Review article

Health-related effects of radiofrequency electromagnetic fields: an update

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Abstract

Several studies have reported associations of exposures to radiofrequency electromagnetic fields (REF) with neoplasia. Other research did not confirm that. Epidemiological studies are associated with selection, recall and other bias. A narrative review, analyzing mechanisms, may be more informative than a systematic one, assessing studies of different quality and reliability. A moderate increase of registered incidence reported for some diseases has been out of proportion to the rapid expansion of mobile communication, being explainable by improvements of diagnostics. In some experiments, REF was associated with an increase in some age-related tumors and, at the same time, with a prolonged survival of exposed animals. Thermal and non-thermal effects of REF are reviewed here. In conclusion, there is neither convincing evidence nor theoretic plausibility of a cause-effect relationship between REF and cancer. Non-carcinogenic effects are generally not harmful up to the thermal damage. Reliable evidence can be obtained by large-scale animal experiments. To reduce the cost of experiments, it would suffice to maintain large animal groups in equivalent conditions and to record the life span. Excessively strict safety regulations are unfavorable for the economy.

Key words: radiofrequency; electromagnetic fields; cancer

Introduction

Realistic risk assessment is important for public health and safety regulations. This review attempts to apply the concept of hormesis [1,2] to radiofrequency radiation (REF). Hormesis is a biphasic dose response: low doses exert protective effects while higher doses are harmful. Among environmental factors acting in accordance with the hormetic pattern are numerous physical and chemical agents. In the hormesis framework, mild exposure to various stressors may elicit an adaptive response that enhances defenses and protects the organism. This protection can be associated with a performance increase that goes beyond that observed in untreated individuals. An evolutionary adaptation to the current level of an environmental factor or to some average from the past can be reasonably assumed. Taking into account fluctuations of solar emissions and atmospheric electricity, there is probably a broad range adaptation to REF.

In the electromagnetic spectrum, structural damage to living tissues per unit of absorbed energy tends to increase with the energy carried by a photon, that is, inversely proportional to the wavelength. This is evident for ionizing radiation as well as for infrared, ultraviolet and visible light, causing thermal damage at absorbed energies that would be harmless for REF warming tissues more uniformly. Apart from REF, a body can be heated by conduction, which means intensification of the Brownian motion of molecules including nucleic acids and proteins, while REF induces currents agitating charged and polar particles. An increased risk of malignancy, genotoxic effects, and disturbances of the DNA repair after repeated heat exposures have been reported [3-9]. Apart from diathermy discussed below, considerable heating of human tissues by REF is unusual. The evidence in favor of genotoxic effects of REF is considered to be weak [10]. The topic is cluttered with publications of questionable reliability. Under such conditions, theoretic considerations gain in importance. Considering low photon energies, there are no grounds for expecting more damage per unit of absorbed energy from REF than from infrared rays or heating by conduction. The 5G wireless technology brings biologically nothing new: it uses REF, which at a

non-thermal level is not expected to cause any damage. REF of all frequencies have been used also in the past.

Experimental studies after

There is experimental evidence in favor of hormetic responses to REF [11-14]. Besides, adaptive responses after pre-exposures to REF have been documented both in vivo and in vitro [15-17]. No plausible mechanisms of carcinogenicity have been proposed so far. Many animal experiments have not found any increase in the cancer risk after long-term exposures to REF [18-20]. Numerous in vitro studies detected neither carcinogenicity nor DNA damage [21-24]. The more research quality criteria were satisfied, the less cellular responses and gene damage was observed [25,26]. In particular, no genotoxicity of REF was detected in cultured astrocytes [27]. The reliability of some experimental data is questionable, as they claim effects at exposures below the limits for the users of mobile phones (MP) [28].

