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Invited Review Paper

Bioelectromagnetics Researches in Japan for Human Protection from Electromagnetic Field Exposures

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Research works on bioelectromagnetics in Japan are reviewed with a focus on the efforts devoted to the issue of human protection from electromagnetic field (EMF) exposures. History of this issue in Japan is briefly reviewed first for all EMF spectra. Then research works on radiofrequency (RF) EMF are summarized in more detail. The RF studies reviewed are mainly conducted in the framework of research program by the Ministry of Internal Affairs and Communications (MIC) started in 1997. Because of this program, collaborations between biology/medicine and engineering have been promoted. The results consistently show no evidence against the safety of RF-EMF within the exposure levels of internationally accepted guidelines. © 2016 Institute of Electrical Engineers of Japan. Published by John Wiley & Sons, Inc.

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1. Introduction

Interaction of electromagnetic fields (EMFs) with living organisms has been a matter of interest for a long time. Static electric and magnetic fields have attracted the attention of those with interest in their potential applications to medical treatments for a long time. On the other hand, it has been less than 100 years since the time-varying electric, magnetic, and EMFs became of interest in relation to health. The issue started with recognition of side effects of diathermy treatment using radiofrequency (RF) energy in the 1930s. It was recognized that excess exposure to RF-EMF caused temperature increase in the exposed part of body resulting in adverse health outcomes such as cataract of the eye. Thus the thermal effect of RF-EMF was recognized as early as the 1930s.

Health hazard due to RF exposures became a matter of serious concern during and after World War II in military occupational health in the United States in the 1940s and 1950s. A comprehensive study program was organized in the U.S. Tri-Service in 1950s and 1960s [1]. Health effects of RF-EMF understood through those studies were predominantly thermal effects, that is, the effect derived from temperature elevation due to RF energy absorption. The first safety standard to limit exposures to RF-EMF was published in 1966 based on this thermal regime [2]. The standard was reviewed and revised periodically in 1974, 1982, and later. In 1985, the Federal Communications Commission (FCC) of the United States set out for the regulation of RF-EMF from fixed radiation facilities based on ANSI C95.1-1982 standard [3].

In the 1970s, health effect of power frequency electric field became a matter of concern. In addition, an epidemiological study raised an issue of possible association between childhood leukemia and magnetic field exposure from power lines in 1979 [4]. This report stimulated concerns about extremely low frequency (ELF) EMF. Studies had been carried out intensively on potential carcinogenicity of ELF magnetic fields during the 1980s and 1990s.

In the 1990s, explosive spread of mobile telephony all over the world raised concerns about potential health risks of weak RF-EMF exposures. The World Health Organization (WHO) organized the International EMF Project to implement a well-organized approach to EMF health issues in 1996.

The epochs of the EMF issue occurred mainly in the United States and Europe in the course of the history mentioned above. Thus it is often said that research activities on this issue in Japan are behind those in other countries. However, the studies have been continually carried out since as early as the 1940s. In this review, we summarize the research efforts on this issue with a focus on activities in Japan to overcome this misunderstanding. In Section 2, a brief overview is presented focusing on the history of activities in Japan regarding the whole spectrum of EMF except static fields. In Sections 3 and 4, recent activities related to studies on RF-EMF in Japan are reviewed.

2. Overview of the Studies in Japan

2.1. Early studies and ELF electric field study

Early studies on the biological effects of RF-EMF were reported by Karl T. Compton in a report of the inspection by GHQ just after World War II [5]. It reported that the Japanese army was interested in the biological effects of high-intensity microwaves. Not only the thermal effect but also nonthermal effects were matters of concern. Unfortunately, the studies were conducted by the military, and no scientific literature is available.

Academic research works targeted on biological effects of EMFs started early in the 1940s in Hokkaido University. The Research Institute for Ultrashort Waves was established in Hokkaido University in 1943, where physiological effects of high-frequency EMF exposures were investigated. The Institute has been reorganized several times, and is currently named the Research Institute for Electronic Science. The major interest of the Institute had been focused on medical applications of EMFs, but studies on the hazard and safety of EMFs have also been included in the scope of its activities [6].

Notable studies in the Institute were those on ELF electric field effects. There were concerns about the potential hazard of ELF electric field in the 1970s. The distinct acute effect was stimulation on the skin. The threshold of stimulation was investigated on more than 30 subjects. The subjects were instructed to stand in a vertical electric field at the power frequency holding an umbrella. The

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umbrella was charged by electrostatic induction, which caused sensation of spark discharge for the subject touching the handle of the umbrella. It was found that the subject seldom sensed the discharge in the field for <3 kV/m. This finding provided the basis for the limit of electric field of 3 kV/m at the edge of ROW (right of way) of the overhead transmission lines [7]. This limit was legislated by the Ministry of International Trade and Industry (MITI), currently Ministry of Economy, Trade and Industry (METI), and is still active in Japan.

Electric field is perturbed by the presence of a human body. Studies on the interaction between electric field and the human body were intensively performed in the above-mentioned Institute in Hokkaido University. They made measurements with human phantoms as well as using numerical analyses [7].

They also focused their attention on the perception of electric field due to the dielectric force exerted on the hair on the skin's surface by an ELF electric field. It was suggested that the sensation might cause stress on animals exposed to electric field applied for animal experiments, resulting in artifacts in the observed behavior of animals [7]. It may cause uneasiness to humans as well. The threshold of sensation was experimentally measured and theoretically analyzed [7–9].

2.2. Risk assessment of ELF magnetic fields

The potential adverse health effect due to exposure to ELF magnetic field became a serious concern in the 1990s in Japan as well as in other countries. Research works were intensively carried out with research grants from government, but the researchers recognized that large-scale experiments were necessary with specifically designed facilities for ELF exposure experiments. Thus a comprehensive research program was organized. Because the fund required for the project was very large, the Tokyo Electric Power Company sponsored the project. In order to keep independence from the interest of industry, a scientific panel was organized, which supervised the research program independently from the industry. The program started early in the 1990s, and the final report was published in 1999. The report was translated into English and published in 2000 [10].

The results consistently showed the absence of any adverse health effects at environmental field strength with evidences from many-sided approaches. Comprehensive descriptions of the research program can be found in the report [10]. It is getting stricter and stricter about the independence from industry when research works for risk assessment are carried out. The trend is natural and reasonable but the significance of high-quality works with strict supervision by neutral scientists should be evaluated from a purely scientific viewpoint.

