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Combined biological and health effects of electromagnetic fields and other agents in the published literature ☆

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ABSTRACT

Electromagnetic field (EMF) radiation exerts both stand-alone and combined effects on biological systems. The present study examines the scope of the combined effects; i.e., identify effects on biological systems from combined exposure to electromagnetic fields/radiation and at least one other agent. Only articles in which the presence of EMF 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.

There is a wide range of potential effects in which EMF plays a supportive role. Beneficial effects include improved treatment of chronic diseases like cancer by enhancing ionizing radiation or chemotherapy, and accelerated healing of wounds and injuries in concert with other agents. Adverse effects, on the other hand, include enhanced carcinogenesis, cellular or genetic mutations, and teratogenicity. It should be noted that community consensus does not exist on these potential effects, either beneficial or adverse, although there is substantial credible scientific evidence supporting the above effects (as the body of this paper shows). In real life, the body is exposed to multiple environmental agents simultaneously, e.g., a variety of EMF, pesticides, food additives, and air pollution. The number of potential environmental agent combinations is large, and each combination could potentially have beneficial or adverse effects; much work remains to be done before definitive statements about EMF safety can be made.

1. Introduction

The electromagnetic spectrum encompasses the entire span of electromagnetic radiation. The spectrum includes gamma rays (short wavelengths ~10^{-13} m and high frequencies ~10^{21} Hz), radio waves (long wavelengths ~10^{2} m and low frequencies ~10^{6} Hz), and the frequencies associated with commercial and residential power (very long wavelengths ~10^{6} m and very low frequencies ~60 Hz). In ancient times, sunlight and its lunar reflections provided the bulk of the visible spectrum (with fire a distant second and lightning a more distant third). Now, many varieties of artificial light have replaced the sun as the main supplier. Additionally, EMFs from other parts of the spectrum have become ubiquitous in daily life, such as wireless computing and telecommunication. In the

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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 EMF from mobile communication devices, occupational exposure, residential exposure, wireless networks, and other EMF sources.

The effects of electromagnetic fields on health can be therapeutic; e.g.,

- "ELF-EMF modulates chemokine production and keratinocyte growth through inhibition of the NF-kappa B signaling pathway and thus may inhibit inflammatory processes. ELF-EMF could represent an additional therapeutic approach in the treatment of skin injury." [1].
- "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" [2].
- Many other similar examples exist for medical therapeutics.

But the effects can also be potentially harmful; e.g.,

- "Extremely low frequency-magnetic fields (ELF-MF) are possible carcinogens to humans and some data suggest that they can act as promoters or progressors." [3].
- "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"] [4].
- 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" [5].
  - "Our study provides some evidence for the first time that MF exposure may have an adverse effect on sperm quality" [6].
  - "Every 1-mG increase of maternal MF [magnetic field] level during pregnancy was associated with a 15% increased rate of asthma in offspring" [7].

These few example citations illustrate the complexity of the problem, compounded further by the lack of comprehensive and long-term data [8] and the intrinsic limitations in the fundamental data. There are two main sources of data types supporting the above analysis, and a number of additional sources.

1.1. 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 physical systems, biological specimens have varying sensitivity to 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 [9].

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" [10]), 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 analysis to draw any conclusions. As Verschaeve and Maes [11] 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 base station.

These EMF combined effects may go in multiple directions. As Whissel and Persinger [12] state, in addressing the possibility of weak 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?" [13] and in a preceding article [14], the 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 combined effects. Most of these papers address combinations, but not their sequencing. For example, a paper published in Radiobiologia [15] 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.

1.2. 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 is taken, which contains 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.

Preceding this study, the first author performed text mining-based retrievals and analyses of documents that mainly examined health effects of EMF 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 EMF were extremely important, and should be the focus of a much more detailed study. This document is the culmination of that 'more detailed study'. The next section provides some brief background material on text mining and previous EMF combined effects studies, followed by the approach, results, and conclusions of the present study.

2. Background

2.1. Text mining

Text mining is the extraction of useful information from large volumes of text [16–18]. Its component capabilities of computational linguistics and information retrieval were the main analytical techniques used in the present study. 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 [19,20], as well as to track the impact of a specific research area across time and applications areas [21,22]. Upgraded versions of these techniques were used for enhanced text-based and citation-based information retrieval in the present study.

