- Bone regeneration using non-ionizing EMF radiation also was mentioned in a number of retrieved papers; e.g.,

  - "PEMFs may be considered a possible tool to improve autologous cell-based regeneration of bone defects in orthopedics" (Ongaro et al. 2014)
  - "Osteogenic differentiation of ASCs was accelerated by multiple-combination biophysical stimulation in vitro. However, both single stimulation and double-combination stimulation were sufficient to accelerate bone regeneration in vivo, while the osteogenic marker expression of those groups was not as high as that of triple-combination stimulation in vitro" (Kang et al. 2014)

4.1.3.2 Harmful Effects

But the effects of non-ionizing EMF radiation can also be potentially harmful:

- "Extremely Low Frequency-Magnetic Fields (ELF-MF) are possible carcinogens to humans and some data suggest that they can act as promoters or progressors." (Gobba et al. 2009).
- "The authors found that ELF-EMFs may be increase the risk of human breast cancer" (Zhao et al. 2014)
- Residents near a "60 kV electric distribution line" experienced the following: "Non statistically significant increases were observed for all and primary cancers; primary cancers were significantly increased among subjects with >30 years' residence and latency. A significant increase for all, primary, and secondary cancers, and a twofold increase for ischaemic diseases, was observed in subjects in the sub-area with the highest exposure" (Fazzo et al. 2009)

- Cellular Neoplastic Transformation Induced by 916 MHz Microwave Radiation (Yang et al. 2012)
- Heavy cell phone use; e.g.,
  - "These additional data support previous findings concerning a possible association between heavy mobile phone use and brain tumours" (Coureau et al. 2014)
  - "an increased risk was found for glioma and use of mobile or cordless phone. The risk increased with latency time and cumulative use in hours and was highest in subjects with first use before the age of 20" ["OR = 4.9"] (Hardell et al. 2011).
  - "Our result suggests that use of mobile phones can be related to the early spontaneous abortions." (Mahmoudabadi et al. 2015)
- Proximity to wireless transmission antennas/cell towers; e.g.,
  - Levitt and Lai performed a comprehensive study of biological effects from cell tower radiation, and found "headaches, skin rashes, sleep disturbances, depression, decreased libido, increased rates of suicide, concentration problems, dizziness, memory changes, increased risk of cancer, tremors, and other neurophysiological effects in populations near base stations" (Levitt and Lai 2010)
  - "We found an association between increased childhood leukaemia incidence and mortality and proximity to TV towers" (Hocking et al. 1996)
  - "The odds ratio for all types of leukemia was 2.15.....among children who resided within 2 km of the nearest AM radio transmitter as compared with those resided more than 20 km from it. For total RFR exposure from all transmitters, odds ratios for lymphocytic leukemia were 1.39.....and 1.59..... for children in the second and third quartiles" (Ha et al. 2007)
  - "There was an association between residential proximity to the television towers and decreased survival among cases of childhood leukemia in North Sydney, Australia." (Hocking and Gordon 2003)
  - "The risk of childhood leukemia was higher than expected for the distance up to 6 km from the radio station.....and there was a significant decline in risk with increasing distance both for male mortality.....and for childhood leukemia" (Michelozzi et al. 2002)
  - "the proportion of newly developing cancer cases was significantly higher among those patients who had lived during the past 10 years at a distance of up to 400 m from the cellular transmitter site.....compared to those patients living further away, and that the patients fell ill on average 8 years earlier..... after 5 years' operation of the transmitting installation, the relative risk of getting cancer had trebled for the residents of the area in the proximity of the installation compared to the inhabitants of Naila outside the area." (Eger et al. 2004)

  - "A comparison of the relative risk revealed that there were 4.15 times more cases [of cancer] in area A [<350 m from the cell tower antenna] than in the entire population." (Wolf and Wolf 2004)
  - A large Brazilian study showed relative risk for neoplasia decreasing as distance from the cell tower antenna increased, ranging from a high of 1.35 for distances between 0 and 100 m to a low of 1.03 for distances between 800 and 900 m. (Dode et al. 2011)

- Adverse effects on nervous system:

  - "Activation of VEGF/Flk-1-ERK pathway induced blood-brain barrier injury after microwave exposure" (Wang et al. 2015)
  - "extensive neurodegeneration on exposure to radio waves. Increased production of reactive oxygen species due to exhaustion of enzymatic and non-enzymatic antioxidants and increased lipid peroxidation indicate extensive neurodegeneration" (Saikhedkar et al. 2014)
  - "The study highlights the detrimental effects of mobile phone radiations on brain during young and adult ages." (Motawi et al. 2014)
  - "Fetal radiofrequency radiation exposure from 800 to 1900 Mhz-rated cellular telephones affects neurodevelopment and behavior in mice" (Aldad et al. 2012)
  - "Autism-relevant social abnormalities in mice exposed perinatally to extremely low frequency electromagnetic fields" (Alsaeed et al. 2014)
  - "Long-term, low-level microwave exposure may inhibit learning and memory by affecting protein and energy metabolic processes and signaling pathways relating to neurological functions or diseases" (Zhao et al. 2015)
  - "case study of brain and nervous system cancers.....The only exogenous risk factor consistently associated with higher incidence was the penetration rate of mobile/cellular telecommunications subscriptions" (de Vocht et al. 2013)
  - "low intensity microwave radiation induces oxidative stress, inflammatory response and DNA damage in brain by exerting a frequency dependent effect" (Megha et al. 2015)
  - Martin Pall has shown that electromagnetic fields activate voltage-gated calcium channels, allowing increased calcium fluxes into the cell, thereby disrupting synapse formation (Pall 2015a). He has also stated that toxic chemicals act in synergy with the electromagnetic fields to enhance the adverse effects, including contributing to autism, among others (Pall 2015b).

- Researchers at Kaiser-Permanente have instrumented humans with magnetic field meters, and tracked exposure over time. Some conclusions are:

  - "prenatal maximum magnetic field exposure above a certain level (possibly around 16 mG) may be associated with miscarriage risk" (Li et al. 2002).
  - "every 1-mG increase of maternal MF [magnetic field] level during pregnancy was associated with a 15% increased rate of asthma in offspring" (Li et al. 2011).

- Numerous studies have shown adverse effects on sperm quality, e.g.:
  - "Our study provides some evidence for the first time that MF exposure may have an adverse effect on sperm quality." (Li et al. 2010).
  - "Electromagnetic radiation at 900 MHz induces sperm apoptosis through bcl-2, bax and caspase-3 signaling pathways in rats" (Liu et al. 2015)
  - "21-day-old rat testicles exposed to 900-MHz EMF in the prenatal term may be adversely affected, and this effect persists after birth" (Hanci et al. 2013)
  - "Exposure to 60 Hz and 1mT EMF can disturb spermatogenesis and may produce subfertility or infertility." (Tenorio et al. 2012)
- Finally, other large-scale studies reviewing adverse effects include The Bioinitiative Report (The Bioinitiative Report 2012) and The Dart Report (Dart et al. 2013).

4.1.4 Importance of Effects of Non-ionizing EMF Radiation Combined with Other Agents

In daily living, we are exposed to myriad potentially toxic stimuli unknown to our ancestors of only a few generations ago. These include both ionizing and non-ionizing radiations of many frequencies, artificial foods, air pollutants, environmental pollutants, occupational pollutants, high technology drugs/surgeries/diagnostics, and sedentary lifestyle practices unknown to other species. Much research has shown that when potentially toxic stimuli are combined, their adverse effects can be increased substantially (see definitions below in Sect. 4.1.6). Unfortunately, most research into effects of potentially toxic stimuli examine them one at a time in isolation. This exposure to a singular stimulus tends to underestimate the toxic influence of combined stimuli.

4.1.5 Relation of Non-ionizing EMF Radiation Combined Effects Studies to Safety Studies

A major reason for conducting non-ionizing EMF radiation effects studies, whether EMF radiation in isolation or combined with other agents, is to help set non-ionizing EMF radiation exposure ceilings for safety and health protection. Federal Communications Commission (FCC) limits for maximum permissible exposure (MPE) is a function of power density, exposure time, frequency, and other variables. The MPE limits for occupational/controlled exposure are different from the population/uncontrolled exposure (Federal Communications Commission Office of Engineering and Technology 1997). As one example for an important frequency band, FCC MPE limits for EMF radiation at 900 Mhz cell tower

frequencies are approximately 6.0×10^6 microwatts/m^2. As will be seen by some results in this chapter (Levitt and Lai 2010; The Bioinitiative Report 2012), these MPE limits are orders of magnitude above levels shown to cause serious disease. In addition, when other toxic stimuli are considered in combination with non-ionizing EMF radiation, the synergies tend to enhance the effects of each stimulus in isolation. In other words, combined exposure to toxic stimuli and non-ionizing EMF radiation translates into much lower levels of tolerance for each toxic stimulus alone. So, the exposure limits for non-ionizing EMF radiation when examined in combination with other potentially toxic stimuli would be far lower than those derived from non-ionizing EMF radiation exposures in isolation.

4.1.6 Goal of Present Chapter

The goal of this chapter is to examine the scope of the non-ionizing EMF radiation combined effects on biological systems; i.e., identify effects on biological systems from combined exposure to non-ionizing electromagnetic fields/radiation and at least one other agent. These interactive effects include additive effects, antagonistic effects, potentiative effects, and synergistic effects, and are defined and discussed in Appendix 1 (A.1.3.1). Other terminology is used in the documents, such as co-promotional, co-mutagenic, co-carcinogenic, etc., but these terms tend to be sub-sets of the more general terms defined above.

4.1.7 Previous Studies on Non-ionizing EMF Radiation Combined Effects

Background studies are discussed in Appendix 1 (A.1.1 and A.1.2). In summary, about 5–7% of total non-ionizing EMF radiation health/biological impact studies (probably less) are concerned with combination-type effects. Most of these previous studies that focused on combination effects of non-ionizing EMF radiation with other stimuli reflect the articles referenced in the body of this chapter, namely, selected non-ionizing EMF radiation ranges in the frequency spectrum combined with usually one or a few co-stimuli. However, none of these review articles in Appendix 1 (A.1.1 and A.1.2) covers the wide range of disciplines and impacts as the present chapter, as well as both adverse and beneficial combined effects. It is the scope of coverage and the comprehensiveness of retrieval using the hybrid search technique, as well as the integration across disciplines, which makes the present chapter unique.

4.1.8 Sources of Non-ionizing EMF Radiation Impacts Data

There are two main sources of data types supporting the above analysis: lab experiments and epidemiological studies. The few example citations shown in Sect. 4.1.3 illustrate the complexity of the problem, compounded further by the lack of comprehensive and long-term data (Kundi 2010) and the intrinsic limitations in the fundamental data.

4.1.8.1 Lab Experiments

One major data type is isolated laboratory experiments on seemingly uniform biological systems, where only one or a very few parameters are varied. Even under these controlled conditions, output response of the biological preparations can vary greatly. In other words, unlike many physical systems, biological specimens have varying sensitivity to the same or slight variations of the stimulus:

(1) Individuals or groups in a population, which would usually be regarded as uniform, may react to millimeter waves (MMW) in rather different or even opposite ways; (2) The factors that determine the MMW sensitivity of a specimen or a population are not yet known or controlled. Irradiation could increase antibiotic resistivity in one experiment and decrease it in the other; (3) The time duration of MMW effects may vary from specimen to specimen. Even robust MMW effects may be well reproducible for a limited time and then disappear; (4) MMW effects could often be revealed only in subjects that are experiencing some deviation from the 'normal' state; (5) Increased sensitivity and even hypersensitivity of individual specimens to MMW may be real (Pakhomov et al. 1998).

Even where laboratory results are not completely conclusive, and the uncertainties are relatively low, it is difficult to extrapolate these single or low parameter lab results to real world effects in human beings. People are exposed to multiple forms of radiation with potential synergistic/additive effects (e.g., "*adverse effects of gamma-rays on cellular functions are strengthened by EMF*" (Cao et al. 2009)), multiple drugs and pollutants, and other potentially damaging influences whose cumulative effects could be synergistic/additive. There have been no comprehensive multivariate sensitivity experiments and analyses to draw any conclusions. As Verschaeve and Maes (1998) state in their review article on genetic, carcinogenic, and teratogenic effects of radiofrequency fields: "*we believe that synergistic investigations deserve special attention. Indeed, people are exposed to many different influences, and theoretically it may well be that a RF-exposure alone is ineffective whereas this exposure might enhance the mutagenicity, carcinogenicity or teratogenicity of chemical or physical factors*". They provide the example of a synergistic effect from RF exposure ***preceding*** the mutagen mitomycin C in an investigation of 954-MHz waves emitted by the antenna of a GSM [Global System for Mobile Communications] base station (Verschaeve and Maes 1998).

These non-ionizing EMF radiation combined effects may go in multiple directions. As Whissel and Persinger (2007) state, in addressing the possibility of weak non-ionizing EMF as an enhancer of drug therapy: "*Very weak (microT range) physiologically-patterned magnetic fields synergistically interact with drugs to strongly potentiate effects that have classically involved opiate, cholinergic, dopaminergic, serotonergic, and nitric oxide pathways. The combinations of the appropriately patterned magnetic fields and specific drugs can evoke changes that are several times larger than those evoked by the drugs alone*." Conversely, as reflected in the provocative article titled "Do electromagnetic fields enhance the effects of environmental carcinogens?" (Juutilainen 2008) and in a preceding article (Juutilainen et al. 2006), the non-ionizing EMF contribution could go in the opposite direction: "*ELF MFs have been reported to enhance the effects of known carcinogenic or mutagenic agents in a few animal studies and in several in vitro studies.....The majority of in vitro studies have reported positive findings..... Animal studies designed according to the classical initiation-promotion concept may not be sufficient for studying the co-carcinogenic effects of MFs, and further studies using novel study designs would be useful*".