2.3. Risk assessment of RF exposure

In the 1960s and 1970s, there were several notable studies on RF-EMF in Japan with the objective of understanding the RF-EMF effects. Yamaura *et al.* investigated the effect of 11-GHz [11] and 2.45-GHz [12] EMFs on nerve impulse activity of the ganglion of crayfish. Suppression of impulse frequency was observed, but after careful investigation they concluded that the change should be attributed to thermal effect due to local heating by microwave energy.

Another pioneering work was performed by Fujiwara and Amemiya at Nagoya University. They examined effect of 2.45-GHz EMF on chrysalises of insects exposed in a terminated waveguide. They examined the absorbed energy of the chrysalises located at the antinodes of the standing waves in the waveguide for electric and magnetic field separately [13,14]. This approach was an early attempt to elucidate the effect of RF and magnetic fields separately. They concluded that temperature elevation was the key parameter of the effect after careful evaluation with dosimetry.

There were other notable studies, but studies in Japan during those years were rarely cited as the scientific basis for international guidelines. The reason was partly because only a few papers were published in English.

The situation changed when the FCC started regulation of RF-EMF exposures. The Ministry of Posts and Telecommunications (MPT) started deliberation on Japanese guidelines to limit exposure to RF-EMF in 1987. The guideline "Radio Radiation Protection Guideline" (RRPG) was submitted to the MPT in 1990 and accepted as the national guideline [15–17]. The RRPG covered 10 kHz–300 GHz and was applicable to both general public and occupational exposures with a two-tier structure. The RRPG was essentially consistent with international ones at that time, such as IRPA/INIRC [18] guidelines and IEEE/ANSI C95.1-1991 standard [19].

In 1997, the MPT revised the guidelines to cover the exposure from mobile phones by introducing the criteria of local specific absorption rate (SAR) [20]. After the revision, RRPG became more consistent with the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines [21], but differences remained in the reference levels, which provided incident electric and magnetic field strengths corresponding to the basic restriction represented by SAR in RF and by induced current density in ELF. The RRPG is now substantially the same as the ICNIRP guidelines after the latest revision in 2015.

In 1997, the MPT decided to organize the Committee to Promote Research on the Possible Biological Effects of EMFs (CPR-EMF) in order to organize a national research program to consolidate the scientific basis for the RRPG. A comprehensive research agenda was discussed in the CPR-EMF, which then supervised the research program funded by the MPT. Numerous studies have been conducted in this framework since 1997. The MPT was restructured to the Ministry of Internal Affairs and Communications (MIC) in 2001, and the MIC continued this research program until 2007, when the CPR-EMF was dissolved. A study group succeeded the role of CPR-EMF, and the research program is still going on.

A remarkable feature of the MPT/MIC program is good collaboration between engineering and medicine/biology groups. The CPR-EMF and its successor coordinated the collaboration. Engineering groups are in charge of development of exposure apparatus and exposure assessment, while biology/medicine groups take the responsibility for biological part of the study. This framework has functioned well and contributed to the improved reliability of the studies.

In the Sections 3 and 4, research works on RF safety in Japan are reviewed. The works addressed in those sections will be mainly from the MIC research program due to the integrity of the study design and transparency of the experimental conditions.

2.4. Intermediate-frequency research

The interest in intermediate frequencies (IFs) has been growing. The term IF is not firmly defined, but WHO and ICNIRP define IF as the frequencies 300 Hz–10 MHz [22]. The major sources of IF-EMF have been electronic article surveillance (EAS) systems, and induction heating (IH) cooking hobs. Recently, wireless charging for electric vehicles has joined, which is about to come into market. This application uses EMF at IF frequencies (e.g. 85 kHz) with a large power (as much as 3–7.7 kW). Exposure to IF-EMF will be likely to become more common in daily lives.

With this trend, urgent research needs have been recognized in Japan. Many studies have been conducted. The IF studies in Japan are found in the review papers published previously [23,24]. More recently, further studies have been conducted and reported. Several studies reported on exposure assessment and dosimetry for wireless power transfer systems [25,26]. Studies on the biological effects of

IF-EMF have also been carried out, and the results were published recently [27–34]. Those studies investigated mainly the effect at frequencies used for IH cooking hobs (20–60 kHz). The results showed no significant effects for the exposures even at much higher levels than safety guidelines. Currently, further studies are going on to investigate the effect at higher frequencies relevant for wireless power transfer systems.

3. Studies on RF Biological Effects

3.1. Characteristics of exposure The frequency range of RF is very broad. The main target frequencies, however, have been those used for mobile communications since the 1990s, when mobile telephony had an explosive growth and raised concerns about health impact due to the use of mobile phones. Therefore, frequencies used in most researches are in the range between 800 MHz and 3 GHz.

The waveform of interest has been changing. In the 1990s, second-generation (2G) digital cellular phones started prevailing over analog phones of the first generation. Those 2G phones mainly employed the time division multiple access (TDMA) system, and the waveforms were pulsed ones. In Japan, PDC (personal digital cellular) system of 2G was most commonly employed, while in Europe GSM (global system for mobile communications) system had the majority. The PDC system has a pulse repetition frequency of 50 Hz with duty ratio of 1/3, while GSM has 217 Hz with duty ratio of 1/8. Pulsed signals were thought to more likely affect the biological functions in a somewhat different mechanism from temperature elevation. Many experiments have been performed using waveforms simulating TDMA signals. The frequencies used for 2G systems were mainly 800–900 MHz and also 1800 MHz in Europe and 1500 MHz in Japan.

While GSM of 2G-TDMA systems is still in operation in Europe and other countries, the 2G systems were completely replaced by third-generation (3G) systems in Japan in 2012. Currently, only 3G or later systems are in operation in Japan. There are two types of 3G systems in Japan; W-CDMA and cdma2000. Both follow the international standard IMT-2000. They both employ code division multiple access (CDMA), and the waveforms are approximately continuous in contrast to waveforms of 2G-TDMA systems. In the following sections, we review studies on mobile phone safety. Some early works employed 2G waveforms and recent ones mainly 3G waveforms in those studies.