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 [23–27]; b) linking disease/technical problem and disparate potential treatment/problem solution literatures directly [23–33]); linking disease/technical problem and disparate potential treatment/problem solution literatures indirectly [23–26]. 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 study, and the experiences from the above references were directly applicable to the requirements of the present study. The focus of the present study 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 EMF promoters/stimuli or combinations ab initio, and identify direct and indirect linkages/mechanisms to potential health impacts, beneficial or adverse.

2.2. EMF co-promoter studies

Most EMF health/biological impact studies focus on one EMF form, with no identifiable co-promoters/stimuli. The initial EMF-in-isolation 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 records, and retrieved over 6000 documents. The present study used a more intense hybrid text-based and citation-based query to search for EMF combinations and their effects, and retrieved under 500 records. Thus, perhaps 5–7% of EMF health/biological impact studies (probably less) are concerned with combination-type effects.

There are relatively few comprehensive review articles covering the combination effects. Juutilainen [13,14] examines cocarcinogens. Stam [34] examines EMF effects on the blood-brain barrier; this study is typical of reviews that may examine EMF effects on an organ or system. Most of the studies focused on combination effects of EMF with other stimuli are like the articles referenced in the body of this study, namely, selected EMF 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 article, 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 study unique.

3. Methods and materials

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

(a) 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);
(b) 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);

(c) Potentiative effects (the increased effect of an agent by concurrent action of another agent that does not have a stand-alone effect); and
(d) 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 conducting this study 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 EMF component on the final combined effects. These four approach components are now described in more detail.

3.1. 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, while Medline has a unique taxonomy/keyword structure called MeSH. Both were used in this study for query development.

3.2. 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 EMF radiation and at least one other agent. A novel hybrid iterative relevance feedback technique, based on Kostoff et al. [19], was used to develop the query. The EMF component of the full query (based on Medline and the SCI) used by the first author for the EMF-in-isolation retrievals was intersected with the terms "synerg* and combined effect*" to form an initial test query (see Appendix 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 [35]. 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 Appendix 1. 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 was 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.

3.3. Identify key biomedical thrusts

The 436 retrieved records were inserted into the text mining software package Vantage Point and into the CLUTO document clustering software package [36]. A factor analysis was performed in Vantage Point 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.

3.4. Extract the mechanisms and principles that describe the influence of the emf 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 EMF-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 and factor matrix summaries.

4. Analysis and results

4.1. Factor matrix analysis

There were 436 records imported into VP and CLUTO (only those with Abstracts). EMF and biomedical-related phrases were selected manually from the list of VP Abstract phrases, and factor analyses were performed with the VP software. Factor matrices ranging from 2 to 64 factors were generated, and the 32 factor matrix appeared to be the best compromise between resolution and integration. Because the factor taxonomy was not significantly different from the document clustering taxonomy, only the latter will be summarized due to space limitations.

4.2. Document clustering taxonomy

A hierarchical taxonomy was generated with 32 leaf (lowest level) clusters (categories). Each record was assigned to one cluster only. This translates to an average of about fourteen records per cluster, about an order of magnitude less documents per cluster than the first author has used in previous text mining studies. It was believed such resolution was required to meet the objectives of the present study.

The three highest levels in the taxonomy are shown in Fig. 1. They are self-explanatory, and will not be discussed further due to space limitations.

4.3. 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. 2). It focuses on impacts, and incorporates the major impact categories. A brief summary of each category is presented first, ending with a short illustrative example. Where possible, integrative mechanisms for the category are discussed.