There may even be a further complicating factor relative to non-ionizing EMF radiation combined effects. Most of these papers address non-ionizing EMF radiation combinations, but not their sequencing. For example, a paper published in Radiobiologia (Tikhonchuk et al. 1987) shows the critical importance of sequencing on the combined effect of microwave and gamma-ray radiation: "*Structural and functional changes in the central nervous system were shown to be the same with both microwave and ionizing radiation having different mechanism of action. When the two types of radiation were delivered in a combination the* ***sequence of delivery was of a significant importance****. Antagonism of the effects was noted when microwave radiation was delivered prior to gamma-radiation. The effect was synergistic when the exposure to microwaves followed gamma-irradiation*." Thus, time sequencing of radiation exposure appears to have different effects. It seems that the residual effect of prior exposures can influence the response on subsequent exposures.

4.1.8.2 Epidemiological Studies

The other major data type is epidemiological studies, which approach the problem from the other end of the parameter spectrum. Here, highly integrated data are taken; they contain the influence of many different types of parameters, genetic make-ups, and sequencing, only a very few of which may be taken into account. Thus, what appears as a subtle effect over a large number of heterogeneous people may be a significant identifiable effect on a much smaller more homogeneous group if the effects of all the operational parameters and their sequencing were taken into account.

As stated above, the first author initially performed text mining-based retrievals and analyses of documents that mainly examined health effects of non-ionizing

EMF radiation in isolation. The results showed the myriad health impacts from a relatively high level vantage point. During the course of that text mining analysis, it became obvious that the combined effects of non-ionizing EMF radiation were extremely important, explained some of the ambiguous results from the non-ionizing EMF-only studies, and needed to be the focus of a much more detailed study. The previous study by the authors (Kostoff and Lau 2013) was the first step in developing a 'much more detailed study', and the present chapter updates and expands the previous study to produce that 'more detailed study'.

4.2 Background and Approach Summary

The approach in this chapter is to: (1) select the most credible global databases of research articles; (2) develop a query that will retrieve the relevant combined non-ionizing EMF radiation effects literature comprehensively; (3) identify the key biomedical thrusts in this retrieved literature; and (4) extract the mechanisms and principles that describe the influence of the non-ionizing EMF radiation component on the final combination effects.

Medline and the Science Citation Index (SCI) were selected as the source databases. An iterative relevance feedback technique was selected to generate the initial query for retrieving relevant articles, and it was augmented by examining the citation network (references, citing papers, records with at least one reference in common) of the papers retrieved by the initial query.

The key biomedical thrusts were identified through text mining approaches developed by the first author, including factor analysis and document clustering of the retrieved records. A final taxonomy based on the factor analysis and document clustering was generated manually. The retrieved records were then assigned manually to each taxonomy category. The non-ionizing EMF radiation-co-promoter-mechanism-disease 'signatures' were extracted by integrating the relevant factors, relevant clusters, and relevant sections of each record in the cluster.

Appendix 1 contains: (1) a brief overview of text mining; (2) a brief summary of past non-ionizing EMF radiation co-promoter studies; (3) the text mining methodology used to identify, retrieve, extract, and analyze the relevant non-ionizing EMF radiation co-promoter articles; (4) the details of the iterative relevance feedback component of the query used, and of the subsequent citation network traversing component of the query.

4.3 Analysis and Results

4.3.1 Taxonomy Structure

The factor analysis-based taxonomy was not significantly different from the document clustering-based taxonomy; only the latter will be summarized due to space limitations. The hierarchical document clustering-based taxonomy had 32 leaf (lowest level) clusters (categories), and each retrieved record was assigned to one cluster only.

The three highest levels in the taxonomy are shown in Fig. 4.1. They are self-explanatory, and will not be discussed further due to space limitations.

4.3.2 Manual Taxonomy

Based on the factor matrix results, the document clustering results, and other grouping studies, a manual taxonomy was generated as a framework for presenting the detailed results (see Fig. 4.2). It focuses on impacts, and incorporates the major impact categories. A brief summary of each category is presented first, ending with

LEVEL 1	LEVEL 2	LEVEL 3
Cluster 1A: Interactive effects from pulsed electric and magnetic fields (combined with other agents) on tumors; other types of interactive effects from electric fields	**Cluster 1A1**: Interactive effects from pulsed magnetic fields on tumors; especially pulsed EMF-induced hyperthermia	Cl 1A1a: Hyperthermia and chemotherapy or gene therapy for patient tum or therapy, especially with magnetic nanoparticles
		Cl 1A1b: Pulsed electromagnetic/magnetic fields and anti-cancer drugs/photodynamics for cell lines
	Cluster 1A2: Pulsed electric fields for improved transdermal delivery of chemotherapeutic agents and for suppressing bacterial growth	Cl 1A2a: Pulsed electric fields/ HIPEF, especially with Nisin,for inactivation, especially of foodborne microorganisms
		Cl 1A2b: Electric fields (especially pulsed), electroporation, electrochemo-therapy and agents for tumor treatment.
Cluster 1B: Interactive effects at the cellular and DNA level from low frequency alternating and static magnetic fields (combined with other agents), and microwaves	**Cluster 1B1**: Combined effects of low frequency electromagnetic fields and other agents on biological processes	Cl 1B1a: Magnetic fields and morphine-induced analgesia
		Cl 1B1b: Magnetic fields (especially ELF) and carcinogens impacts on rats
	Cluster 1B2: Combined effects of static magnetic fields and microwaves with other agents on cells, DNA, and apoptosis	**Cl 1B2a**: Damage from microwaves and other agents, especially on DNA
		Cl 1B2b: Impact of electromagnetic and static magnetic fields, especially with x-rays on oxidative stress

Fig. 4.1 Taxonomy of biomedical thrusts in non-ionizing EMF radiation health effects literature (Major category headings *bolded*)

Fig. 4.2 Manual taxonomy for presenting results (Major categories *bolded*)

CAT #	CATEGORY/SUB-CATEGORY TITLE Code: Shaded denotes mainly adverse effects;Unshaded denotes mainly beneficial effects
4.3.2.1	**Impact on cancer**
	Hyperthermia
	Chemotherapy
	Ionizing radiation and other treatments
	Chemical promoters
	Electromagnetic promoters
4.3.2.2	**Impact on neural system**
	Enhanced analgesia
	Enhanced performance and reduced seizures
	Reduced analgesia effectiveness
	Performance degradation
4.3.2.3	**Impact on circulatory system**
	Enhance heart, vascular
	Degrade heart, vascular
4.3.2.4	**Impact on immune system**
	Enhance immune system performance
	Degrade immune system performance
4.3.2.5	**Impact on endocrine system**
	Enhance endocrine system performance
	Degrade endocrine system performance
4.3.2.6	**Impact on skeletal system**
4.3.2.7	**Impact on genes**
	Positive genetic impacts
	DNA damage
	Mutations
	Teratogenicity
4.3.2.8	**Impact on cells**
	Permeation (beneficial effects)
	Apoptosis (cancer cells)
	Apoptosis (healthy cells)
	Cell proliferation
	Oxidative damage
	Permeation (adverse effects)
	Cell growth, differentiation, proliferation, morphology
4.3.2.9	**Impact on micro-organisms**
4.3.2.10	**Attenuation of EMF effect**
4.3.2.11	**Other**

one or more short illustrative examples. Where possible, integrative mechanisms for the category are discussed.

4.3.2.1 Impact on Cancer

This category includes non-ionizing EMF radiation combinations that help in the treatment of cancer, as well as combinations that promote the growth of cancer. Some of the later categories in this overall taxonomy, in particular those that deal with the impact of non-ionizing EMF radiation combinations on genes and cells, are related, since e.g. DNA damage or oxidative damage could eventually lead to cancer. These later categories were treated separately, since the cellular or genetic impacts were central to the research, not the cancer potential (although the latter was mentioned in many cases). The present category specifically includes non-ionizing EMF radiation for hyperthermia combined with other agents, and non-ionizing EMF radiation combined with chemotherapy, ionizing radiation, ultrasound, chemical promoters, and electromagnetic promoters from other segments of the spectrum. Generally, the non-ionizing EMF radiation that resulted in positive effects was short electric pulses (electroporation) or relatively short RF exposures for hyperthermia, and the non-ionizing EMF radiation that resulted in adverse effects was long power frequency exposures or relatively long RF exposures.

Hyperthermia

In the synergistic use of hyperthermia (generated by microwave heating of magnetic particles) combined with other agents to treat tumors/cancer, the high temperatures within the tumors enhance apoptosis (programmed cell death), and augment the apoptotic impacts of the other agents. ***While athermal (non-thermal) microwave effects cannot be ruled out***, the thermal effects were the main focus of the hyperthermia research reported here. Examples include combination of hyperthermia with: (a) doxorubicin to target controlled drug release for tumors (Purushotham and Ramanujan 2010); (b) TNF-alpha gene therapy for tumor growth reduction (Ito et al. 2001); (c) immunotherapy (hsp70 gene therapy) to reduce tumor growth and induce systemic antitumor immunity (Ito et al. 2003); (d) 3D–conformal radiotherapy for steep decrease of PSA values (Deger et al. 2002); (e) "When hyperthermia was performed immediately after application of electric pulses.....greater than additive antitumour effectiveness was observed..... ***Single treatment, application of electric pulses or hyperthermia had minor or no effect on tumour growth***." (Karner et al. 2004).

Chemotherapy

The synergistic use of non-ionizing EMF radiation with chemotherapy involves mainly electroporation (electric pulses that transiently permeabilize the cell membrane) combined with anticancer drugs that can enter the cells more efficiently in the short period when pores have been established.

Permeability or permeabilization in the present context reflects the transient establishment of pores by non-ionizing EMF radiation, usually in the cell membrane. In its positive role, it is used to assist chemotherapy, as well as the delivery of other types of drugs. However, in its negative role, it may allow unwanted toxic materials to enter cells or allow toxic materials to penetrate e.g. the blood-brain-barrier through non-ionizing EMF radiation-loosened endothelial tight junctions. Lange and Sedmak (Lange and Sedmak 1991) present an interesting example of the lethality enhancement of Japanese Encephalitis Virus by microwave radiation assisting entry of the virus into the central nervous system. Since the present chapter was organized by systems rather than phenomena, concepts such as permeability appear in a number of different sections in myriad applications

Bleomycin tends to be the main anticancer drug used with electroporation for electrochemotherapy, although other drugs have appeared as well. Examples include: (a) electroporation and bleomycin for pancreatic adenocarcinomas (Jaroszeski et al. 1999); (b) electroporation and TLR-9 ligands, CpG oligodeoxynucleotides for a systemic antitumor response on a contra-lateral untreated tumor (Roux et al. 2008); (c) cisplatin for hamster oral fibrosarcoma (Fulimoto et al. 2005); (d) cisplatin and electrogene therapy with p53 on murine sarcomas (Grosel et al. 2006); (e) "with electroporation, the cytotoxicity of BLM [Bleomycin] in electroporated cells was increased by as much as 95.7-fold compared to that of non-electroporated MBT-2 cells..... the ***anticancer effect of BLM can be considerably potentiated by applying EP***." (Ogihara and Yamaguchi 2000).

Ionizing Radiation and Other Treatments

The combination of ionizing and non-ionizing radiation enhances the apoptotic effect of each modality on cancer cells, although multiple non-ionizing forms (such as EMF radiation and ultrasound) have been used successfully as well. These combinations are quite lethal on cells, so collateral damage on healthy cells needs to be avoided by precision targeting. Gamma and x-radiation appear to be the two main ionizing radiation modes used. While different non-ionizing EMF radiation forms were used overall, the majority were in the form of electric

pulses, and these were the most successful in the combinations examined. Examples include: (a) electric pulses and Co-60 gamma radiation for subcutaneous glioma tumors, which destroyed the tumor vasculature and caused DNA-related damage from reactive oxygen (Engstrom et al. 2001); (b) electric pulses and ultrasound for significant retardation of mouse tumor growth (Haro et al. 2005); (c) "Studies on tumor growth kinetics have shown a significant growth delay (by 50% to that of control) 7 days after treatment of tumor with radiation [Co-60 gamma rays] and electroporation. The results suggest that ***radiocytotoxicity of tumor cells in vitro as well as in vivo were enhanced significantly by electric pulses***, which may offer a potentially improved treatment of cancer." (Shil et al. 2005).

Chemical Promoters

The three previous sub-sections addressed proactive use of non-ionizing EMF radiation combined with other agents for cancer treatment. The following sub-sections in this cancer section reflect modeling of reactions to environmental non-ionizing EMF radiation combined with other agents that might possibly promote cancer.

There are two main components involved in the non-ionizing EMF radiation co-promotion of cancer or other diseases. One component actively induces biological changes that could result in disease, and this can be termed the proactive component (e.g., carcinogenic chemicals, other radiation forms). The other component reduces the biological resistance to the proactive component, and serves as a 'passive' promoter of disease. Thus, as one example in the present subsection shows, where EMF and DMBA-induced cancer was enhanced in one substrain of rat but not another, genetics could be viewed as a 'passive' promoter of non-ionizing EMF radiation-induced disease. As another example in a later section shows, where blood-brain-barrier permeation was enhanced in diabetic rats but not normal rats, the presence of existing disease could be viewed as a 'passive' promoter of non-ionizing EMF radiation-induced disease. While the co-promoters identified in the present chapter are the proactive component, the role of the 'passive' promoters should not be discounted.