The experiments were intended to simulate real situations of exposure as exactly as possible. It is important to distinguish between local exposure and whole-body exposure. Exposures from phones are local exposures focused on the head especially in the brain. On the other hand, exposures from base stations are whole-body exposures. The exposure levels are determined in reference to the basic restrictions represented in terms of SAR [W/kg]. They are 2 W/kg averaged over any 10 g tissue for local exposure and 0.4 W/kg averaged over the whole body (whole-body average SAR or WBA-SAR) for whole-body exposures [20,21]. Exposure levels for experiments are usually selected higher than or at least comparable to the basic restrictions. Exposures in the real environment are usually much lower than the levels of basic restrictions [35]. Therefore, some studies selected low-level exposures comparable to the real environment in order to examine whether potential effects due to chronic low-level exposures exist.

The exposure conditions are the most important factors in the experiments on EMF studies. In the following sections, however, the descriptions of the exposure conditions may not necessarily be clear enough because of the page limit of this review. It is recommended that detailed exposure conditions should be referred to, if necessary, in the original articles.

3.2. Human studies There has been a question as to whether weak EMF could affect functions of human central nervous systems resulting in deterioration in the well-being, sleep disorder, changes in behavioural ability, and so on. Many studies have been conducted with equivocal results suggesting the presence or absence of such effects. As a motivation of these studies, it should be noted that there is a not-small number of people who complain symptoms due to “hypersensitivity” to EMF exposures. Many studies have been carried out to investigate whether a weak RF-EMF could cause physiological changes in the human central nervous system, by means of human provocation studies.

3.2.1. Exposure from a phone A series of studies on this issue were conducted in Japan by Ugawa and colleagues at the Fukushima Medical University. They first investigated the effects of EMF from 2G mobile phone terminals. They examined possible effects on the brain function due to exposure to EMF from a phone located near the human head. A real 2G phone (PDC, 900 MHz) was used as a source emitting the maximum power (800 mW in temporal peak power) with the control by a digital cellular phone communication tester. As results, they found no short-term adverse effects on auditory brainstem responses (ABRs) or middle latency responses (MLRs) by a 30 min exposure [36]. In subsequent studies, they reported the absence of any effects on somatosensory evoked potentials (SEPs) [37] or on eye movement (sacchade) [38] and on motor evoked potential [39] by exposure to EMF from 2G phones under the same exposure condition.

Then they conducted studies on 3G phone terminals. They employed a real W-CDMA phone at 1950 MHz as the exposure source with the control by a base station emulator to emit maximum output power of 250 mW. The duration of exposure was 30 min. They examined effect on regional cerebral blood flow but found no significant change due to the exposure [40]. They also reported no effect on the inhibitory control of saccades [41].

Several studies have reported that exposure to EMF from mobile phones might affect electroencephalograms (EEG) during sleep [42]. The evidences were variable and inconsistent. Thus further studies have been recommended. The same group designed a study to examine the possible effects of exposure to EMF simulating W-CDMA signals on human sleep. They recorded sleep EEGs with polysomnograms, and collected data from questionnaires about subjective feelings the next morning. Sleepiness, sleep insufficiency, sleep variables, and the EEG power spectrum were evaluated. From the results they concluded that the exposure had no detectable effects on human sleep variables, the EEG power spectra, or sleep spindles [43].

Overall, their studies have shown consistently negative data against previously reported unstable positive phenomena.

3.2.2. Exposure from base stations Regarding the exposure from base stations, there have been concerns about possible health effects in the public because of the chronic nature of the exposure even though the level is quite low. There are people who report some symptoms which they attribute to low-level chronic EMF exposures. Furubayashi *et al*. [44] conducted a double-blind, cross-over provocation study to examine whether subjects with mobile phone-related symptoms (MPRS) were more susceptible than control subjects to the effect of EMF emitted from base stations. Subjects were given four EMF exposure conditions: continuous, intermittent exposure, and sham exposures with or without acoustic noise. The frequency was 2.14 GHz, with waveform simulating W-CDMA base station signal. Subjects were 11 women with MRPS and 43 women without MPRS as control.

The results showed that the MPRS group did not differ from the controls in their ability to detect exposure to EMF. Nevertheless, they consistently reported discomfort more than control, regardless of the actual exposure to EMF. There were no significant changes in their autonomic functions. The results also showed that MPRS subjects were more sensitive to acoustic noise regardless of presence or absence of EMF exposure. In conclusion, they found no evidence of any causal link between hypersensitivity symptoms and exposure to EMF from base stations.

An important finding obtained from this study was that the population of MPRS was 1.2% among women in Japan estimated from 2472 returned questionnaires distributed to 5000 women for the purpose of recruitment of subjects. They followed up this finding with additional survey of men in Japan. They obtained the same result of 1.2% as the proportion of MPRS in men.

A number of studies have reported that the symptoms are not directly caused by EMFs but should be attributed to the ”nocebo” effect based on double-blind experiments of human provocation studies. This study has confirmed the same understanding as previous results. Nevertheless, this issue is still a matter of concern over the world.

3.3. Epidemiology

Epidemiology is expected to provide the most significant evidence for human health risk assessment because it directly observes what happens on humans. An international collaborative study had been organized with participation of 13 countries by the initiative of WHO and the International Agency for Research on Cancer (IARC), a part of WHO. This international project was called INTERPHONE [45], and the end point of the study was the association between mobile phone use and incidence of tumors in the head and neck, especially brain tumors.

A Japanese study group participated in this international project. The group submitted the collected data following the protocol for the international study. In parallel, they conducted national studies. Results of case–control national studies in Japan did not indicate any association between mobile phone use and the incidence of acoustic neuroma [46] or brain tumors [47]. The data on acoustic neuroma was analyzed in a different way as a case–case analysis [48]. The result suggested possible elevation of risk for acoustic neuroma associated with heavy use of mobile phones. The authors discussed the result carefully, and concluded that the apparent elevation of risk should be attributed to the detection bias in the process of diagnosis and the recall bias in the reported questionnaire.

It has become more and more convincing that exposure assessment is crucially important for epidemiological studies especially when the potential risk of EMF is explored. Studies on exposure assessment have been intensively conducted in Japan for the INTERPHONE and associated studies in Japan. The SAR distributions in the brain was categorized into five groups corresponding to five categories of phones [49]. Local SAR at the location of tumor was estimated from the available data from questionnaires [50,51]. The derived exposure index was used in a part of the final analysis of the Japanese national study on brain tumor [47]. The results indicated no elevation of risk except for some sporadic values without consistency.