4.4. Category 1. Impact on cancer

This category includes EMF combinations that help in the treatment of cancer (89 records), as well as combinations that

LEVEL 1	LEVEL 2	LEVEL 3
Cluster 57: Interactive effects from pulsed electric and magnetic fields (combined with other agents) on tumors; other types of interactive effects from electric fields (117)	Cluster 51: Interactive effects from pulsed magnetic fields on tumors, especially pulsed EMF-induced hyperthermia (49)	Cl 40: Hyperthermia and chemotherapy or gene therapy for patient tumor therapy, especially with magnetic nanoparticles (27)
		Cl 46: Pulsed electromagnetic/ magnetic fields and anti-cancer drugs/ photodynamics for cell lines (22)
	Cluster 52: Pulsed electric fields for improved transdermal delivery of chemotherapeutic agents and for suppressing bacterial growth (68)	Cl 10: Pulsed electric fields/ HIPEF, especially with Nisin, for inactivation, especially of foodborne microorganisms (16)
		Cl 49: Electric fields (especially pulsed), electroporation, electrochemo-therapy and agents for tumor treatment (52)
Cluster 61: Interactive effects at the cellular and DNA level from low frequency alternating and static magnetic fields (combined with other agents), and microwaves (319)	Cluster 58: Combined effects of low frequency electromagnetic fields and other agents on biological processes (142)	Cl 50: Magnetic fields and morphine-induced analgesia (50)
		Cl 55: Magnetic fields (especially ELF) and carcinogens impacts on rats (92)
	Cluster 60: Combined effects of static magnetic fields and microwaves with other agents on cells, DNA, and apoptosis (177)	Cl 56: Damage from microwaves and other agents, especially on DNA (84)
		Cl 59: Impact of electromagnetic and static magnetic fields, especially with x-rays on oxidative stress (93)

Fig. 1. Taxonomy of biomedical thrusts in emf health effects literature.

CAT #	CATEGORY/SUB-CATEGORY TITLE Code: Shaded denotes mainly adverse effects Unshaded denotes mainly beneficial effects
1	**IMPACT ON CANCER**
1a	Hyperthermia
1b	Chemotherapy
1c	Ionizing radiation and other treatments
1d	Chemical promoters
1e	Electromagnetic promoters
2	**IMPACT ON NEURAL SYSTEM**
2a	Enhanced analgesia
2b	Enhanced performance and reduced seizures
2c	Reduced analgesia effectiveness
2d	Performance degradation
3	**IMPACT ON CIRCULATORY SYSTEM**
3a	Enhance heart, vascular
3b	Degrade heart, vascular
4	**IMPACT ON IMMUNE SYSTEM**
4a	Enhance immune system performance
4b	Degrade immune system performance

5	**IMPACT ON ENDOCRINE SYSTEM**
5a	Enhance endocrine system performance
5b	Degrade endocrine system performance
6	**IMPACT ON SKELETAL SYSTEM**
7	**IMPACT ON GENES**
7a	Positive genetic impacts
7b	DNA damage
7c	Mutations
7d	Teratogenicity
8	**IMPACT ON CELLS**
8a	Permeation (beneficial effects)
8b	Apoptosis (cancer cells)
8c	Apoptosis (healthy cells)
8d	Cell proliferation
8e	Oxidative damage
8f	Permeation (adverse effects)
8g	Cell growth, differentiation, proliferation, morphology
9	**IMPACT ON MICRO-ORGANISMS**
10	**ATTENUATION OF EMF EFFECT**
11	**OTHER**

Fig. 2. Manual taxonomy for presenting results.(Major categories capitalized and bolded).

promote the growth of cancer (32 records). Some of the later categories in this taxonomy, in particular those that deal with the impact of EMF 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 EMF for hyperthermia combined with other agents, and EMF combined with chemotherapy, ionizing radiation, ultrasound, chemical promoters, and electromagnetic promoters from other segments of the spectrum. Generally, the EMF radiation that resulted in positive effects was short electric pulses (electroporation) or relatively short RF exposures for hyperthermia, and the EMF radiation that resulted in adverse effects was long power frequency exposures or relatively long RF exposures.

4.4.1. 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 [37]; b) TNF-alpha gene therapy for tumor growth reduction [38]; c) immunotherapy (hsp70 gene therapy) to reduce tumor growth and induce systemic antitumor immunity [39]; d) 3D-conformal radiotherapy for steep decrease of PSA values [40]; e) " When hyperthermia was performed immediately after application of electric pulses.... greater than additive antitumor effectiveness was observed.... Single treatment, application of electric pulses or hyperthermia had minor or no effect on tumor growth." [41].