The combinations of non-ionizing EMF radiation and tumor-promoting substances, such as DMBA and TPA, tend to dominate the papers in this sub-section. While the majority of non-ionizing EMF radiation used in the research are power frequency, there are a representative number in the RF range. The effects tend to be synergistic. Examples include: (a) EMF ELF and DMBA for increasing number and size of mammary tumors (Baum et al. 1995); (b) microwave radiation for a significant acceleration of the development of benzopyrene-induced skin cancer and in

shortening of life span of the tumor-bearing hosts (Szudzinski et al. 1982); (c) EMF ELF to enhance the induction of mammary gland tumors in rats using nitrosomethyl urea and reduce the mean latent period of tumor development (Beniashvili et al. 1991); (d) solvents, lead, and pesticides/herbicides were only associated with glioma in workers also exposed to moderate or high levels of ELFMF (Navas-Acien et al. 2002); (e) ELF-MF exposure to strengthen all-trans-retinoic acid [neuronal differentiating agent] effects on neuroblastoma cells (Marcantonio et al. 2010); (f) "long-term exposure of DMBA-treated female Sprague-Dawley rats in an alternating MF of low flux density promotes the development and growth of mammary tumors, thus indicating that MF exposure exerts tumor-promoting and/or compromoting effects" (Mevissen et al. 1998); (g) "MF exposure significantly increased mammary tumor development and growth in SD1 [one substrain of Sprague-Dawley DMBA-exposed rats] but not SD2 [another substrain of Sprague-Dawley DMBA-exposed rats obtained from the same breeder] rats. These data indicate that ***the genetic background plays a pivotal role in effects of MF exposure***." (Fedrowitz et al. 2004); (h)" tumor-promoting effects of life-long RF-EMF exposure may occur at levels supposedly too low to cause thermal effects" following treatment of mice with the carcinogen ethylnitrosourea (Lerchl et al. 2015).

Electromagnetic Promoters

The combination of non-ionizing EMF radiation with other low frequency electromagnetic radiation dominated this section. The much larger promoter combination of non-ionizing EMF radiation with ionizing radiation tended to concentrate on cellular and genetic damage as a precursor to cancer, and is addressed in those later cellular and genetic sections. They are not included here to avoid redundancy, although one example is provided here linking ELF-EMF and gamma radiation to increased rates of cancer in animals. Examples include: (a) power frequency magnetic and electric fields for enhanced leukemia and lung cancer risk (Miller et al. 1996); (b) "Residing near TPP [thermoelectric power plant] or HPL [high-power lines] confers a higher risk of AML [acute myeloblastic leukemia], with synergistic effect between both factors" (Rodriguez-Garcia and Ramos 2012); (c) "The combination of weak steady-state and weak low-frequency alternating magnetic fields activates SOD in Ehrlich ascites carcinoma cells and catalase in liver cells by 3.7 and 1.3 times, respectively ($p < 0.05$), which can result from enhanced production of ROS induced by combined exposure to magnetic fields with the specified parameters." (Sergeeva et al. 2011); (d) "Although ***no association was found for childhood leukemia in relation to measured ELF or static magnetic fields alone***, an increasing trend of leukemia risk with measured ELF fields was found for subjects within these static field.....findings suggest that the risk of childhood leukemia may be related to the ***combined effects of the static and ELF magnetic fields***." (Bowman et al. 1995); (e) " Life-span exposure to sinusoidal-50 Hz magnetic field and acute low-dose γ radiation induce carcinogenic effects in Sprague-Dawley rats" (Soffritti et al. 2016).

4.3.2.2 Impact on Neural System

This category includes non-ionizing EMF radiation combinations that enhance neural system performance, as well as combinations that degrade neural system performance. The present category specifically includes non-ionizing EMF radiation-agent combinations for enhanced analgesia, enhanced performance and reduced seizures, enhanced pain, and performance degradation (memory, learning, motor activity, behavior, sensory perception). Compared to the previous cancer-related category, more use is made of complex physiologically patterned magnetic fields to influence the neural system in the present category.

Because of ion resonance effects related to the total magnetic field exposure, and the different types of ions present, results can vary greatly for different field combinations and resonance conditions. For example, DC and AC fields at the calcium cyclotron frequency lower the locomotor and exploratory activity of test subjects, whereas action of the fields at the magnesium cyclotron frequency enhances these forms of behavioral activity. Different field values can either reduce, have no effect on, or increase e.g. endogenous opioid mediated analgesia through releasing/inhibiting endogenous opioids or enhancing/decreasing the activity of opioid signalling pathways. Finally, in some cases, the behavioral effects of a drug can be modified by brief exposure to a low-level non-ionizing EMF field even when the radiation level alone has no apparent effects on the behavior.

Enhanced Analgesia

This subsection includes a broad range of non-ionizing EMF radiation frequencies combined with diverse analgesics, although the examples focus on radiofrequencies. These examples include: (a) microwaves to enhance the duration of phenobarbital-induced sleep (Benson et al. 1983); (b) "***In combination with either of the anaesthetics*** used [ketamine or chloral hydrate], mm waves increased the duration of anaesthesia by approximately 50%.....exposure of mice to mm waves in vivo releases endogenous opioids or enhances the activity of opioid signalling pathway." (Rojavin and Ziskin 1997)

Enhanced Performance and Reduced Seizures

This subsection covers a broad frequency range, and includes complex patterned fields as well. Some of the perfomance enhancements include sleep and memory, but there are also efforts aimed at reducing seizures and improving motor activity in the impaired. Examples include: (a) EMF ELF enhancement of morphine-induced conditional behaviors (Lei et al. 2005); (b) static magnetic field enhancement of anticonvulsant effects (on auditory-induced seizures in mice) in combination with phenytoin (McLean et al. 2003); (c) reduction of damage to lithium and

pilocarpine-seized rats by early exposure to computer-generated LTP-patterned magnetic fields (Lagace et al. 2009); (d) "intermittent, AC pulsed applications of picotesla flux density EMFs improve Parkinsonian symptoms in part by ***enhancing the patient's response to levodopa***.....intermittent applications of AC pulsed EMFs of picotesla flux density reverse the course of chronic progressive PD." (Sandyk 1997).

Reduced Analgesic Effectiveness

This subsection focuses on pain exacerbation, or more specifically the reduction of pain blockage by analgesics. Most of the frequencies used are power level, although a very few radiofrequencies were included. This subsection, in juxtaposition with the previous section on 'enhanced analgesia' illustrates the complexity of co-promotional non-ionizing EMF radiation effects, especially in the effects on neural systems. Reading of many papers on the neural effects shows the existence of 'windows', where non-ionizing EMF radiation in one frequency range in combination with other co-promoter and environmental variables produces one type of result, while non-ionizing EMF radiation in another frequency range in combination with similar co-promoters and environmental variables can produce radically different results. This means any conclusions about the effects of non-ionizing EMF radiation and co-promoters on the neural system have to be conditioned on the specific non-ionizing EMF radiation, co-promoters, and environmental variables operable at the time of the experiment.

Morphine tended to be the main co-promoter in this subsection, although other substances were used as well. Examples include: (a) competitive antagonism of morphine by methylnaltrexone, where microwave energy might facilitate entry of methylnaltrexone into the central nervous system (Quock et al. 1986a); (b) "The magnetic field exposures ***inhibited the degree of morphine-induced analgesia*** in a field intensity-dependent manner.....these data demonstrated a functional relationship between the behavioral effects of morphine in mice and the strength of the 60-Hz magnetic field." (Ossenkopp and Kavaliers 1987).

Performance Degradation

This subsection focuses on neural system performance degradation, and contrasts with the previous section on neural system performance enhancement. The main frequency ranges were ELF, RF, and complex magnetic fields, and there was a wide range of co-promoters. Examples include: (a) potentiation by EMF ELF pre-exposure during morphine treatment of dopamine D2 receptor (D2R) density in the rat dorsal hippocampus following withdrawal (Wang et al. 2008); (b) linear summation of TBS patterned complex magnetic field treatment with the contextual fear learning impairment evoked by agmatine treatment alone (McKay and Persinger 2003); (c) "simultaneous exposure to lead and RF from mobile phone

use was associated with increased ADHD symptom risk" (Byun et al. 2013); (d) co-application of EMF with iron overload increased lipid peroxidation as compared to EMF alone, while the increase in antioxidant defenses triggered by the sole iron overload was abolished, suggesting that EMF exposure may be harmful in young adults by impairing the antioxidant defenses directed at preventing iron-induced oxidative stress (Maaroufi et al. 2011); (e) "The exposure to the EMF also potentiated haloperidol catalepsy: ***it decreased the drug threshold dose and increased the catalepsy duration***. The EMF influence on the haloperidol effects was of a prolonged character" (Shtemberg et al. 2001); (f) "The dose of iron alone used in present study, was unable to induce any effect. However, the 128 mT SMF in the presence of iron ions in the body can induce disruption in the emotional behavior and can produce oxidative stress in brain tissue of rats." (Elferchichi et al. 2015).

4.3.2.3 Impact on Circulatory System (Heart, Blood, Vascular)

This category includes non-ionizing EMF radiation combinations that enhance cardiovascular system performance, as well as combinations that degrade cardiovascular system performance.

Enhance Heart, Vascular

Many of the enhancement components were variants on baroreflex sensitivity (BRS), performed by researchers who co-authored frequently. The baroreflex is responsible for maintaining a stable blood pressure (BP) despite changes in body positions and fails in many autonomic disorders. The baroreflex regulates BP by changing the heart rate (vagal component) and total peripheral resistance (adrenergic component). A substantial number of the papers in this section focused on the relation of non-ionizing EMF radiation, especially static magnetic fields, to changes in the baroreflex sensitivity. However, there were some papers that showed static magnetic fields enhanced the effectiveness of anti-cancer drugs, possibly by increasing membrane permeability. Examples include: (a) static magnetic field prevention of significant decrease of BRS induced by verapamil administration (Gmitrov and Ohkubo 1999); (b) static magnetic field induced increment in microcirculatory blood flow, and was counter-acted by geomagnetic disturbance (which also decreased BRS) (Gmitrov 2007); (c) "***SMF may enhance nicardipine-induced hypotension by more effectively antagonizing the Ca2+ influx through the Ca2+ channels compared with the nicardipine treatment alone***. In addition, the enhanced antihypertensive effects of the SMF on the nicardipine-treated rats might be, at least in part, related to the increased NOx, primarily due to the upregulation of inducible nitric oxide synthase." (Okano and Ohkubo 2006); (d) "application of a SMF could alter membrane permeability, increasing the flow of the anticancer drugs. This may be one of the reasons why ***SMF can strengthen***

the effect of anticancer drugs" (Liu et al. 2011); (e) "***SMF increased the effectiveness of paclitaxel-chemotherapy significantly***." (Gellrich et al. 2014).

Degrade Heart, Vascular

There were very few articles in this section, the main example being enhanced risk of acute myocardial infarction among ELF EMF exposed subjects with genetic susceptibility to the disease: "The authors evaluated the relation between occupational exposure to extremely low frequency (ELF) magnetic fields and mortality from cardiovascular diseases....***the risk of AMI*** [acute myocardial infarction] ***was strengthened among ELF magnetic field-exposed subjects with genetic susceptibility to the disease***...." (Hakansson et al. 2003).

4.3.2.4 Impact on Immune System

This category includes non-ionizing EMF radiation combinations that enhance immune system performance, as well as combinations that degrade immune system performance. A number of studies e.g. focused on modifying neutrophil activity by adjusting the carrier and modulation frequencies of the EMF for calcium ion resonance. This reflects the proactive use of non-ionizing EMF radiation for enhancing immune system performance. There could be other situations where non-ionizing EMF radiation is being used for other purposes, and it exerts adverse impacts on the immune system. Some of this is included in the later sections on cellular impacts.

Enhance Immune System Performance

This subsection covers a wide range of non-ionizing EMF radiation frequencies, ranging from power frequency to very high radiofrequencies, with a number of pulsed electric field frequencies as well. While a broad range of co-promoters is covered, some of the more exciting results involve the enhancement of DNA vaccines. Examples include: (a) use of electric pulses to administer a DNA and IL-12 adjuvant combination to obtain a tenfold increase in antigen-specific IFN-gamma(+) cells (Hirao et al. 2008); (b) pulsed EMFs potentiated the effect of A(2A) or A(3) agonists on cell proliferation in bovine chondrocytes and fibroblast-like synoviocytes (Varani et al. 2008); (c) electroporation and DNA as good adjuvants in promoting efficient Th1-directed responses during DNA vaccination (Gronevik et al. 2005); (d) "Intramuscular (i.m.) delivery of a plasmid encoding anthrax toxin protective antigen (PA) using electroporation (EP), a potent DNA delivery method, rapidly induced anti-PA IgG and toxin neutralizing antibodies within 2 weeks following a single immunization in multiple experimental species.....These results suggest that ***EP may be a valuable platform technology for***

the delivery of DNA vaccines against anthrax and other biothreat agents." (Luxembourg et al. 2008).