The recognition of the significance of recall bias motivated the development of software-modified phones (SMPs) that enabled recording various parameters of communications including call time, type of communication, output power, and so on. The new SMPs developed in Japan were modified from 3G (cdma2000) phones and were unique in their ability to record the laterality of use estimated from the information from a gravity sensor. A study was performed to examine the recall accuracy of laterality of use by using the new SMPs. A total of 198 subjects were instructed to use SMPs for 1 month. The results showed that recall was prone to small systematic and large random errors for both the number and duration of calls and that the laterality of use was misclassified by 19% of the subjects. The authors stated that the results should be interpreted cautiously in epidemiological studies of mobile phone use based on self-assessment considering the large random recall error for the amount of calls and misclassification of laterality [52].

3.4. Animal studies

3.4.1. Carcinogenicity Health risk of carcinogenicity, especially the risk of brain tumor, has been of largest concern since the 1990s when mobile phone use was explosively increasing. Early studies were carried out in Nagoya City University in the 1990s. Those studies preceded the MPT/MIC research program, but they were the root of the subsequent series of studies conducted in research programs.

Imaida *et al*. examined rat liver carcinogenesis due to localized exposure on the liver to pulsed EMF simulating TDMA signal by means of medium-term liver bioassay. This method allowed obtaining conclusion with only an 8-week period of experiment in total, including a 6-week exposure period. The method was chosen because of the quickness in consideration of the urgency of the issue due to the rapidness of increase of mobile phone use. The waveform and frequencies of the PDC system were employed. The maximum local SAR in the liver was 2.0 W/kg in temporal average (temporal peak was 3 times of the average). The number of rats was 48, 48, and 24, for exposed, sham-exposed, and cage control groups, respectively. The result showed no increase in liver carcinogenesis for the 929.5-MHz PDC signal [53]. Another experiment was performed the next year with the same protocol except the frequency, which this time was 1439 MHz. The result was consistent with the previous one and showed no increase in the incidence of liver cancer [54].

After those studies, the authors set out for the next stage. A 2-year bioassay was planned to examine the possible effect of brain tumor promotion this time. The endpoint was N-ethylnitrosourea (ENU)-induced brain tumors. The number of rats for one experiment was about 500 (5 groups, 2 levels of dose) for this series of experiments.

They first conducted a 2-year bioassay for 2G waveform exposure. The rats were exposed to pulsed waveform of a PDC system at 1439 MHz for 90 min a day, 5 days a week. The radiating antenna was located in the vicinity of the rat's head to achieve localized exposure. The brain's average SAR was 0.67 W/kg for the low exposure group and 2.0 W/kg for the high exposure group in temporal average. The results showed no increase in brain tumors [55].

The same protocol was applied to 3G phone signal exposures. The waveform was that of W-CDMA phones at 1950 MHz. Other conditions were the same as those in the previous study. The result, again, showed no significant increase in brain tumor in the exposed groups [56].

3.4.2. Effects of localized exposure on brain It has been questioned whether localized RF exposure on the head could cause any effects on physiological, functional, or organic changes in the brain. Besides brain tumor bioassay, various studies have been carried out to explore possible effects on the brain.

In the 1990s, several studies reported increase in blood–brain barrier (BBB) permeability due to exposures to pulsed RF-EMF at levels below or comparable to the basic restriction [57–59]. BBB is a function of the brain capillary vessels to prevent unwanted molecules from permeating into the cerebrospinal fluid. An increase in the permeability of the BBB can result in increased risk of brain diseases such as brain tumor as well as neurological symptoms such as headaches. Thus those reports attracted serious attention.

In Japan, a group at the University of Tokyo started animal experiments to examine the reproducibility of the reported phenomenon. The results showed no change in BBB permeability with exposures to EMF of TDMA signal of the PDC system at 1439 MHz at 2 W/kg [60]. Later, an independent group examined the effect on young rats in consideration of a hypothesis that young and immature animals might be more vulnerable to EMF exposures. The experiments were also performed with TDMA waveform at 1439 MHz. The results showed no effect on BBB-related gene expression by local exposure of the head to EMFs at 0, 2, and 6 W/kg of SARs for 90 min/day for 1 or 2 weeks [61].

Brain barrier consists of not only BBB but also the blood–cerebrospinal barrier (BCB). Ushiyama *et al*. examined the effect on BCB of rats exposed locally on the brain to EMF of 1439-MHz TDMA waveform at 9.5 W/kg for adult and 10.4 W/kg for juvenile rats in brain average. The results showed no change in the BCB function [62].

Brain barrier permeability is one of the indices that represent brain microcirculation, but there are a number of other parameters that behave interactively. Effect on those parameters should also be investigated to establish the safety of mobile phone use. Masuda *et al*. reported many results of investigations to elucidate the effects of RF-EMF exposures on the brain. They focused on changes in several brain microcirculatory parameters, including the BBB function. Experiments were performed with a figure-of-eight applicator, which enabled highly localized exposure on the brain and real-time direct observation of brain circulation through a cranial window in the skull of the animal [63]. Frequency and waveform were those of the 2G-TDMA system at 1439 MHz. Under the local exposure condition at an average SAR of 2.0 W/kg in the target brain tissue, no significant changes were found in hemodynamics, leukocyte behavior, and permeability of BBB in juvenile and adult rat brains using *in vivo* imaging and histological evaluation [64–68].

The authors had observed increases in local cerebral blood flow along with a significant temperature elevation under the conditions at much higher exposure of >10 W/kg [69]. Those results suggested that RF-EMF exposure was unlikely to cause biological effects in the brain at the exposure level below the ICNIRP guideline, which does not cause a significant temperature elevation.

3.4.3. Effect of whole-body exposure Exposures to EMF from mobile phone base stations are several orders of magnitude lower than the limit values of exposure guidelines. In spite of the weakness of the exposure, there have been concerns about possible health risks of chronic EMF exposures from base stations. The question asked was whether long-term exposures could cause adverse health effect even at lower levels than in established guidelines. Animal studies have been done to explore such a possible cumulative effect of RF-EMF exposures.