4.4.2. Chemotherapy

The synergistic use of EMF with chemotherapy mainly involves 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 EMF, 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 EMF-loosened endothelial tight junctions. Lange and Sedmak [42] 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 paper 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 electroporation and: a) bleomycin for pancreatic adenocarcinomas [43]; b) TLR-9 ligands, CpG oligodeoxynucleotides for a systemic antitumor response on a contra-lateral untreated tumor [44]; c) cisplatin for hamster oral fibrosarcoma [45]; d) cisplatin and electrogene therapy with p53 on murine sarcomas [46]; 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." [47].

4.4.3. 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 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 EMF 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 electric pulses and: a) Co-60 gamma radiation for subcutaneous glioma tumors, which destroyed the tumor vasculature and caused DNA-related damage from reactive oxygen [48]; b) ultrasound for significant retardation of mouse tumor growth [49]; 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." [50].

4.4.4. Chemical promoters

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

> There are two main components involved in the EMF 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 EMF-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 EMF-induced disease. While the co-promoters identified in the present study are the proactive component, the role of the 'passive' promoters should not be discounted.

The combinations of EMF and tumor-promoting substances, such as DMBA and TPA, tend to dominate the papers in this sub-section. While the majority of EMFs 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 [51]; 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 [52]; 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 [53]; d) solvents, lead, and pesticides/herbicides were only associated with glioma in workers also exposed to moderate or high levels of ELFMF [54]; e) ELF-MF exposure to strengthen all-trans-retinoic acid [neuronal differentiating agent] effects on neuroblastoma cells [55]; f) "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." [56].

4.4.5. Electromagnetic promoters

The combination of EMF with other low frequency electromagnetic radiation dominated this section. The much larger promoter combination of EMF 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. Examples include: a) power frequency magnetic and electric fields for enhanced leukemia and lung cancer risk [57]; b) "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." [58].

4.5. Category 2. Impact on neural system

This category includes EMF combinations that enhance neural system performance (29 records), as well as combinations that degrade neural system performance (30 records). The present category specifically includes EMF-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 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 signaling pathways. Finally, in some cases, the behavioral effects of a drug can be modified by brief exposure to a low-level EMF field even when the radiation level alone has no apparent effects on the behavior.

4.5.1. Enhanced analgesia

This subsection included a broad range of EMF frequencies combined with diverse analgesics, although the examples focus on radiofrequencies. These examples include: a) microwaves to enhance the duration of phenobarbital-induced sleep [59]; b) "In combination with either of the anesthetics used [ketamine or chloral hydrate], mm waves increased the duration of anesthesia by approximately 50%.... exposure of mice to mm waves in vivo releases endogenous opioids or enhances the activity of opioid signaling pathway" [60].

4.5.2. Enhanced performance and reduced seizures

This subsection covers a broad frequency range, and includes complex patterned fields as well. Some of the performance 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 [61]; b) static magnetic field enhancement of anticonvulsant effects (on auditory-induced seizures in mice) in combination with phenytoin [62]; c) reduction of damage to lithium and pilocarpine-seized rats by early exposure to computer-generated LTP-patterned magnetic fields [63]; 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." [64].

4.5.3. 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 EMF effects, especially in the effects on neural systems. Reading of many papers on the neural effects shows the existence of 'windows', where EMF in one frequency range in combination with other co-promoter and environmental variables produces one type of result, while EMF 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 EMF and co-promoters on the neural system have to be conditioned on the specific EMF, 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 [65]; 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." [66].

4.5.4. 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 [67]; b) linear summation of TBS patterned complex magnetic field treatment with the contextual fear learning impairment evoked by agmatine treatment alone [68]; c) 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 [69]; d) "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" [70].

4.6. Category 3. Impact on circulatory system (heart, blood, vascular)

This category includes EMF combinations that enhance cardiovascular system performance (19 records), as well as combinations that degrade cardiovascular system performance (3 records).