Degrade Immune System Performance

This small subsection includes some emphasis of non-ionizing EMF radiation effects on spleen and thymus, but does not seem to have the same theme commonality as most other sections. An example is: (a) "C3H mice have been used to investigate the effect of a combination of cyclophosphamide (CY) and electromagnetic fields (PEMF).....we found that the effect of PEMF is evident only if mice are exposed during the 24 h following CY injection. The data reported here indicates that ***PEMF exposure after CY injection increases the damage [bone marrow labeling index, spleen labeling index, spleen colonies] induced in mice by CY***." (Cadossi et al. 1991).

4.3.2.5 Impact on Endocrine System

This (small) category includes non-ionizing EMF radiation combinations that enhance endocrine system performance, as well as combinations that degrade endocrine system performance.

Enhance Endocrine System Performance

This small subsection emphasizes drug delivery and chick embryos. The drug delivery is accompanied by pulsed electric fields while the chick embryos are tested using power frequencies. Examples include: (a) synergistic enhancement of percutaneous absorption of insulin by a combined use of electric pulses and iontophoresis (Tokumoto et al. 2006); (b) protection of chick embryos against damage from UV light exposure by power frequency EM field exposures of appropriate duration (Dicarlo et al. 1999); (c) "A lipid formulation.....was tested as an in vivo enhancer for the transcutaneous delivery of insulin.....The formulation enhanced the transport of insulin through the epidermis by 40- to 100-fold.....Application of electroosmosis across the formulation-treated epidermis enhanced the transport of insulin by an additional tenfold.....***The synergistic application of anionic lipid formulation and electroosmosis offers a promising non-invasive technique to deliver insulin transcutaneously***." (Murthy et al. 2006).

Degrade Endocrine System Performance

This subsection is too small to have any unifying theme, although the following three examples exhibit strong clarity: (a) demonstration that prolonged use of

cellular telephones may lead to reduced melatonin production, and elevated 60-Hz MF exposures may potentiate the effect (Burch et al. 2002); (b) Atrazine, an endocrine-disrupting compound, had a synergistic effect on degranulation of cutaneous mast cells at both low and high doses in combination with EMFs (Rajkovic et al. 2010); (c) "Environmental EMFs apparently lack the energy necessary to function as aneugens, but the possibility exists that EMFs could influence the incidence of aneuploidy synergistically because EMFs can activate the neuroendocrine system, and ovulation and oocyte meiotic maturation are under neurohormonal control..... The results support the hypothesis that ***EMF exposure can promote the occurrence of aneuploidy caused by an aneugen*** via a mechanism involving the neuroendocrine system." (Mailhes et al. 1997).

4.3.2.6 Impact on Skeletal System

This category includes non-ionizing EMF radiation combinations that enhance skeletal system performance. The emphasis is on enhancing bone growth (mainly for accelerated fracture repair) or preventing bone loss, with the main mechanism being stimulation of cell proliferation. The EMF range is concentrated in power frequencies and pulsed EMFs, with a wide range of co-promoters. Examples include: (a) synergy of daily rotary non-uniform magnetic field exposure with calcium supplementation to increase the indices of thigh bone density, energy absorption, maximum load, maximum flexibility, and elastic deformation in ovarectomized rats (Zhang et al. 2006); (b) combination of BMP-2 and PEMF stimulation for augmenting bone formation to a greater degree than treatment with either single stimulus (Selvarnurugan et al. 2007); (c) "BMC and PEMFs might have a separate effect on osteochondral regeneration, but it seems that they have a greater effect when used together (Veronesi et al. 2015); (d) "Osteogenic differentiation of ASCs was accelerated by multiple-combination biophysical stimulation in vitro. However, both single stimulation and double-combination stimulation were sufficient to accelerate bone regeneration in vivo, while the osteogenic marker expression of those groups was not as high as that of triple-combination stimulation in vitro." (Kang et al. 2014); (e) "pulsed electromagnetic field (PEMF) plus BMP-2 upregulates intervertebral disc-cell matrix synthesis more than either BMP-2 alone or PEMF alone" (Okada et al. 2013); (f) "These results demonstrate that ***PEMF enhances osteogenic effects of BMP-2 on MSCs*** [mesenchymal stem cells] ***cultured on calcium phosphate substrates***, suggesting that PEMF will improve MSC response to BMP-2 in vivo in a bone environment." (Schwartz et al. 2008).

4.3.2.7 Impact on Genes

This category includes non-ionizing EMF radiation combinations that have beneficial impacts on genes, as well as combinations that that have adverse impacts. While potential diseases are mentioned in some of these articles, genetic issues

were the main focus of the studies, and these records were therefore classified under the genetic issues rather than the diseases. The main non-ionizing EMF radiation forms are ELF, RF, and some static magnetic fields. The main co-promoters are chemical, ionizing radiation, and thermal/heat shock.

Positive Genetic Impacts

The main non-ionizing EMF radiation frequencies in this small subsection are at the very low end of the spectrum, and the co-promoters are typically neither the chemicals nor the ionizing radiation. Examples include: (a) EMF ELF and mild heat shock to strongly enhance the expression of the lacZ reporter gene (Junkersdorf et al. 2000); (b) "It was found that ***transfection of Chinese hamster ovary cells by naked plasmid DNA was enhanced by combined exposure of the cells to ultrasound..... and a magnetic field***.....in the presence of one of two different microbubble/nanoparticle preparations." (Stride et al. 2009).

DNA Damage

This relatively large subsection includes two main frequency groups: radiofrequencies at cell phone and wireless Internet levels, and ELF power frequencies. Examples include: (a) enhancement of human lymphocyte DNA damage effects (induced by mitomycin and 4-nitroquinoline-1-oxide, UV-mimetic agent) by 1.8 GHz RFR (Wang et al. 2005); (b) enhancement of the number of apurinic/apyrimidinic sites (induced by methyl methane sulfonate or H_2O_2) by exposure to ELF magnetic fields, due to enhanced activity or longer lifetime of radical pairs (Koyama et al. 2008); (c) "....exposure of the cells to static or 50 Hz magnetic fields (MF) and simultaneous treatment with a known oxidant, ferrous chloride, may affect the oxidative deterioration of DNA molecules.....Lymphocyte exposure to MF at 7 mT did not increase the number of cells with DNA damage in the comet assay. Incubation of lymphocytes with 10 mug/ml FeCl2 did not produce a detectable damage of DNA either. However, ***when the FeCl2-incubated lymphocytes were simultaneously exposed to 7 mT MF the number of damaged cells was significantly increased*** and reached about 20% for static MF and 15% for power frequency MF. In the control samples about 97% of the cells did not have any DNA damage." (Zmyslony et al. 2000); (d) "Pre-treatment with MF enhanced menadione-induced DNA damage, DNA repair rate, and micronucleus formation in human SH-SY5Y neuroblastoma cells" (Luukkonen et al. 2011); (e) "Gd induces DNA damage and apoptotic cell death in human lymphocytes and that ELF-EMF enhances the cytotoxicity and genotoxicity of Gd." (Cho et al. 2014); (f) "872 MHz CW RF radiation at 5 W/kg might enhance chemically induced ROS production and thus cause secondary DNA damage" (Luukkonen et al. 2009); (g) "The frequency of micronucleated astrocytes in the 10mg/kg BW bleomycin plus EMF exposure group.....was 1.6 times higher than that in the 10mg/kg BW bleomycin plus sham-

exposure group." (Miyakoshi et al. 2012); (h) "Exposure to a 60-Hz, 2 mT ELF-MF for 6 h produced increased gamma-H2AX expression, as well as gamma-H2AX foci production, a common DNA double-strand break (DSB) marker.....2 mT ELF-MF exposure potentiated the expression of gamma-H2AX and gamma-H2AX foci production when combined with IR [ionizing radiation], but not when combined with H_2O_2" (Yoon et al. 2014).

Mutations

This relatively large subsection is almost exclusively power frequency EMF, with half the co-promoters being ionizing radiation. Examples include: (a) "ELF EMF increases x-ray-induced mutations and alters the spectrum of mutations" (Koyama et al. 2005); (b) ELF-EMF is mutagenic as a single agent and can potentiate the mutagenicity of ionising radiation (Mairs et al. 2007); (c) "exposure to ELFMF may induce mutations and enhance X-ray-induced mutations, resulting from the inactivation of NF-kappa B through the inhibition of tyrosine phosphorylation" (Ding et al. 2000); (d) "peripheral blood cells exposed to both ionizing radiation and EMF ELF magnetic fields demonstrated an enhanced frequency of near tetraploid chromosome complements, a feature not observed following exposure to only ionizing radiation" (Hintenlang 1993); (e) "The co-exposure of cells to BLM [bleomycin] and ELF-EMF led to a significant increase in the frequencies of MN [micronuclei] and aneuploidy compared to the cells treated with BLM alone.....ELF-EMF enhances the cytotoxicity of BLM" (Cho et al. 2007); (f) "The interaction of extremely low frequency electromagnetic fields (ELF-EMF) on the frequency of micronuclei (MN) and sister chromatid exchange (SCE) induced by benzo(a)pyrene (BP) in human lymphocytes was examined.....The co-exposure of cells to BP and 0.8 mT ELF-EMF for 24 h, followed by BP exposure for 48 h led to significant increases in the frequencies of MN and SCE compared to BP treatment for 72 h..... The obtained results suggest ***that low density ELF-EMF could act as an enhancer of the initiation process of BP*** rather than as an initiator-of mutagenic effects in human lymphocytes." (Cho and Chung 2003).

Teratogenecity

This modest-sized subsection focuses on RF EMF frequencies, uses mainly 2-methoxyethanol and cytosine arabinoside as co-promoters, and targets fetus development and malformations in the research. Examples include: (a) concurrent RF radiation exposure changed the shape of the dose-effect (dose-related developmental toxicity [external and skeletal malformation]) curve of 2-methoxyethanol (Nelson et al. 1997); (b) combination of microwave-induced hyperthermia and gamma radiation was highly teratogenic, indicating a mutual potentiation of the embryotoxic action of these two teratogens (Roux et al. 1986); (c) microwave-radiation enhanced the teratogenic effect of cytosine-arabinoside in mice

(Marcickiewicz et al. 1986); (d) "the study results appear to suggest that the combined use of nicotine and cell phones might result in more pronounced detrimental effects on the health of smokers" (Boga et al. 2015); (e) "The incidence of resorption and dead fetuses was not affected by PMF [pulsed magnetic field] but was increased by ara-C [a cytosine arabinoside] injection.....the incidence of CP [cleft palate] and/or CL [cleft lip] in the PMF group is not significantly greater than that in the control group. A significantly higher incidence of CP and/or CL was found in the PMF + ara-C group (49%) than the ara-C alone group (26.1%). These data suggest that PMF might enhance the development of ara-C-induced CP and/or CL.....it is concluded that the very ***weak embryotoxic effects of PMF exposure may be revealed and enhanced in combination with a teratogenic agent.***" (Chiang et al. 1995).

4.3.2.8 Impact on Cells (Permeation, Apoptosis, Oxidative Damage, Cell Growth, Cell Differentiation, Cell Proliferation)

This category includes non-ionizing EMF radiation combinations that have beneficial impacts on cells, as well as combinations that have adverse impacts. While potential diseases are mentioned in some articles, cellular issues were the main focus of the studies, and these records were classified under the cellular issues rather than diseases.

Beneficial Cellular Impacts
This subsection includes mainly pulsed EMF and power frequencies, with a broad variety of co-promoters. Three mechanisms are dominant: electroporation to allow drug entry into cells; enhanced apoptosis for destroying cancer cells; and enhanced cell proliferation for accelerating wound and fracture repair.

Permeation (Beneficial Effects)

This subsection covers mainly pulsed electric fields for electroporation, with the eventual goal of improved drug delivery. Examples include: (a) synergistic electroporation/iontophoresis transdermal delivery of indomethacin in contrast to iontophoresis or electroporation alone (Wang et al. 2007); (b) feasibility demonstration of electroporation to deliver and maintain the overall efficacy of an anthrax-plague DNA vaccine cocktail whose individual components have qualitative immunological differences when combined (Albrecht et al. 2012); (c) For Leishmaniasis, "use of electroporation and silver nanoparticles simultaneously can induce greater accumulation of particles in infected cells, besides higher toxicity.....In parasites and cells receiving both treatments, higher toxicity was observed in comparison to each treatment given individually, showing a synergic effect on promastigotes" (Dolat et al. 2015); (d) "The objective of this study was to enhance and optimize the skin permeation of MTX [methotrexate] using two physical techniques: an erbium:

yttrium-aluminum-garnet (Er:YAG) laser and electroporation.....Application of the laser and electroporation significantly enhanced the permeation of MTX. The enhancing effect was more pronounced after applying the laser.....***A combination of laser pretreatment and subsequent electroporation for 10 minutes resulted in a higher drug permeation than either technique alone***" (Lee et al. 2008).

Apoptosis (Cancer Cells)

This subsection covers pulsed EMF power and static magnetic fields, in that order. Most of the focus is accelerated destruction of cancer cells, and co-promoters tend to be photofrequency sources and drugs. Examples include: (a) pulsed magnetic fields (PMF) in combination with UVC radiation have the ability to augment the cancer cell killing effects of UVC radiation, and the effects appear to be greater when PMF and UVC are applied at the same time (Ruiz-Gomez and Martinez-Morillo 2005); (b) "This study was designed to test whether extremely low frequency electromagnetic field (ELF-EMF) could enhance the apoptosis-induction effect of X-ray radiotherapy on liver cancer cell line BEL-7402 in vitro....These findings suggested ***that ELF-EMF could augment the cell apoptosis effects of low doses of X-ray irradiation on BEL-7402 cells in a synergistic and cumulative way.***" (Jian et al. 2009).