Takahashi *et al*. investigated the effect of weak EMF on pregnant rats and their offspring to evaluate the potential adverse effects of long-term whole-body exposure to EMFs simulating those from mobile phone base stations. The rats were exposed for 20 h a day during the gestation and lactation periods. No abnormal findings were observed either in the dams or in the two generations of offspring [70]. The same group subsequently made a further experiment with the same exposure condition. The observation was extended to the third generation of offspring, with extended biological examinations carried out over three generations. The results showed no abnormalities in the mother rats and in the three generations of offspring in any biological parameters including neurobehavioral function [71].

3.4.4. Hazard on eyes Eye is an organ that is not protected by the skin. The eyeball has been considered thermally isolated from other parts of body. Therefore, eyes are considered one of the vulnerable organs to be protected from exposure to RF-EMF. Cataract has been an established hazard due to excess heating caused by RF exposures [72]. The threshold of cataract provided a major part of the rationale for limiting local exposure in terms of maximum local SAR in the current guidelines [20,21].

In the 1980s, Kues *et al*. reported corneal injury due to exposure to RF-EMF at much lower levels than the threshold of cataract [73]. It was reported that the phenomenon was specific to primates, and experiments with other animals such as rabbits were not relevant. No replication studies followed soon. Considering this report together with the follow-up studies by the same group, some safety guidelines incorporated cautionary limits on eyes in order to avoid the suggested hazard on cornea [17,74].

Kamimura *et al*. [75], however, reported a negative result on this phenomenon by tracing the method of Kues' except for administration of anesthesia. The corneal endothelial damage in the monkey eye was not observed without anesthesia even at higher exposure levels than the threshold obtained with anesthesia reported by Kues *et al*. [73]

A series of studies on corneal injury have been continued by a group at Kanazawa Medical University. They did not use primates but rabbits as animals for experiments by establishing a methodology to investigate corneal injury with rabbit eyes in advance. They examined the effect of anesthesia on corneal injury [76]. As many as 43 male pigmented rabbits were exposed to 2.45-GHz continuous RF-EMF, either with anesthesia or without anesthesia. The exposed eyes showed various symptoms of injury. The group under systemic anesthesia showed much stronger symptoms than those treated without anesthesia. The more pronounced ocular effects in the anesthetized rabbits were associated with the significantly higher ocular temperatures in the eyes. The authors concluded that systemic anesthesia should affect thermal regulation resulting in the lowered threshold of eye injury. The results indicated that temperature elevation was the key parameter to determine the threshold.

The same group investigated the effects of quasi-millimeter and millimeter wave exposures on the eye [77]. Rabbits were exposed in the eye to 18, 22, 26.5, 35, 40 GHz continuous waves at 200 mW/cm^2 for 3 min. The changes in temperature in various parts of the eye were measured. It was found that temperature elevations were dependent on various factors, including the penetration depth, convection of the aqueous humor, and so on. As a result, the temperature elevation characteristics were dependent on frequency. They also investigated ocular injury due to exposure to 60-GHz millimeter waves [78].

3.5. *In vitro* studies Cellular researches provide the means to explore the mechanisms of interaction between EMF and biological functions. Numerous studies have been conducted and reported. Cellular studies are classified into two categories: genotoxicity and non-genotoxicity studies [79]. The former had been of largest concerns. Genotoxic effects, however, have not been clearly observed due to the non-ionizing nature of EMF. Thus the latter has become a matter of growing interest in recent years. Regarding cellular studies, an excellent review has been published recently [79]. Therefore, *in vitro* studies will be just outlined only briefly here.

Several studies had suggested possible genotoxic effect of RF-EMF on micronucleus formation [80], on chromosomal damages [81], and on DNA strand breaks [82,83]. A number of studies have tried to replicate those phenomena, but most of them failed in replication unless a significant temperature rise occurred due to the absorption of the applied RF energy. Studies by Miyakoshi and colleagues have contributed much to confirming the absence of such effects [84–88]. It is considered RF-EMF does not cause genotoxic effect based on those studies.

Non-genotoxic effects include effects on cell proliferation, apoptosis, gene expression, and immune response. There have been reports claiming that RF-EMF could cause those effects resulting in health damages [89]. While several reports suggested the existence of such effects, the majority of studies have not confirmed reproducibility of these phenomena. Effect of RF-EMF on gene expression has been a matter of concern. Many studies have examined presence or absence of such effects comprehensively using novel methodologies such as microarray analysis. Recent studies conducted in Japan have provided strengthened evidence against the presence of such effects [90–95].

4. Studies on Dosimetry and Exposure System

4.1. Human models for numerical dosimetry Owing to the rapid progress in computer technology together with computational electromagnetics, we can include realistic models in the computation of EMFs. Numerical dosimetry is one of the most effective applications of this technology. Use of finite-difference time-domain (FDTD) method using voxel human models became common in the 1990s [96]. Various head models had been developed, but whole-body models were not common except for models developed in the United States [97] and in the UK [98]. Those models were developed for Caucasian men, and were not be suitable for representing Japanese men and women.

Development of whole-body Japanese human models thus started in collaboration between NICT (at the time Communications Research Laboratory, CRL), Kitasato University, and other groups. A male model (TARO) and a female model (HANAKO) were developed from magnetic resonance imaging (MRI) data of male and female volunteers. The male and female whole-body voxel models are composed of approximately 8 million and 6 million 2-mm voxels (three-dimensional blocks), respectively. Each voxel is labeled with tags representing more than 50 types of tissues and organs, and assigned with the electrical properties of the the respective tissue/organ [99]. These electrical properties are used in numerical EMF analyses.

Those numerical models have been improved to be applicable to various computation conditions simulating realistic situations. One improvement was the development of models that can take arbitrary postures [100,101]. Those models allow computation simulating realistic use of ubiquitous wireless devices, for example.

Another area of progress was the development of child models with different ages. The original model was TARO, which was modified by scaling adaptively to reflect the trend of dimension of each part changing with growth [102]. In order to make exposure assessment for pregnant women, pregnant female models at different stages of pregnancy were also developed [103].

4.2. SAR characteristics for children

4.2.1. Local SAR in child head There was a controversy whether local peak SAR in a child's head was higher than that of an adult when a mobile phone was used in the vicinity of the head. Gandhi's group reported a considerable increase in the local peak SAR in children's heads [104], while Kuster's group claimed that there was no significant difference in the SAR between children and adults [105].