4.6.1. 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 EMF, especially static magnetic fields, to changes in the baroreflex sensitivity. Examples include: a) static magnetic field prevention of significant decrease of BRS induced by verapamil administration [71]; b) static magnetic field induced increment in microcirculatory blood flow, and was counter-acted by geomagnetic disturbance (which also decreased BRS) [72]; 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." [73].

4.6.2. 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...." [74].

4.7. Category 4. Impact on immune system

This category includes EMF combinations that enhance immune system performance (20 records), as well as combinations that degrade immune system performance (5 records). However, these record numbers could be somewhat misleading for this category. 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 EMF for enhancing immune system performance. There could be other situations where EMF 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.

4.7.1. Enhance immune system performance

This subsection covers a wide range of EMF 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 10-fold increase in antigen-specific IFN-gamma(+) cells [75]; b) pulsed EMFs potentiated the effect of A(2A) or A(3) agonists on cell proliferation in bovine chondrocytes and fibroblast-like synoviocytes [76]; c) electroporation and DNA as good adjuvants in promoting efficient Th1-directed responses during DNA vaccination [77]; 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." [78].

4.7.2. Degrade immune system performance

This small subsection included some emphasis of effects on spleen and thymus, but did 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." [79].

4.8. Category 5. Impact on endocrine system

This (small) category includes EMF combinations that enhance endocrine system performance (7 records), as well

as combinations that degrade endocrine system performance (3 records).

4.8.1. Enhance endocrine system performance

This small subsection emphasized drug delivery and chick embryos. The drug delivery was accompanied by pulsed electric fields while the chick embryos were tested using power frequencies. Examples include: a) synergistic enhancement of percutaneous absorption of insulin by a combined use of electric pulses and iontophoresis [80]; b) protection of chick embryos against damage from UV light exposure by power frequency EM field exposures of appropriate duration [81]; 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 10-fold.... The synergistic application of anionic lipid formulation and electroosmosis offers a promising non-invasive technique to deliver insulin transcutaneously." [82].

4.8.2. 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 [83]; 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 [84]; 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." [85].

4.9. Category 6. Impact on skeletal system

This (small) category includes EMF combinations that enhance skeletal system performance (9 records). 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 [86]; b) combination of BMP-2 and PEMF stimulation for augmenting bone formation to a greater degree than treatment with either single stimulus [87]; c) "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." [88].

4.10. Category 7. Impact on genes

This category includes EMF combinations that have beneficial impacts on genes (6 records), as well as combinations that that have adverse impacts (56 records). 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 EMF forms are ELF, RF, and some static magnetic fields. The main co-promoters are chemical, ionizing radiation, and thermal/heat shock.

4.10.1. Positive genetic impacts

The main EMF 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 [89]; 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." [90].

4.10.2. 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 [91]; b) enhancement of the number of apurinic/apyrimidinic sites (induced by methyl methane sulfonate or H2O2) by exposure to ELF magnetic fields, due to enhanced activity or longer lifetime of radical pairs [92]; 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." [93].

4.10.3. Mutations

This relatively large subsection was almost exclusively power frequency EMF, with half the co-promoters being ionizing radiation. Examples include: a) ELF EMF enhances X-ray-induced mutations and alters the spectrum of mutations [92]; b) ELF-EMF is mutagenic as a single agent and can potentiate the mutagenicity of ionizing radiation [94]; 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 [95]; 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 [96]; e) "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." [97].

4.10.4. 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 [98]; b) combination of microwave-induced hyperthermia and gamma radiation was highly teratogenic, indicating a mutual potentiation of the embryotoxic action of these two teratogens [99]; c) microwave-radiation enhanced the teratogenic effect of cytosine-arabinoside in mice [100]; d) "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." [101].

4.11. Category 8. Impact on cells (permeation, apoptosis, oxidative damage, cell growth, cell differentiation, cell proliferation)

This category includes EMF combinations that have beneficial impacts on cells (28 records), as well as combinations that have adverse impacts (37 records). 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.

4.11.1. 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.

4.11.1.1. 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 [102]; 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 [103]; c) "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 min resulted in a higher drug permeation than either technique alone" [104].

4.11.1.2. 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 [105]; 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." [2].