Apoptosis (Healthy Cells)

The previous subsection on cellular apoptosis focused on non-ionizing EMF radiation-enhanced destruction of cancer cells. This subsection focuses on non-ionizing EMF radiation-enhanced destruction of healthy cells, and includes power frequency EMF, and pulsed and static electric fields. Co-promoters include ionizing radiation, photoradiation, and drugs. Examples include: (a) -dexamethasone-induced apoptosis but not spontaneous apoptosis was substantially increased in thymocytes from 60 Hz field-exposed animals (Ismael et al. 1998); (b) "Combined exposure of MF and MNP-SiO2 resulted in remarkable cytotoxicity and increased apoptosis in PC12 cells." (Jia et al. 2014); (c) "combined effect of EF [electric field] plus ionising radiation.....In cells exposed to EF, death increased substantially compared to irradiation alone.....***Application of an EF following irradiation greatly increases cell death***. The observation that the DNA repair shoulder in the survival curve of *C. albicans* is suppressed when cells are exposed to irradiation+EF suggests that EF likely inactivate cellular recovering processes. The result for the number of nuclei with -H2AX foci in MRC5 cells indicates that an ***EF interferes mostly in the DNA repair mechanisms***." (Arruda-Neto et al. 2009).

Cell Proliferation

This section covers mainly power frequency EMF, with a wide variety of non-radiation promoters and an emphasis on wound healing. Examples include: (a) combination of a 50-Hz sinusoidal magnetic field and fibrin glue has significantly favorable effects on healing of experimental colon anastomosis (Girgin et al. 2009); (b) "investigate the effects of topical application of an *Aloe vera* gel combined or not with microcurrent application on the healing of skin wounds surgically induced in Wistar rats.....the group treated ***with microcurrent plus Aloe vera presented an earlier onset of the proliferative phase*** compared to the control group and animals treated with *Aloe vera* gel alone.....Simultaneous application of *Aloe vera* gel and microcurrent is an excellent choice for the treatment of open wounds thus indicating a synergistic action of these two applications" (Mendonca et al. 2009).

Adverse Cellular Impact

This section focuses on oxidative damage, permeation, and cell growth/proliferation.

Oxidative Damage

The present subsection includes power frequency EMF, radiofrequency, and static magnetic field, in that order, and co-promoters that are mainly metals and chemicals. Examples include: (a) combination of CCl4 injection and SMF exposure caused an increase in lipid peroxidation in the liver exceeding that caused by either treatment alone (Watanabe et al. 1997); (b) exposure of intact erythrocytes incubated with an oxygen-radical generating system (Fe(II)/ascorbate) to a magnetic field induced a significant further decay in hexokinase activity as well as a twofold increase in methemoglobin production compared with red blood cells that were exposed to the oxidant system alone (Fiorani et al. 1997); (c) "single EMF exposure in 1800 MHz frequency significantly reduced antioxidant capacity both in healthy animals and those with paw inflammation. A certain synergic mode of action between applied electromagnetic fields and administered tramadol in rats treated with CFA" [Complete Freunds Adjuvant] was observed (Bodera et al. 2013); (d) demonstrated that the combined effect of static magnetic field and Cadmium increased oxidative damage in rat brain as compared with Cadmium-exposed rats (Amara et al. 2011); (e) "The effects were more pronounced after treatment with both Cd and EMF than at the treatment with each exposure alone..... This work concluded that combined exposure to Cd and EMFs might increase the risk of plasma damage via enhancing free radical generation and protein oxidation." (Hassan and Abdelkawi 2014); (f) "Effects of melatonin, extremely-low-frequency magnetic field (ELF-MF), and their combination on AT478 murine squamous cell carcinoma line were studied..... These results strongly suggest that ***ELF-MF***

attenuates antioxidative actions of melatonin on cellular level." (Zwirska-Korczala et al. 2004).

Permeation (Adverse Effects)

The previous subsection on positive impacts of cellular permeation showed the benefits of non-ionizing EMF radiation-enhanced permeation, especially for drug delivery. However, as shown in the present subsection, permeation can also allow toxic substances to penetrate cellular membranes and other barriers. This subsection covers power frequency and radiofrequency, focuses mainly on brain penetration, and covers mainly drug co-promoters. Examples include: (a) microwave irradiation facilitated central effects of domperidone (a drug which acts mainly in the periphery), by possibly altering the permeability of the blood-brain-barrier (BBB) and increasing the entry of domperidone to central sites of action (Quock et al. 1987); (b) methylatropine pretreatment and microwave irradiation resulted in a central anticholinergic action by methylatropine; microwave radiation may enhance passage of quaternary ammonium compounds like methylatropine across the BBB and B-CSFB (Quock et al. 1986b); (c) "investigated the effect of long-term exposure to modulation magnetic field (MF), insulin, and their combination on blood brain barrier (BBB) permeability in a diabetic rat model.....DM [diabetes mellitus] and MF [50 hz magnetic field] increase BBB permeability; ***in combination, they cause more increase in BBB permeability***, and insulin decreases their effect on BBB." (Gulturk et al. 2010).

Cell Growth, Differentiation, Proliferation, Morphology

This subsection covers mainly power frequency EMF and radiofrequency. The main co-promoter is TPA, but other drugs are used, as well as some ionizing radiation. Examples include: (a) combination of EMF and gamma-ray exposure to SHG44 cells resulted in a synergistic effect by triggering stress response, which increased reactive oxygen species (Cao et al. 2009); (b) effect of 60-Hz EMF at 1G on cell differentiation is approximately equivalent to treatment of the cells with 250–500 pg/ml TPA [tumor-promoting phorbol ester]; effect of both EMF and TPA treatment on differentiation is additive at low TPA concentrations (Tao and Henderson 1999); (c) "In NB69 simultaneous administration of MF and ROL induced an additive effect on cell proliferation, associated to increased DNA content" (Trillo et al. 2012); (d) "investigated whether exposure to 60-Hz sinusoidal magnetic fields (0.3–1.2 G for 3–72 h) would cause proliferation of human astrocytoma cells. Sixty-Hertz magnetic fields (MF) caused a time- and dose-dependent increase in proliferation of astrocytoma cells.....and strongly potentiated the effect of two agonists (the muscarinic agonist carbachol and the phorbol ester PIMA).....***These data indicate that MF can increase the proliferation of human astrocytoma cells and strongly potentiate the effects of two agonists***. These findings may provide a

biological basis for the observed epidemiological associations between MF exposure and brain tumors." (Wei et al. 2000).

4.3.2.9 Impact on Micro-organisms

This category covers the use of (mainly) pulsed electric fields to destroy bacteria for improving food storage or developing superior strains. Examples include: (a) combination of nisin and mild pulsed electric field (applied to vegetative cells of Bacillus cereus) resulted in a reduction of 1.8 log units more than the sum of the reductions obtained with the single treatments, indicating synergy (Pol et al. 2000); (b) combined treatments of electric field and chemical mutagen N-methyl-N′-nitro-N-nitroso-guanidine (NTG) for the strain improvement of Saccharomyces sp. in ethanol production (1) increased the lethal effect and auxotrophic mutation rate of NTG, (2) increased the chances of obtaining superior yeast strains for the ethanol production from tapioca, (3) produced a higher number of improved clones (Kim and Lee 1998); (c) "in the clinical setting, combining systemic antibacterial therapy with PEF will yield a synergistic effect leading to improved eradication of mesh infections" (Khan et al. 2016); (d) "electric fields generated using insulated electrodes can inhibit the growth of planktonic *Staphylococcus aureus* and Pseudomonas aeruginosa and that the effect is amplitude and frequency dependent, with a maximum at 10 MHz. ***The combined effect of the electric field and chloramphenicol was found to be additive***.." (Giladi et al. 2008).

4.3.2.10 Attenuation of Non-ionizing EMF Radiation Effect

This category focuses on ameliorating non-ionizing EMF radiation effects through combinations. Researchers have identified adverse impacts resulting from exposure to EMF, and have searched for agents that will ameliorate these adverse effects. The EMF frequencies covered are split between power frequencies and radiofrequencies, mainly at cell phone level. While a number of adverse effects are targeted, the main focus is reducing oxidative damage, followed by reducing DNA damage. The main ameliorating agents are propolis, melatonin, Vitamins C and E, and zinc. Noise is used in many examples to cancel out the EMF field effects. Examples include: (a) L-carnitine seems to have protective effects on the 2.45-GHz-induced blood toxicity (oxidative damage) by inhibiting free radical supporting antioxidant redox system (Gumral et al. 2009); (b) bee venom is demonstrated to have a radioprotective (915 MHZ) effect against basal and oxidative DNA damage (Gajski and Garaj-Vrhovac 2009); (c) long-term exposure to low-frequency EMF increases lipid peroxidation in the brain, which may be ameliorated by Zinc supplementation (Bediz et al. 2006); (d) CAPE [Caffeic acid phenethyl ester, a major component of honeybee propolis] exhibits a protective effect on mobile phone-induced and free radical mediated oxidative renal impairment in rats (Ozguner et al. 2005); (e) significant inhibition of the increased human

epithelial amnion cell proliferation when a noise field was superimposed on an EMF ELFfield (Raskmark and Kwee 1996); (f) "investigate the effects of 12 kV/m electric (E) field sourced by power lines on oxidative and nitrosative stress, and antioxidant status.....examine the protective effects of N-Acetyl-L-cysteine (NAC) and epigallocatechin-gallate (EGCG) in the liver tissues of guinea pigs against the possible detriments of electromagnetic field exposure.....extremely low frequency (ELF) electric field has potential harmful effects on the living organisms by enhancing the free radical production. ***NAC and EGCG might have hepatoprotective effects in ELF-E field induced oxidative and nitrosative stress***." (Guler et al. 2008).

4.3.2.11 Other

This category covered papers difficult to assign to any of the previous sections. There was a broad range of topics covered, and a broad range of combinations, with a few papers focusing on the impact of a static magnetic field combined with non-ionizing EMF radiation on ion resonances. Examples include: (a) magnetotherapy with the magnetic field inductor applied over a dressing with native naphthalane oil + routine therapy (prodectin, parmidin) enhanced recovery and is recommended for the treatment of trophic ulcers of the shins, complicated by bacterial eczemas (Guseinzade et al. 1991)); (b) extremely low-frequency magnetic field and aluminum solution synergistically enhanced the growth of spruce seedlings (*Picea abies*) (Ruzic et al. 2000); (c) "exposure to static magnetic field causes accumulation of reactive oxygen species in *V. faba* and natural radioactivity of soil exaggerates oxidative stress" (Jouni et al. 2012); (d) Microsecond pulsed magnetic field improves efficacy of antifungal agents on pathogenic microorganisms. (Novickij et al. 2014); (e) combination of CCl4 injection and static magnetic field exposure induced elevation of the hepatic metallothionein content exceeding that induced by either treatment alone (Satoh et al. 1996); (f) "Groups of male CBA/J mice were injected with Salmonella typhimurium lipopolysaccharide (LPS) and irradiated with 2450 MHz (CW) microwaves. The 50% lethal dose (LD50) of LPS was determined for mice irradiated at 30, 20, 10 and 5 mW/cm2 immediately following injection.. ***A significant decrease in the LPS dose required to kill 50% of the mice was observed at power densities of 20 and 30 mW/cm2***." (Riddle et al. 1982).

4.3.3 Non-ionizing EMF Radiation-Biological Mechanisms Matrix

In order to gain further insight to the relation between biological mechanisms and varieties of EMF, a non-ionizing EMF radiation-biological mechanisms matrix was

generated. All Abstract phrases (with a frequency of three or greater) generated by the VP software were examined, and those that were biomedically related (~800) were extracted. Additionally, all of these Abstract phrases that could be related specifically to an EMF band, either textually or numerically (ELF [25–100 Hz]; SMF [0 Hz]; cellphone [~800–2000 MHz]; WiFi [~2450 MHz]; Radar [50 MHz–100 GHz], PEF, PEMF) were extracted, and combined by band. Two matrices of these two groups of phrases were generated, but will only be summarized due to space limitations.

4.3.3.1 Extremely Low Frequency

This section reflects the AC power frequency band, and the main focus of the research was adverse effects resulting from exposure to residential or occupational wiring and equipment. The main phrase grouping reflects enhancement of DMBA-induced mammary tumors by ELF. Another grouping reflects the activation of protein kinase C by the tumor-promoting phorbol esters, such as TPA, with a related grouping focused on enhancing the suppression of gap junctional intercellular communication, again by inhibiters such as TPA. There is a smaller group related to suppression of melatonin and its potential impact on carcinogenesis. There is a broader group with two components, one related to cell survival and enhanced apoptosis, and the other addressing enhanced cell proliferation and differentiation. Finally, a group shows enhanced DNA damage and mutagenicity from ELF combinations with ionizing radiation (x-ray, gamma) or chemicals/drugs (MMC, H_2O_2, Menadione).

4.3.3.2 Pulsed Electric Field (PEF)

This section reflects pulsed electric fields, and the research focus was proactive use of this technology for improved health and food preservation. The most fundamental grouping reflects increased permeation of cell membranes by PEF for improved drug delivery. Primary emphasis is on enhanced chemotherapy for tumor reduction, with a secondary emphasis on use of PEF as an adjuvant for DNA vaccines. Another thrust area is enhancement of [e.g. nisin] preservation factor-inactivated micro-organisms [e.g. Listeria].