Wang and Fujiwara [106] reported the explanation for the contradiction. They calculated the local peak SAR under the same conditions as those previously employed by Gandhi's and Kuster's groups, which were slightly different from each other. They found that a considerable increase in the maximum local SAR in the children's heads when they fixed the output power of the monopole-type antenna according to Gandhi's condition [104], while no significant differences was found when they fixed the effective current at the feeding point of the dipole-type antenna used by Kuster [105]. Their finding suggested that the contradictory conclusions drawn by the two groups might have been due to the different conditions in their numerical calculations.

4.2.2. Whole-body average SAR characteristics For whole-body exposure, one of the topics was to quantify the relationship between the basic restrictions (internal field strength or SAR) and the reference levels (external field strengths of incident EMFs). It should be noted that the whole-body average SAR (WBA-SAR) should never exceed the allowable limit of basic restrictions by any exposures below the reference levels.

Early studies had made calculations by using simple geometrical models to allow analytical methods or block models with coarse resolution due to the limitation of computational resources [107]. Recent progress in computational electromagnetics and realistic human models has allowed us to revisit the relationship between incident field strengths and WBA-SAR with much improved accuracy.

Dimbylow first pointed out the inconsistency between WBA-SAR and the reference levels for children at the whole-body resonance frequency and around 2 GHz by computation using a realistic human model [108]. The child models in this study were made by simple scaling with uniform ratios according to growth. Therefore, child models did not have realistic proportions in the dimensions of the body parts. Wang *et al*. performed a similar calculations using realistic Japanese adult and child models developed by a scaling technique with ten different scaling factors for the body width, nine different scaling factors for the body thickness, and six different scaling factors along the body axis [109]. The results were consistent with the previous study and confirmed the previous finding.

Hirata *et al*. showed that the dominant factors to determine the WBA-SAR were dielectric constant of the tissue at the resonance frequency and the body surface area [110]. The variability of WBA-SAR in different human body has been computationally replicated by different research groups. Based on the computed results, empirical estimation formulae have been derived for human models in ungrounded [111] and grounded conditions [112]. In order to validate the computational results, measurement of WBA-SAR of human volunteers in a reverberation chamber has been conducted in the gigahertz frequency bands for the first time [113].

4.3. Development and dosimetry for exposure systems It is recognized that precise, quantitative descriptions of exposure conditions are crucially important in the assessment of potential effects of RF-EMF on biological systems [114]. Collaboration between biology/medicine and engineering is a key factor for reliable studies on this issue. Recent RF studies in Japan have had good collaboration between them owing to the activities made by the MIC projects (see Section 2.3). In the following, we show some examples of the development of exposure apparatuses and dosimetry for experiments cited in the previous section.

Effect of exposure from mobile phones on brain has been a matter of concern. Animal experiments are an important approach to this issue. There was, however, a problem of designing an exposure apparatus for this purpose. The exposure should be done in the same frequency band as actual phones. Animals used for experiments are mainly rodents, and their dimensions are comparable to the wavelength of EMF from mobile phones. The ratio of maximum local SAR in brain to WBA-SAR is therefore much smaller in animals than in humans. The effect of localized SAR in brain, if any, might be hidden in animal experiments because whole-body effect due to excess WBA-SAR might be dominant in animals. Highly localized exposure apparatuses were necessary to perform experiments on local exposures.

A highly localized exposure on the brain of rat was achieved by using a figure-of-eight loop antenna in the 1.5-GHz band [63] and in the 2-GHz band [115]. These exposure apparatuses had also the capability of real-time direct observation of brain circulation during exposure through a cranial window implanted in the skull of rat. The apparatus was used in experiments on brain-localized exposures [64–68].

One of the most important tests in risk assessment is the 2-year bioassay for carcinogenicity. An exposure system for this purpose has been developed [116]. The challenges were to reduce WBA-SAR compared to the local SAR in brain, to minimize constrained stress, to allow sufficient number of animals exposed simultaneously, and to provide fail-safe systematic management of the exposure protocol. The exposure system developed had overcome those difficulties, and long-term experiments had been carried out with the system [55,56].

Besides highly localized exposures, there was a need for experiments to investigate potential effects of low-level, long-term, whole-body exposures similar to those from base stations. In order to perform animal experiments for this purpose, animals should be kept unconstrained to simulate chronic exposures of humans from the base stations. An exposure system was developed, and exposure assessment had been done by a group at Nagoya Institute of Technology. They developed a whole-body exposure system for a multi-generation/multi-frequency bioeffects at frequencies between 800 MHz and 5.2 GHz [117]. A reverberation-chamber-type exposure system was also designed for this purpose [118,119]. The accuracy of conventional two-step dosimetry method for animals in a reverberation chamber was confirmed with an S-parameter method for the first time to achieve precise dosimetry [120,121]. Using the exposure system, the multi-generational whole-body exposure experiments were performed (see Section 3.4.3) [71]. In their experiment, animals were exposed on the whole body to RF-EMF of eight different communication signals between 800 MHz and 5.2 GHz simultaneously.

Local exposure on rabbit eye was another issue of challenge needed for animal experiments on the eye. A group at NICT developed an exposure setup with a small waveguide antenna to achieve a localized exposure at 2.45 GHz on the rabbit eye [122]. Localization was achieved by using a dielectric-loaded waveguide to reduce the dimension of the aperture. This apparatus was used for animal experiments on eye hazards [76].

A new apparatus was developed for experiments on the eye injury caused by millimeter-wave exposures [123]. Millimeter waves were focused by a lens antenna to avoid unnecessary exposure outside the eye. The frequencies were 26.5, 35, 40, 60, 75, and 95 GHz. Numerical dosimetry was accompanied by the development of the apparatus to obtain detailed exposure characteristics. The apparatus was actually used for animal experiments [77].

Development of exposure apparatuses for *in vitro* experiment is another matter of challenge. A new type of *in vitro* exposure apparatus for millimeter waves was developed recently [124].