4.11.1.3. Apoptosis (healthy cells). The previous subsection on cellular apoptosis focused on EMF-enhanced destruction of cancer cells. This subsection focuses on EMF-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 [106]; b) "combined effect of EF [electric field] plus ionizing 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." [107].

4.11.1.4. 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 [108]; 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" [109].

4.11.2. Adverse cellular impact

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

4.11.2.1. 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 [110]; 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 [111]; c) demonstrated that the combined effect of static magnetic field and Cadmium increased oxidative damage in rat brain as compared with Cadmium-exposed rats [112]; d) "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." [113].

4.11.2.2. Permeation (adverse effects). The previous subsection on positive impacts of cellular permeation showed the benefits of EMF-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 [114]; 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 [115]; 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." [116].

4.11.2.3. 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 [10]; b) effect of 60-Hz EMF at 1 G 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 [117]; c) "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." [118].

4.12. Category 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 [119]; b) combined treatments of electric field and chemical mutagen N-methyl-N′-nitro-N-nitrosoguanidine (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, and 3) produced a higher number of improved clones [120]; c) "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...." [121].

4.13. Category 10. Attenuation of EMF effect

This category focuses on ameliorating EMF 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 [122]; b) bee venom is demonstrated to have a radioprotective (915 MHz) effect against basal and oxidative DNA damage [123]; c) long-term exposure to low-frequency EMF increases lipid peroxidation in the brain, which may be ameliorated by Zinc supplementation [124]; 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 [125]; e) significant inhibition of the increased human epithelial amnion cell proliferation

when a noise field was superimposed on an EMF ELFfield [126]; 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." [127].

4.14. Category 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 EMF 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 [128]); b) extremely low-frequency magnetic field and aluminum solution synergistically enhanced the growth of spruce seedlings (Picea abies) [129]; c) combination of CCl4 injection and static magnetic field exposure induced elevation of the hepatic metallothionein content exceeding that induced by either treatment alone [130]; d) "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/cm^2 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/cm^2." [131].

4.15. EMF—biological mechanisms matrix

In order to gain further insight to the relation between biological mechanisms and varieties of EMF, an EMF-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.

4.15.1. 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, H2O2, Menadione).

4.15.2. Pulsed electric field

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].

4.15.3. 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.

4.15.4. Cell phones

This section relates to effects of mobile communication frequencies. The focus of the research was identifying adverse health impacts from exposure to the 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.

4.15.5. 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 symproms in dopamine-deficient diseases.

4.15.6. WiFi

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

4.15.7. Radar

This section covers a wide range of high frequency EMF, 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.

5. Discussion and conclusions

EMFs can serve as initiators of health effects, as well as serve as co-promoters or potentiators of biochemical agents, both beneficial and adverse. However, as this study has shown, the numbers and types of impacts are increased substantially when EMFs function in combination or as co-promoters. There were many examples where either 1) EMFs by themselves had no effect, but enhanced the demonstrated individual effect of another agent or 2) EMFs by themselves had no effect and other agents by themselves had no effect, but in combination the two had an effect. In other words, there is an enhancement of the singular effects.

Generally, the combined effects occurred 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.

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

The documents selected for this study required that the EMF component of the combination have some impact. In many articles not selected for the study, the EMF-agent combination may have been similar to the EMF-agent combination selected for the study, but the presence of the EMF 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, 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 EMF 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 EMF parameter space. This overlap would provide some indication or estimate of potential real-world health effects.

The first step in this process would identify major areas of disagreement where strong adverse effects have been shown or predicted by the proponents. These 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 real-world conditions. People are not exposed only to EMFs in isolation, or EMFs 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 EMF, harmful only when combined with EMF 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. EMF could provide the 'tipping point' of multiple potential harmful agents.

A final observation. An exhaustive search process retrieved slightly over 300 papers devoted to environmental effects of EMF co-promotion published in the previous 30-40 years. Given the potential impact of EMF, and the real-world importance of EMF as a co-promoter, there appears to be a major disconnect between the magnitude of the problem and the research available to understand and ameliorate the problem. A concerted effort to overcome this gap is required.

Appendix 1. Query used for information retrieval

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 (("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)

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 "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)

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