4.3.3.3 Static Magnetic Field

The effect was mainly on circulatory system improvement. However, static magnetic fields were used copiously in the total research to modify the effects of the geomagnetic field or alternating magnetic fields. One group focused on the combined impact of artificial static and geomagnetic field on cardiovascular regulation, especially the regulation of the baroreflex sensitivity. A related group focused on

the combined effect of static magnetic fields and blood pressure modifiers on blood pressure. There were effects of combined ELF EMF and static magnetic fields [sometimes combined with other agents] on genotoxicity, especially chromosomal damage and micronuclei. A fundamental underlying driver is the effect of the superposition of the static magnetic field on either the geomagnetic field or an alternating magnetic field to provide a net magnetic field that can allow or suppress ion resonances for selected ions.

4.3.3.4 Cell Phones

This section relates to effects of mobile communication frequencies. The focus of the research was identifying adverse health impacts from exposure to relevant radiofrequencies, and how to ameliorate the adverse impacts. Generation of reactive oxygen species and the subsequent oxidative damage are central to effects from radiofrequency radiation combined with other agents, in this frequency range. Enhancement of DNA damage was also evident. Some research was focused on synergistic teratogenic effects from combined administration of RF radiation and chemical agents, especially 2-methoxyethanol. A number of articles focused on agents that, when combined with this range of radiofrequency radiation, helped reduce the oxidative damage resulting from use of the radiofrequency radiation alone. These agents included caffeic acid phenethyl ester [CAPE]/honeybee propolis, melatonin, zinc, and xanthine oxidase, among others.

4.3.3.5 Pulsed EMF

This medical therapeutic section relates to pulsed electromagnetic fields. There is some overlap with pulsed electric fields in improving drug delivery and photodynamic therapy (especially for cancer therapy) by increasing cell membrane permeability transiently. Another key positive impact is the combined effect of bone morphogenetic proteins and pulsed electromagnetic fields in augmenting bone formation. Additionally, there is a combined effect of AC pulsed magnetic fields (typically employed in transcranial stimulation) and dopaminergic medications on stimulating dopaminergic neurons and dopamine receptors to enhance dopamine release and alleviate symptoms in dopamine-deficient diseases.

4.3.3.6 WiFi

This section relates to wireless communication frequencies, particulary wireless Internet. Unlike the effects shown in the previous PEMF sub-section, where the non-ionizing EMF radiation combined impacts tended to be positive, the non-ionizing EMF radiation combined impacts in this section are almost universally negative. The combined effect of 1) magnetic fields at these frequencies and

2) analgesics on the central nervous system tended to be negative, for example, in learning, memory, and stereotypy. In additions, these combinations were shown to promote tumors, enhance drug-induced lethality, enhance DNA damage and teratogenic effects, decrease LPS LD50 dose, and alter phagocytic activity (which could be attenuated by vitamins C and E).

4.3.3.7 Radar

This section covers a wide range of high frequency non-ionizing EMF radiation, and was meant to include those frequencies beyond WiFi. The combined effect data in this frequency region is minimal, and relates to the combined effect of modulated millimeter waves and phorbol ester [PMA] on neutrophil respiratory bursts.

4.4 Discussion and Conclusions

4.4.1 Overview

Non-ionizing EMF radiation can serve as an initiator of health effects, as well as serve as a co-promoter or potentiator of biochemical agents, both beneficial and adverse. However, as this chapter has shown, the numbers and types of impacts are increased substantially when non-ionizing EMF radiation functions in combination or as a co-promoter. There were many examples where either (1) non-ionizing EMF radiation by itself had no observable effect, but it enhanced the demonstrated individual effect of another agent or (2) non-ionizing EMF radiation by itself had no observable effect and other agents by themselves had no measurable effects, but in combination the two had a pronounced effect. In other words, there is an enhancement of the singular effects.

Generally, the combined effects occured in 'windows' for specific combinations of multiple variables, or stated another way, in specific regions of parameter space. Thus, combined effects could be observed at one dose rate but not at another, at one frequency but not at another, at one intensity but not at another, at one modulation pattern but not at another, at a different sequence of exposure, and so on. This large combinatorial parameter space makes drawing conclusions about combined effects difficult in many cases, since the effect will display only under the proper combination of variables and parameters within limited ranges of each.

4.4.2 Frequency Grouping

The overall results could be frequency-grouped into three major categories. One category contained pulsed electric fields and pulsed magnetic/electromagnetic

fields. A second category contained extremely-low frequency electromagnetic fields, cell phone radiofrequency fields, and WiFi radiofrequency fields. The third smaller category contained static magnetic fields.

The first category, which could be termed the Treatment category, tended to use non-ionizing EMF radiation proactively to enhance therapeutic treatment, whether for enhanced drug delivery, accelerated wound and fracture healing, or bacterial inactivation for prolonged food storage. The second category, which could be termed the Environmental Exposure category, tended to identify the overwhelmingly detrimental reactive effects from exposures to non-ionizing EMF radiation used for non-treatment purposes, such as electrical appliances, residential wiring, and wireless communications. These reactive health effects included enhanced oxidative damage, enhanced DNA damage, enhanced mutagenicity, enhanced teratogenicity, and many others. The third category, which could be termed the Superposition category, superpositioned the static magnetic field with other magnetic fields (geomagnetic or alternating) to provide a net magnetic field that could have a multiplicity of positive or negative health consequences by allowing or suppressing ion resonances for selected ions.

The non-ionizing EMF radiation in the Treatment category tended to be relatively short-term, especially those that were pulsed, whereas the non-ionizing EMF radiation in the Exposure category that had adverse health impacts tended to require relatively long exposures. The static magnetic fields in the Superposition category, when used as co-promoters with other non-ionizing EMF radiation, required an intensity on the order of magnitude comparable to the other non-ionizing EMF radiation. Even with other non-EMF agents, the static magnetic fields tended to have relatively substantive intensities.

4.4.3 Windows in Parameter Space

The documents selected for this chapter required that the non-ionizing EMF radiation component of the combination have some impact. In many articles not selected for this chapter, the non-ionizing EMF radiation-agent combination may have been similar to the non-ionizing EMF radiation-agent combination selected for this chapter, but the presence of the non-ionizing EMF radiation component did not affect the outcome (especially in the Environmental Exposure category for the adverse health impacts). What could account for this difference? For a given combination, one or more of the studies could have had poor research, or one or more of the studies could have had preconceived bias. Or, the experimental conditions for the two studies were sufficiently different that the 'window' in parameter space required for the effect to be observed was not present in one study but was present in another study.

There appears to be sufficient data among diverse research groups that adverse health effects from non-ionizing EMF radiation combinations exist in at least selected 'windows' of parameter space. Overall, the number and extent of these 'windows' need to be identified, to ascertain their overlaps with the operational

non-ionizing EMF radiation parameter space. This overlap would provide some indication or estimate of potential real-world health effects.

4.4.4 Resolving Differences

The first step in this process would identify major areas of disagreement, where strong adverse effects have been shown or predicted by the proponents, and typically no adverse effects have been shown or predicted by the opponents. The above studies, focused on the conditions that produced these adverse effects, would be re-done with multiple performers participating, representing diverse viewpoints. The study criteria would match objectives, methodology, and operational environment as closely as possible. Any differences in results could be examined on a uniform basis.

The second step would involve expanding the parameter values to understand the boundaries of the 'window' in parameter space in which adverse health impacts can occur. The third (and most difficult) step is the inclusion of other potential co-promoters to reflect more closely the following real-world conditions. People are not exposed only to non-ionizing EMF radiation in isolation, or non-ionizing EMF radiation combined with one potential co-promoter. People are exposed to many potentially harmful agents, either harmful in their own right, harmful only when combined with non-ionizing EMF radiation, harmful only when combined with non-ionizing EMF radiation and one or more other agents, and so on. For example, there could be three agents which, by themselves, would exhibit no harmful effects, and in any combination of two might exhibit no harmful effects, but in combination of three would exhibit harmful effects. Non-ionizing EMF radiation could provide the 'tipping point' of multiple potential harmful agents.

Unfortunately, to identify these potential harmful combinations experimentally would require astronomical levels of effort. In a recent eBook (Kostoff 2015), the first author identified ~800 pervasive foundational causes of disease; i.e., 800 tangible contributing factors to myriad diseases, and these results were viewed as an extremely conservative estimate. The number of potential combinations of these pervasive contributing factors to disease would be determined by the binomial coefficient. For example, the number of combinations of three potentially toxic stimuli from the list of 800 is 800!/(3!*797!), or approximately 85 million, and the number of combinations of two is approximately 320,000. Thus (in the latter case), we would need to perform 320,000 experiments to identify potentially harmful effects of any two toxic stimuli (from the ~800 identified in (Kostoff 2015)) combined with non-ionizing EMF radiation. Given the problem of 'windows' in parameter space described above, each experiment would be fairly complex, involving examination over large ranges of parameters such as non-ionizing EMF radiation frequency, intensity, duration, etc. Realistically, we would need to prioritize the pool of potential toxic stimuli, and then examine their effects in very small combinations with non-ionizing EMF radiation.

4.4.5 Limitations of Text-Based Analyses

A final observation. An exhaustive search process retrieved under 500 papers total for non-ionizing EMF radiation combined therapeutic and environmental adverse effects, with about 350 papers devoted to the environmental adverse effects of non-ionizing EMF radiation co-promotion published in the previous 30–40 years. Given the potential impact of non-ionizing EMF radiation, and the real-world importance of non-ionizing EMF radiation as a co-promoter, there appears to be a major disconnect between the magnitude of the problem and the research reported in the published literature available to understand and ameliorate the problem. What accounts for such a large disconnect: (1) underfunding of the research on adverse effects and/or (2) underreporting of the adverse effects? Appendix 2 addresses the issue of underreporting the adverse health effects of substances/phenomena like non-ionizing EMF radiation.

Appendices

A.1 Appendix 1 – Text Mining Query Used for Information Retrieval

Appendix 1 contains: (a) brief overview of text mining; (b) brief summary of past EMF co-promoter studies; (c) text mining methodology used to identify, retrieve, extract, and analyze the relevant EMF co-promoter articles from the premier biomedical literature; (d) details of the iterative relevance feedback component of the query used, and of the subsequent citation network traversing component of the query.

A.1.1 Text Mining Overview

Text mining is the extraction of useful information from large volumes of text (Hearst 1999; Feldman et al. 1998; Kostoff et al. 2001a). Its component capabilities of computational linguistics and information retrieval were the main analytical techniques used in the present chapter. A typical text mining study of the published literature involves the development of a query for comprehensive information retrieval, an analysis of the database using computational linguistics and bibliometrics, and an integration of the processed information.

Computational linguistics identifies the main technical/medical themes of the database(s) being examined as well as the relationships among these themes. Computational linguistics has been used to enhance information retrieval and increase awareness of the global technical literature (Kostoff et al. 1997; Greengrass 1997), as well as to track the impact of a specific research area across

time and applications areas (Davidse and VanRaan 1997; Kostoff et al. 2001b). Upgraded versions of these techniques were used for enhanced text-based and citation-based information retrieval in the present chapter.

Computational linguistics has been used in three modes to identify potential innovation and discovery: (a) co-occurrence of disease/technical problem and potential treatment/problem solution in the same article for identifying innovation (Kostoff and Briggs 2008; Kostoff et al. 2008b, c, d; Kostoff 2012); (b) linking disease/technical problem and disparate potential treatment/problem solution literatures directly (Kostoff and Briggs 2008; Kostoff et al. 2008a, b, c, d, e; Kostoff 2008, 2011, 2012; Swanson 1986; Swanson et al. 2001; Kostoff and Patel 2015; Kostoff and Los 2013); linking disease/technical problem and disparate potential treatment/problem solution literatures indirectly (Kostoff and Briggs 2008; Kostoff et al. 2008b, c; d). While these three modes each have their own distinctive features, they share the common requirement for an 'intelligent' query that targets documents with specific characteristics while filtering out 'noise'. That was also the main requirement for the present chapter, and the experiences from the above references were directly applicable to the requirements of the present chapter. The focus of the present chapter was on co-occurrence of two or more promoters/stimuli in the same article (mode a), but modes b) and c) were used informally to help further understand the mechanisms linking the promoters/stimuli to the health impacts. Modes b) and c) could be used to start with non-ionizing EMF radiation promoters/stimuli or combinations ab initio, and identify direct and indirect linkages/mechanisms to potential health impacts, beneficial or adverse.

A.1.2 EMF Co-promoter Studies

Most non-ionizing EMF radiation health/biological impact studies focus on one non-ionizing EMF radiation form, with no identifiable co-promoters/stimuli. The initial comprehensive non-ionizing EMF radiation retrieval performed by the first author used a text-based query to search the Medline/Science Citation Index databases for a wide range of EMF radiation records, and retrieved over 6000 documents. The present chapter used a more intense hybrid text-based and citation-based query to search for non-ionizing EMF radiation ***combinations*** and their effects, and retrieved under 500 records. Thus, perhaps 5–7% of non-ionizing EMF radiation health/biological impact studies (probably less) are concerned with combination-type effects.