4.4. Thermal analysis related to RF exposures

4.4.1. Introduction to thermal analysis Since thermal effect is the only established health effect of RF exposures, temperature elevation caused by absorbed energy from RF-EMF is the most crucial index to be worried about. For whole-body exposure, core temperature elevation ($>1\,^{\circ}$C) induces altered thermoregulation. For localized exposure, excess temperature elevation in the head and brain is one of the concerns for the use of wireless communication devices located near the head. The temperature elevation inside the human body, however, cannot be measured directly. In order to overcome this difficulty, computational schemes to estimate temperature elevations are highly required.

A well-known bioheat equation was proposed by Pennes [125] as a mathematical model to describe the dynamical behavior of temperature distribution in the human body. This formula has the capability of handling inhomogeneous media, and takes into account the heat conduction, basal metabolism, blood flow, and heat production due to absorption of microwave energy and heat transfer between body and air. Thermal responses were described with a simplified human model.

The effectiveness of this thermal response model was verified through the work by Foster and Adair [126]. This model was incorporated into the bioheat equation by Bernardi *et al*. [127], taking into account the increase in blood flow and sweating rate with the temperature elevation. This combined formula enables the computation of the temperature elevation in an anatomically based human body model in the time domain. Later, Hirata *et al*. improved the model of core temperature change and validated the mathematical model by comparing with animal experiment [128].

4.4.2. Whole-body exposure and core temperature It has been questioned whether the current reference levels of guidelines are relevant for children. Children are considered more vulnerable to impacts from the environment. In addition, a peak in the WBA-SAR has been recently found for children in the gigahertz band [108,109], where the WBA-SAR of children apparently exceeded the basic restrictions (see Section 4.2.2) for incident field at the reference levels. Core temperature elevation should be investigated to discuss this issue.

The variation of blood temperature should be taken into account in the analysis of temperature elevation due to whole-body exposure. For plane-wave exposures at the ICNIRP reference level [21], the maximum temperature elevation in the ankle was calculated as $0.7\,^{\circ}$C at 40 MHz where whole-body resonance occurred in a human standing on the perfect ground [127]. Hirata *et al*. investigated the core temperature elevation in ungrounded models of adult and child for exposures at the resonance frequencies (70 and 130 MHz, respectively) determined by the body heights as well as 2 GHz where the WBA- SAR shows the second peak [129,130]. These studies suggested that the dominant factor affecting the core temperature was the modeling of sweating. In particular, the variability of core temperature elevation was shown to be $\pm 20\%$. The core temperature elevation in the child model was smaller than that in the adult because of larger body surface area-to-mass ratio. The application of this dominant factor was shown to be effective by Hirata *et al*. [131].

The variability of core temperature elevation in different human body models was computed for frequencies from 30 MHz to 6 GHz [132]. No clear difference was observed in the ratio of core temperature elevation to the WBA-SAR (defined as the heating factor) in the adult models when assuming the same thermoregulatory response. The heating factor was almost constant for frequencies up to a few gigahertz and then decreased gradually with the increase of the frequency. An additional main finding was that the presence of the thermoregulatory response suppresses the temperature elevations especially in the body core. The core temperature elevation in the elderly was shown to be 10% larger than that in the young adult due to the decreased capability of sweating, which is attributable to the decreased thermal sensitivity of the skin [133].

Overall, core temperature elevation in different human models was less than $1\,^{\circ}$C for WBA-SAR of 4 W/kg, regardless of gender and age difference. WBA-SAR is a good metric for adult to estimate core temperature elevation, and the current basic restriction is conservative. For the child, the basic restriction in WBA-SAR is more conservative than for the adult in terms of core temperature elevation.

4.4.3. Temperature elevation due to handset The maximum local SAR is limited in the guidelines for protection from localized exposure to EMF. The limits in ICNIRP guidelines [21], for example, are 10 and 2 W/kg averaged over any 10 g tissue for occupational and general public exposures, respectively. Another set of limit values are recommended at 8 and 1.6 W/kg averaged over any 1 g tissue [19]. The basis for the limit lies in the temperature elevation to be less than about 1 °C. In addition to the discrepancy in the limit values among guidelines, we need to consider the difference in the frequencies used for mobile communications. Penetration of EMF into tissue becomes smaller as the frequency becomes higher. The penetration characteristics should cause a difference in the characteristics of temperature elevation. Thus detailed investigations are warranted to estimate temperature elevation due to local-body exposures.

Several studies have reported results on this issue [134–139]. In these studies, the blood temperature in humans was assumed to be constant in consideration of the small output power of RF sources of interest compared to the heat generation due to basal metabolism (around 100 W for adult). Hirata and Shiozawa investigated the correlation between the maximum local SAR and maximum temperature elevation in the head and brain with various conditions on frequency, polarization, feeding positions, and radiating structure [139]. Hirata *et al.* then showed that the effect of blood flow was the most dominant factor that determines the temperature elevation based on the bioheat equation [140]. It was also shown that the temperature elevation had a good correlation with the maximum local SAR when the averaging mass of SAR was in the range 10–20 g, which approximately coincides with the averaging mass defined in the international guidelines (10 g) [141]. They also showed that pinna should be excluded to have good correlation. The rationale for the basic restriction on maximum local SAR has been a matter of controversy for a long time. Investigations by Hirata and colleagues have contributed much to this issue.

4.4.4. Temperature elevation in rabbit eye It has been shown that injury in the eye occurs depending on the temperature in each part of the eye based on the series of experiments with rabbit eye (see Section 3.4.4) [76,77]. Those experiments were performed in close collaboration with the dosimetry research group.

Kojima *et al.* measured the temperature in the rabbit eye with and without administration of anesthesia, and found that higher temperature elevation occurred with anesthesia [76]. Hirata *et al.* computationally confirmed the reduction of blood flow in the rabbit eye under anesthetized condition [142] on the basis of the findings by Kojima *et al.* [76].

Acute ocular injuries caused by quasi-millimeter and millimeter-wave (MMW) exposures have also been investigated. Experiment and computation were carried out interactively. The heat induced by the exposure was conveyed not only to the cornea but also to the crystalline lens. Frequency-dependent corneal temperature elevations were observed; the exposure to 40-GHz MMW resulted in a 1.6-fold higher temperature rise than to 18-GHz quasi-MMW [77] and a 1.3-fold higher temperature rise than with 75 GHz [123]. Thermal injuries of different types and levels have been observed at 60 GHz [78]. The measured and computed temperature elevation in those studies were compared, and the results confirmed a good agreement in the ocular tissues [123].

A new method for temperature distribution measurement in the rabbit eye has been developed by Suzuki *et al.* by using a microencapsulated thermotropic liquid crystal (MTLC) [143]. This method provided the means to visualize distribution of temperature inside the anterior chamber of rabbit eye. In addition, it allowed real-time observation of convection of aqueous humor in the anterior chamber, which significantly contributes to heat transportation in the eye. Useful data have been obtained from the MTLC measurement together with conventional temperature measurement with a fluoroptic thermometer. The data have been used for numerical analysis to identify the threshold of eye injury caused by MMWs. The numerical analysis was performed in consideration of convection of the aqueous humor [144].

4.4.5. Temperature elevation in human eye Numerical approach is applicable to human eyes. Hirata *et al.* investigated the relationship between the eye-average SAR and temperature elevation in the lens in the frequency range 0.6–6 GHz [111]. Weak standing waves in the eye were observed to cause a higher SAR at specific frequencies. The SAR averaged over the eye was below the basic restriction for the incident field at the reference level. The temperature elevations obtained by Bernardi *et al.* [145] and Hirata *et al.* [111] were comparable at 6 GHz.

Hirata pointed out the defect of the isolated eye model [146], because the SAR outside the eyeball could not be taken into account in the calculation of temperature elevation. This should result in the underestimation of temperature elevation. He then proposed to take into account the whole head model with an equivalent blood flow of choroid and retina tissues. His results showed good correlation between eye-average SAR and maximum temperature elevation in the lens. Based on this correlation, maximum temperature elevation at eye-average SAR of 10 W/kg was estimated as 1.5°C or more.

Several studies have reported computed temperature elevation in the eye for localized and plane-wave exposures. The results have been consistent with each other, and the dominant parameters affecting the temperature were summarized in Hirata *et al.* [147].

Numerical studies revealed that the polarization of the antenna was one of the factors affecting the SAR distribution, resulting in different temperature elevations. Oizumi *et al.* evaluated the temperature elevation in the eye and skin for localized and whole-body exposures [148]. They suggested that facial burning was the dominant effect rather than cataract formation in the human head model, which supported the finding by Kramar [149] obtained from experiments with monkeys.

Computational approaches based on multiphysics have now been recognized as powerful means for the health risk assessment of EMF exposures. These approaches have the strength in their ability to extrapolate animal data to human data with reasonable accuracy. The studies summarized above have contributed much to the understanding of EMF effects on the eye.

4.5. Microwave hearing Microwave hearing (MWH) is an auditory phenomenon in which one perceives sound when pulsed microwaves are exposed on the head. This phenomenon has been known since the 1950s through the experience of personnel on warships with high-power radar. The effect was carefully investigated in the 1960s and 1970s using both experimental [150,151] and theoretical [152] approaches. Those studies revealed the mechanism of MWH. The microwave pulse causes a small but acute temperature elevation in the brain, which generates thermal expansion of tissue, resulting in elastic waves. The thermoelastic waves propagate in brain and stimulate auditory organs in the same manner as in ordinary hearing [152,153].

Early theoretical study assumed a simple, homogeneous head model and SAR distribution to allow an analytical approach. The analysis assumed sinc function as the SAR distribution in the sphere head model [152]. This assumption had a problem of negative energy absorption, which is against physical principles. In addition, the main source of thermal expansion was assumed at the center of the sphere where a sharp hot spot existed.

Shibata and Fujiwara pointed out the problem and assumed a modified SAR distribution of a sinc function with offset to avoid negative SAR as well as to take surface heating into account [154]. Their result showed that the waveform of thermoelastic waves differed significantly from the result from a previous study [152] without surface heating.

The rapid progress in numerical computation enables us to simulate much more realistic situations. Watanabe *et al*. proposed FDTD analysis of MWH not only for SAR calculation but also for acoustic wave calculation [155]. An anatomically realistic head model was employed for the analysis, which allowed realistic shape of the head and existence of the skull. The results showed that surface heating was the main source of thermoelastic waves and the hot spot in the center did not play any significant role. The result confirmed the relevance of the hypothesis proposed by Shibata and Fujiwara.

Lin *et al*. [156] subsequently reported quantitative investigation with realistic numerical models of humans and animals by the same approach as the Japanese study [155]. Those studies provided quantitative understanding of this phenomenon, which has been in some cases exaggerated for the problem of public phobia about microwave hazard.

5. Summary and Conclusion

Researches on bioelectromagnetics in Japan were reviewed with a focus on the efforts devoted to the issue of human protection from EMF exposures. History of this issue in Japan was briefly reviewed first for the whole spectrum, including ELF, IF, and RF, in Section 2. Then researches on RF-EMF were summarized in more detail in Sections 3 and 4.

The RF studies introduced in Sections 3 and 4 are mainly related to the research program by the MIC, which started in 1997. The studies were coordinated by the committee in the MIC. The committee established close collaborations between biology/medicine and engineering. Owing to this structure, reliable bioassay was performed with precise exposure assessment and control of exposure conditions.

The results of these studies consistently showed no hazardous effect of RF-EMF within the exposure levels of internationally accepted guidelines. Especially, the studies in this program did not reproduce any of previous studies suggesting the existence of health effects when the experiments were carefully performed with the collaboration of biology/medicine and engineering to improve reliability of the experiments.

A few studies among the reviewed reports were not funded by government but by industry associations such as the Association of Radio Industries Businesses (ARIB). Those researches were funded with formal contracts between the sponsor and the institution under the relevant code of research ethics. The significance of the results should be taken into account in the health risk assessment as factors in total scientific knowledge even though the funds were derived from industry. It is important that majority of funding comes from neutral sources to keep the right way. This is the case in recent Japanese RF studies where the majority of fund comes from MIC. It is a challenging issue to manage the involvement of industries in funding in a sound way. The fund from government is limited and is not likely to continue until the concerns are completely settled.

The applications of EMF energy are evolving, and the usage of spectrum, waveforms, and exposure conditions are changing. There are still gaps of knowledge in the potential health impact of exposures to IF, MMW, and terahertz EMFs. The investigations should be continued to establish the safe use of EMFs. Researches in Japan are expected to continue contributions to the issue to establish a healthy society with harmonized evolution of technology.

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