There are relatively few comprehensive review articles covering the combination effects. Juutilainen (2008; Juutilainen et al. 2006) examines cocarcinogens. Stam (2010) examines non-ionizing EMF radiation effects on the blood-brain barrier; this study is typical of reviews that may examine non-ionizing EMF radiation effects on an organ or system. Lee et al. examine the carginogenic potential of 60 Hz ELF-MF (1 mT) alone or in combination with ionizing radiation (IR), hydrogen peroxide (H_2O_2), or c-Myc overexpression (Lee et al. 2012).

Most of these previous studies that focused on combination effects of non-ionizing EMF radiation with other stimuli are like the articles referenced in

the body of this chapter, namely, selected non-ionizing EMF radiation ranges in the frequency spectrum combined with usually one or a few co-stimuli. However, none of these review articles covers the wide range of disciplines as the present chapter, as well as both adverse and beneficial combined effects. It is the scope of coverage and the comprehensiveness of retrieval using the hybrid search technique, as well as the integration across disciplines, which makes the present chapter unique.

A.1.3 Methodology: Document Identification, Retrieval, Extraction, Analysis

A.1.3.1 Definitions of Combined/Interactive Effects

The goal of this chapter is to examine the scope of the non-ionizing EMF radiation combined effects on biological systems; i.e., identify effects on biological systems from combined exposure to non-ionizing electromagnetic fields/radiation and at least one other agent. These interactive effects include:

A.1.3.1.1 Additive effects (the combined effect of two or more agents acting in the same general direction approximates the sum of the effects of the agents administered separately, subject to the maximum possible effects in biological systems);
A.1.3.1.2 Antagonistic effects (the combined effects of two agents acting in different/opposite directions are smaller than the effect of any one of them in stand-alone mode);
A.1.3.1.3 Potentiative effects (the increased effect of an agent by concurrent action of another agent that does not have a stand-alone effect); and
A.1.3.1.4 Synergistic effects (the combined effect of two or more agents is significantly greater than the sum of the effects of each agent administered alone, subject to the maximum possible effects in biological systems).

Other terminology is used in the documents, such as co-promotional, co-mutagenic, co-carcinogenic, etc., but these terms tend to be sub-sets of the more general terms defined above.

The approach in this chapter is to: (1) select the most credible global databases of research articles; (2) develop a query that will retrieve the relevant combined effects literature comprehensively; (3) identify the key biomedical thrusts in this retrieved literature; and (4) extract the mechanisms and principles that describe the influence of the non-ionizing EMF radiation component on the final combined effects. These four approach components are now described in more detail.

A.1.3.2 Select Global Databases

The two premier biomedical research article databases are the Web of Science (WOS-Science Citation Index/Social Science Citation Index/Arts and Humanities Citation Index-SCI/SSCI/A&HCI) and Medline. Each has its unique strengths.

WOS has the capability for citation linkages (references, citing papers, papers that share at least one reference), while Medline has a unique taxonomy/keyword structure called MeSH. Both databases were used in this chapter for query development.

A.1.3.3 Develop Retrieval Query

The first step in query development is to define the scope of the study topic. The scope selected was effects on biological systems from combined exposure to non-ionizing EMF radiation and at least one other agent. A novel hybrid iterative relevance feedback technique (based on Kostoff et al. 1997) was used to develop the query. The non-ionizing EMF radiation component of the full query (based on Medline and the SCI) used by the first author for the comprehensive non-ionizing EMF radiation retrievals was intersected with the terms "synerg* and 'combined effect*'" to form an initial test query (see A.1.3.6.1. for complete initial test query). This initial query was inserted into the SCI search engine, further filtering was performed by restricting to biomedical Subject Areas (each SCI record has one or more Subject Area keywords assigned to it), and about eighty records were retrieved. These were termed the *core records*. The query was then expanded by examining the local citation network for each of the core records.

First, all the records that cited the *core records* were retrieved (~700), and were examined manually to select relevant non-duplicative records (~90). These were termed the *core citing records*. Second, all the references to the *core records* and *core citing records* that were in the SCI were examined manually to select relevant non-duplicative records (~150). These were termed the *core record references* and *core citing record references*. Third, some of the records that shared references with the *core records* and *core citing records* were examined, as follows.

> The SCI has a feature called Related Records. For a record of interest, the Related Records feature will display all records in the SCI database that share at least one reference in common with the record of interest. These Related Records can be ordered by the number of references in common. The numbers of Related Records can range from zero (all the references in the record of interest were cited only once) to hundreds of thousands for a large block of highly cited references. Typically, the numbers of Related Records for a record of interest range from hundreds to tens of thousands. In practice, only a few of the Related Records for each record of interest can be examined for relevance, due to the large volumes involved.

The protocol used was to examine the twenty-forty records with the most shared references for each of the *core records* and *core citing records*, and extract those non-duplicative records deemed relevant (~75). These were termed the *core records related records* and the *core citing records related records*. Many of the Related Records tended to display repeatedly on the twenty-forty records with the

most shared references, and the marginal utility of this approach decreased with time. This can be visualized as a well-connected network, where the same material is being accessed repeatedly. Like any network problem, the path to new information is less through complete-link type approaches and more through single-link type approaches. Unfortunately, the numbers of records with two or one shared references are large compared to the numbers of records with many shared references, and there were too many of these low shared reference records to examine manually.

Fourth, all the relevant records retrieved above were combined, and imported into the Vantage Point (VP) software (Vantage Point 2015). Text patterns in the Abstracts and Titles were examined, and were added to the initial test/text query. The additional query terms are shown in A.1.3.6.2. These terms were inserted into the SCI search engine, with further filtering done by Subject Area. About 500 records were retrieved and examined manually, and those deemed relevant (~135) were extracted. The total of about 530 records were then examined in detail, *stricter criteria were applied for relevance*, and 436 records with Abstracts were judged to be relevant. Obviously, the citation and text linkages could have been continued in an iterative manner, and more relevant records would have been found. However, the marginal utility of both approaches was beginning to decrease, especially for the citation linkages, and the manual selection approach was becoming infeasible.

A.1.3.4 Identify Key Biomedical Thrusts

The 436 retrieved records were inserted into the VP text mining software package and into the CLUTO document clustering software package (CLUTO 2015). A factor analysis was performed in VP using 32 factors, and a hierarchical taxonomy was generated in CLUTO using 32 clusters. Text mining was performed on each factor and cluster, to identify the key biomedical phrases representative of the group and the titles of papers in the group. Based on reading the titles and phrases, and reading of many paper Abstracts in each group as well, the theme of each group was identified.

A.1.3.5 Extract the Mechanisms and Principles that Describe the Influence of the Non-ionizing EMF Radiation Component on the Final Combined Effects

This is the key analytic step. Based on the two groupings identified by the clustering and factor analysis described above, and a reading of all the Abstracts, a final taxonomy was generated. The records were assigned manually to each taxonomy category. The non-ionizing EMF radiation-co-promoter-mechanism-disease 'signatures' were extracted by integrating the relevant factors, relevant clusters, and relevant sections of each record in the cluster. These relevant sections are displayed in the narrative section following the clustering summaries and taxonomy (Figs. 4.1 and 4.2).

The records were updated by repeating the above process for years 2012–2016, and adding the additional relevant records to the existing taxonomy categories.

A.1.3.6 Iterative Relevance Feedback Query

A.1.3.6.1 Initial Test Query

Topic=((EMF OR "Electromagnetic Field*" OR "Radio-Frequency Radiation" OR "Radio-Frequency Irradiation" OR "RF-Radiation" OR "RF-Irradiation" OR "Microwave Radiation" OR "Microwave Irradiation" OR "Mobile Phone*" OR "Cell* Phone*" OR "Wireless Phone*" OR "Cordless Phone*" OR "Mobile Telephone*" OR "Cellular Telephone*" OR "Wireless Telephone*" OR "Cordless Telephone*" OR "Base Station*" OR "RF-Transmission Tower*" OR "Cell Tower*" OR (("Magnetic Field*" OR "Electric Field*") AND ("Power Line*" OR "Low Frequency" OR "Power Frequency" OR "Intermediate Frequency" OR "Transmission Line*" OR "Electric Power Transmission"))) AND (synerg* OR "combined effect*")) AND Document Type=(Article OR Review)

Refined by: Subject Areas=(Biology OR Behavioral Sciences OR Biophysics OR Cell Biology OR Environmental Sciences OR Toxicology OR Public, Environmental & Occupational Health OR Orthopedics OR Radiology, Nuclear Medicine & Medical Imaging OR Health Care Sciences & Services OR Developmental Biology OR Pharmacology & Pharmacy OR Neurosciences OR Materials Science, Biomaterials OR Oncology OR Parasitology OR Biotechnology & Applied Microbiology OR Physiology OR Biochemical Research Methods OR Biochemistry & Molecular Biology OR Reproductive Biology OR Rheumatology OR Genetics & Heredity OR Surgery)

A.1.3.6.2 Additional Terms in Refined Query

Topic=(("magnetic field*" OR EMF* OR microwaves OR "microwave radiation" OR "microwave exposure*" OR "microwave irradiation" OR "electromagnetic field*" OR "RF radiation" OR ELF-MF* OR "mobile phone*" OR PEMF* OR EMR OR "Electromagnetic radiation" OR ELF OR "Radiofrequency field*" OR "radiofrequency radiation" OR ELF-EMF OR "cell* phone*" OR "electric power" OR "electromagnetic noise" OR IFC OR "pulsed magnetic field*" OR "CELL TOWER*" OR "static MF" OR "electric field*" OR electricity OR "electromagnetic EM field*" OR "electromagnetic radiation" OR "EM field exposure*" OR geomagnetic OR "power line*" OR electroporation OR electrofusion OR electrochemotherapy OR electropermeabilization))

AND ("combin* effect*" OR potentiat* OR synerg* OR "combin* exposure*" OR co-exposure OR "combin* treatment*")) AND Document Type=(Article OR Review)

Refined by: Subject Areas=(Biophysics OR Biology OR Neurosciences OR Biochemistry & Molecular Biology OR Radiology, Nuclear Medicine & Medical

Imaging OR Toxicology OR Oncology OR Cell Biology OR Public, Environmental & Occupational Health OR Medicine, Research & Experimental OR Physiology OR Genetics & Heredity OR Microbiology OR Immunology OR Endocrinology & Metabolism OR Medicine, General & Internal OR Clinical Neurology OR Surgery OR Behavioral Sciences OR Developmental Biology OR Hematology OR Orthopedics OR Psychiatry OR Urology & Nephrology OR Dermatology OR Infectious Diseases OR Psychology, Experimental OR Cardiac & Cardiovascular Systems OR Gastroenterology & Hepatology OR Health Care Sciences & Services OR Neuroimaging OR Respiratory System OR Rheumatology OR Veterinary Sciences OR Virology OR Dentistry, Oral Surgery & Medicine OR Medical Informatics OR Nutrition & Dietetics OR Obstetrics & Gynecology OR Parasitology OR Pathology OR Pediatrics OR Peripheral Vascular Disease OR Psychology OR Psychology, Multidisciplinary OR Reproductive Biology)

A.2 Appendix 2 – Underreporting of Adverse Effects of EMF Radiation

Most of the papers in this chapter (~70%) focused on adverse health effects of non-ionizing EMF radiation combined with other agents. There is a growing literature providing evidence that adverse events in the biomedical literature are underreported; some of this literature is summarized in Chapter 9 of (Kostoff 2015). References 71–125 of (Kostoff 2015) are a modest sample of studies showing how adverse events in the biomedical literature have been, and are being, underreported. What are the reasons for, and consequences of, such underreporting of adverse events from non-ionizing EMF radiation?

A.2.1 Full Reporting of Adverse Events

A literature in which adverse events were fully reported would have the following characteristics:

- all critical research problems necessary for credible policy are addressed/funded;
- all research performed is credible and high quality;
- all research findings are submitted for publication;
- all papers are reviewed by unbiased experts before publication;
- all high quality research submissions are published;
- all published articles are available to the general public;
- all accessible articles are easily retrieved.

A.2.2 Underreporting of Adverse Events

Adverse events are not reported fully in part because of the following reasons.

A.2.2.1 Critical Research Not Funded

Some critical research problems are not addressed/funded, for myriad reasons:

- the combinatorics parameter space is too complex to address all the areas;
- the funds available to the sponsor organization are insufficient to cover all critical research areas;
- the process for setting funding priorities within the sponsor organization is poor;
- selection based on potential for favorable results;
- external pressures effectively limit what topics can be funded, including
  - industry pressure to suppress topics that may have commercial sensitivity, and/or
  - government pressure to suppress topics that may have political sensitivity.

  The pressures may operate intra-organizationally or inter-organizationally.

A.2.2.2 Research Not Submitted for Publication

Some research findings are not submitted for publication, for myriad reasons:

- national security classification, or classification for other reasons;
- organizationally proprietary;
- no organizational or individual publishing tradition, with equally little incentive to publish;
- costs associated with submissions for publication (time and money), which some organizations may not be willing to spend.

Most disturbing is the potentially deliberate suppression of research findings. This may result from:

- negative findings, which many organizations/journals/researchers are reluctant to publish;
- adverse events, which many industrial and governmental organizations in the biomedical community are reluctant to publish;
- commercial sensitivity, which industry would rather not be published;
- political sensitivity, which government would rather not be published; and,
- unethical research, whose performers would rather not be published, and whose quality may be relatively low due to lack of research oversight and lack of reproducibility.

A.2.2.3 Poor Research Published; Good Research Not Published

Some research that enters the literature may be of low quality, due to:

- poor peer review (where the peer review process and/or the peer reviewers are of low quality) or no peer review;
- contribution to the journal Editor's pre-determined agenda.

Some high quality research may not get published, due to:

- poor peer review or biased peer review;
- lacking editorial expertise to judge the quality of the research;
- non-contribution to the journal Editor's pre-determined agenda;
- not viewed as potentially contributing to increasing journal's Impact Factor

A.2.2.4 Manufactured Research

Finally, some/much research that enters the published literature may be deliberately distorted or skewed; this research can be termed "manufactured research". The purpose of this manufactured research is to both

- counter publications showing adverse effects from specific products and
- sow confusion among the public and decision-makers, not allowing the consensus required for policy.

The books Merchants of Doubt (Oreskes and Conway 2011) and Doubt is Their Product (Michaels 2008) describe this 'research manufacturing' process quite well. A few illustrative biomedical examples of some of the more egregious misrepresentations of science mentioned above, especially suppressed and manufactured research, are presented in Chapter 9 of (Kostoff 2015).

A.2.2.5 Published Research Not Easily Accessible

Some good published research may not be easily accessible to the public and the decision-makers, because of:

- publication in relatively obscure media or foreign languages only;
- publication behind high paywalls;
- poor search engines/algorithms.

A.2.2.6 Incentives for Inadequate Literature

There are many disincentives for an adequate literature, including.

- **Industry:** financial advantages for concealing the adverse effects of their products and services.
- **Government:** supporting corporate and large donor interests (through selective topic sponsorship and suppressed/distorted research findings) to lay the **groundwork for future industry employment.**
- **Journal Editors:** maintaining industry-sponsored professional society and/or advertising support through selective publication favorable to sponsors.
- **Research performers:** receiving and maintaining grants by working on topics of interest to, and producing results desired by, corporate and government sponsors; producing publications aligned with the interests of journal sponsors or advertisers in order to increase publication likelihood; laying the groundwork for future industry employment and/or consultancies by not publishing findings antithetical to the interests of industry.

In this section, we have identified the disincentives (for an adequate literature) for four classes: Industry, Government, Journal Editors, Research Performers. There are individuals who span multiple classes. For example, a person who works in government may also be a research performer and a journal Editor. The incentive (for an inadequate literature) associated with e.g. their government function may 'spill over' to their journal Editor and research performer roles. So, even though the journal may not have industry or government financial support as a source of potential bias, the potential biases arising from the government or research performer affiliations of the Editor could (in theory) influence the journal Editor role.

A.2.2.7 Policy Implications of Inadequate Literature

There are myriad important drivers of government policy; the three critical drivers of policy considered now will be technical literature, interests of political donors, and interests of the electorate.

Three options that relate policy to technical literature are:

- Option 1: The topical area is non-sensitive commercially or politically (e.g., weather satellite research, age of universe research). There is little incentive for much 'manufactured research' in these topical areas. Donors and voters would agree with, or be indifferent to, policy dictated by adequate literature; donors and voters agree with policy dictated by inadequate literature; policy reflects literature.
- Option 2: The topical area is sensitive commercially and/or politically (e.g., EMF health impacts). There is incentive for much 'manufactured research' in these topical areas, and our own studies have confirmed this. In this case, donors and voters would ***disagree*** with policy dictated by adequate literature. The donors are driven by profit, and the voters are addicted to the specific technology in this case (e.g., wireless communications). Thus, donors and voters agree with policy dictated by inadequate literature.

- In the case of EMF health impacts, the policy on EMF exposures that would be required as the result of an objective reading of the credible technical literature (severe restrictions on the use of wireless communications, etc) would not be acceptable to the vast majority of donors and voters. Thus, the policy in practice reflects the interests of the donors and voters, not the dictates of an adequate technical literature.
- Option 3: The topical area is sensitive commercially and/or politically (e.g., exposures/treatments that cause disease). There is incentive for much 'manufactured research' in this case, and our own studies have confirmed this. In this case, donors would disagree with policy dictated by an adequate literature, whereas the voters would ***agree*** with policy dictated by adequate literature. The donors are driven by profit, whereas the voters are driven by the benefits of technology in this specific case. ***Unlike the previous option, the voters are not addicted to the technology, since its application may be unpleasant in many cases.*** The donors still agree with policy dictated by inadequate literature, whereas the voters agree with policy dictated by inadequate literature, ***only because they believe it is adequate***. This means that some literatures may be highly manufactured to maintain voter support. The policy reflects donors, not adequate technical literature.

In conclusion, the published technical literature is inadequate for myriad reasons, and the degree of inadequacy is unknown and may be unknowable. The fraction of inadequacy due to deliberate misinformation is unknown, but may be large for topical areas with commercial or political sensitivity.

A.2.2.8 Alleged Under- and Distorted Reporting of Non-ionizing EMF Radiation Adverse Effects

In the course of the present research, we have received numerous oral and written statements by non-ionizing EMF radiation researchers, and have seen many anecdotes reported, describing how adverse effects from non-ionizing EMF radiation have been suppressed as topics of research by the sponsoring agencies, and suppressed or distorted in the published research literature. This is not surprising; many government operations depend on the use of wireless communications, many industrial organizations are involved in producing wireless communications devices and systems, and many utilities involve high non-ionizing EMF radiation as part of their daily operations. If non-ionizing EMF radiation levels were required to be drastically reduced for safety purposes, the effect on our economies and many government operations would be devastating.

Two examples will be discussed in this section: alleged publication bias in a leading radiation journal (Slesin 2006) and the Bioinitiative Report (2012).

A.2.2.8.1 Alleged Journal Bias on Publishing Adverse Effects

As the reader will see from the following example, obtaining data to support and validate allegations of journal bias is extremely difficult. Dr. Louis Slesin has been publishing a newsletter addressing myriad issues related to microwave radiation, and it is aptly entitled 'Microwave News' (MN). We came across this newsletter during the course of our initial non-ionizing EMF radiation health impacts study (Kostoff and Lau 2013), and found the MN articles were quite accurate in the areas where they overlapped our study.

In 2006, MN published an article entitled "Radiation Research" and The Cult of Negative Results (Slesin 2006). It was a unique study with major contributions from Dr. Henry Lai, a leading researcher in the technical area of the article. The study's focus was essentially to ascertain how reflective (of the microwave-induced genotoxicity publications in the larger technical literature) were those articles published in the journal *Radiation Research* on this topic.

In short, MN found that:

- [In the larger technical literature on microwave-induced genotoxicity] "There is just about an even split between effect and no-effect papers";
- "A clear—and disconcerting—pattern emerges: 32 of the 35 studies that were paid for by the mobile phone industry and the U.S. Air Force show no effect. They make up more than 75% of all the negative studies. You don't need to be a statistician to infer that money, more often than not, secures the desired scientific result";
- "A similar loss of balance occurs when you look at only the papers published in Radiation Research.....Over the last 16 years, only one positive paper on microwave genotoxicity has appeared in Radiation Research. During the same time, the journal has published 21 negative genotox papers. (Australia's Pam Sykes, the lead author of the lone positive paper, was denied money for a follow-up and soon moved on to other research areas.)....80% of the negative papers (17 out of 21) published in Radiation Research were paid for by either industry or the U.S. Air Force." (Kostoff and Lau 2013).

At this point, the statements in MN are only ***allegations***. There could be journal bias, or the best papers submitted to the journal happen to be the ones showing the absence of an impact of microwaves on genotoxicity. How could this issue be resolved?

One could (in theory) re-evaluate the original peer reviews of all the manuscripts submitted to the journal on this topic for bias. Unfortunately, we would then have the issue of determining the biases of the second group of reviewers, a difficult task. Additionally, even for reviewers who are unbiased, there is not always complete agreement. Scientists can sometimes have very differing opinions on the value of the same concept. Proving deliberate bias for a journal is extremely difficult, and may border on the impossible in practice.

Further, while funding source was used as an important metric to assess potential bias in the above study, it is by no means definitive. The determining factor is

'intent'; were the researchers incentivized to bias their findings? If a researcher had no observable funding sources that could be interpreted as predisposing to potential bias, but wanted to obtain either (1) funding from industry or (2) future employment with industry, then one could argue the researcher had some predisposition to bias in favor of industry. How would we ever know this? Even if the researcher eventually received a grant from industry, or employment with industry, how would we know whether the researcher 'intended' to pursue these funding opportunities at the time the research was being performed and published?

Finally, how well this particular example reflects all, or any, other technical/biomedical journals relative to the presence or absence of potential bias, is unknown.

A.2.2.8.2 The Bioinitiative Report

The Bioinitiative Report (2012) was written by a large number of world-class experts in science and public health policy in 2007, and updated in 2012. It assessed safety of non-ionizing EMF radiations at myriad frequencies. Its main message is that the present permissible non-ionizing EMF radiation exposure limits are orders of magnitude too high to protect against potential adverse health effects from non-ionizing EMF radiation. The Report recommends permissible chronic non-ionizing EMF radiation exposure limits of about one milligauss in the power frequency range (~60 Hz), and about ten microwatts/m^2 in the outdoor RF range. Contrast that with the ICNIRP (International Commission on Non-Ionizing Radiation Protection; an independent scientific organization) reference levels for general public exposure of about 800 milligauss (time varying magnetic field unperturbed rms value) in the 60 Hz power frequency range (ICNIRP n.d.), and the FCC (a regulatory agency) MPE power density limits of about 6.0×10^6 microwatts/m^2 at ~900 Mhz cell phone RF frequencies (Federal Communications Commission Office of Engineering and Technology 1997). These are three to six orders of magnitude higher than recommended in the Bioinitiative Report.

Why is there such a difference, and how does this difference relate to the underreporting of adverse health effects from non-ionizing EMF radiation? The answer is partially stated and partially implied within Section 3 of the Bioinitiative Report (The Existing Public Exposure Standards), as follows:

> Professional bodies from technical societies like IEEE and ICNIRP continue to support "thermal-only" guidelines routinely defend doing so a) by omitting or ignoring study results reporting bioeffects and adverse impacts to health and wellbeing from a very large body of peer-reviewed, published science because it is not yet "proof" according to their definitions; b) by defining the proof of "adverse effects" at an impossibly high a bar (scientific proof or causal evidence) so as to freeze action; c) by requiring a conclusive demonstration of both "adverse effect" and risk before admitting low-intensity effects should be taken into account; e) by ignoring low-intensity studies that report bioeffects and health impacts due to modulation; f) by conducting scientific reviews with panels heavily burdened with industry experts and under-represented by public health experts and independent scientists with relevant low-intensity research experience; g) by limiting public participation in standard-setting deliberations; and other techniques that maintain the status quo.

> Much of the criticism of the existing standard-setting bodies comes because their contributions are perceived as industry-friendly (more aligned with technology investment and dissemination of new technologies) rather than public health oriented.

There are many published studies that bolster the above conclusions, and address the influence of industry funding on scientific results. For example (Huss et al. 2007): "We examined the methodologic quality and results of experimental studies investigating the effects of the type of radiofrequency radiation emitted by hand-held cellular telephones. We hypothesized that studies would be less likely to show an effect of the exposure if funded by the telecommunications industry, which has a vested interest in portraying the use of mobile phones as safe. We found that the studies funded exclusively by industry were indeed substantially less likely to report statistically significant effects on a range of end points that may be relevant to health. Our findings add to the existing evidence that single-source sponsorship is associated with outcomes that favor the sponsors' products..... Most previous studies of this issue were based on studies of the efficacy and cost-effectiveness of drug treatments. A recent systematic review and meta-analysis showed that studies sponsored by the pharmaceutical industry were approximately four times more likely to have outcomes favoring the sponsor's drug than studies with other sources of funding.....The influence of the tobacco industry on the research it funded has also been investigated.....To our knowledge, this is the first study to examine this issue in the context of exposure to radiofrequency electromagnetic fields."

Chapter 9 of reference (Kostoff 2015) shows this problem is endemic to many industries and government agencies. Given the difficulty of obtaining this type of information, much of which is provided by 'whistleblowers', we should not under-estimate the amount of distorted non-ionizing EMF radiation adverse effects findings published in the literature, nor under-estimate the amount of non-ionizing EMF radiation adverse effects findings suppressed from publication by government, industry, and the journals themselves.

To conclude, this sub-section has provided reasons for adverse health effects of myriad substances (including non-ionizing EMF radiation) being underreported in the premiere biomedical literature, or entering this literature in distorted form. Since there is no way to gauge the extent of this under/distorted-reporting, the quality and credibility of the 'premiere' biomedical/non-ionizing EMF radiation adverse effects literature is unknown. Therefore, any types of meta-analyses or scientometric analyses of this literature will have unknown quality and credibility. The most sophisticated scientometric analysis cannot compensate for a highly-flawed database.

Equally damaging is the effect of this flawed database on the larger scientific enterprise. Science can be viewed as a never-ending construction project, where the building blocks and support structures are the documents from past scientific studies. If some, or many, of these building blocks are flawed, the upper parts of the structure will be weakly supported, and may collapse. Through the citation process, the misleading findings at the lower parts of the structure are promulgated

to the upper portions, and the dilution of quality increases. While the propensity for misconduct is greatest in areas of commercial and political sensitivity, the broad reach of basic science will have a 'spill-over' adverse impact on myriad directly and indirectly related areas of science.

Disclaimer The views in this chapter are solely those of the authors, and do not necessarily represent the views of Georgia Institute of Technology or any of its components, or of the Institute for Defense Analyses.

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