The supposed synergism between REF, some carcino-, and mutagens needs further research [10,29-34]. As mentioned above, there are documented adaptive responses such as the protection by REF from subsequent damage by mutagens and ionizing radiation. Certain REF effects, regarded to be non-thermal, can in fact be caused by a local elevation of tissue temperature or hotspots [29,31]. Controversial findings about REF impact on fertility and sperm quality [35-38] may be largely attributed to a temperature elevation, considering the heat sensitivity of spermatogenesis. According to recent reviews, it is unclear if REF affects fertility beyond a hyperthermic effect [39,40]. It can be reasonably assumed that a warm bath or sitting on a heated surface would have a comparable effect per unit of energy absorbed by the gonads. Even exposures with high specific absorption rate (SAR) around 2770 W/kg produced no alteration of reproductive efficiency in hens [41]. In Drosophila, there were no significant differences in the development of eggs by females exposed to REF (400-800 W/kg) and those exposed to heat alone. Only high power densities, higher than the levels to which human populations are typically exposed and the limits set by international guidelines, produced changes in reproductive patterns [41,42].

Thermal effects of REF from MP at SAR below 2 W/kg are negligible [43-45]. It was estimated that only SAR more than 4 W/kg may result in a tissue temperature elevation by approximately 1°C [41]. For comparison, the upper limit of SAR set by the Federal Communications Commission [46] for public exposures from MP is 1.6 W/kg. In some experiments, where radiation from MP was applied, the exposure time (9-19 hours/day) was much longer than in MP users [44,47,48] (discussed below), while in another study (exposure 6 hours/day), the rats were immobilized by restraints [45], thus being potentially exposed to a local heating and hotspots. The NTP Report [44] has been broadly discussed [49-51]. Groups of 90 male and 90 female rats were exposed to 1.5, 3, or 6 W/kg REF. Exposures to GSM- or CDMA-modulated REF (900 MHz, ~ 9 hours/day) were associated with an incidence increase of glioma in the brain and schwannoma in the heart of male rats. The strongest evidence was found for heart schwannoma at the maximal SAR (6 W/kg) [44]. The only clearly positive result of the DNA damage test was observed in hippocampus of male rats exposed to the CDMA-modulated REF with SAR 6 W/kg [44]. The NTP study was only partially blinded [49], a subjectivity thus being not excluded. In particular, histological assessment of supposedly precancerous and other lesions may be more or less subjective. The most important result was that the overall survival was longer in exposed male rats than in the control animals: 28% of controls survived until the end of the study vs. 50-68% and 48-62% animals in the exposed groups (GSM and CDMA modulation, respectively). The shorter life span in controls must have resulted in the underrepresentation of age-related lesions [44,49]. For the animals exposed to GSM-modulated REF at the end of the two-year period, survival of all exposed male groups was significantly longer than that of the controls. For CDMA-modulated REF, the difference was statistically significant in the 1.5 and 3 W/kg groups. Survival of exposed female rats tended to be longer than in controls after prolonged exposures (513-724 days); the difference was statistically

significant in the 6 W/kg CDMA female group [44]. The net benefit reflected by the life duration, compatible with hormesis, is obviously more important than the incidence of rare age-related tumors, not influencing the average life span.

The differences between exposed and control groups may be caused by a slight but prolonged heating by REF. The recorded elevation of subcutaneous temperature by ~0.7 °C in the 6 W/kg SAR group was probably an underestimation because measurements were taken 1-5 min post-exposure, while the temperature returned to the baseline within 10 min [44,49]. Exposures ≥10 W/kg induced excessive heating associated with a mortality increase [51]. The SAR values more than 4 W/kg may be associated with thermal effects with or without measurable temperature elevation due to local heating or hot spots [41,44,52,53]. Average temperatures were higher than in controls at exposures ≥6 W/kg both for GSM and CDMA modulations. Male rats were more sensitive than females to REF-induced heating because the males are bigger. The increase in body temperature under the impact of REF is more pronounced in bigger and older animals [44,51]. Along the same lines, rats are more sensitive to REF-induced heating than mice [51]. This may explain the absence of increased frequency of schwannoma in mice: the evidence of REF carcinogenicity in mice was considered ambiguous [49,51,54,55].

The above considerations pertain also to experiments at the Ramazzini Institute, where rats were exposed to 1835 MHz GSM-modulated signals 19 hours/day with SAR 0.001-0.1 W/kg from prenatal life until natural death [47,48]. Temperatures were not reported; the heating may have been negligible considering the low SAR compared to the NTP experiments discussed above. No significant survival differences between the treated and control groups were recorded. However, analyzing the graphs in the article [47], it can be seen that survival of exposed rats of both genders tended to be longer than in controls. The main result of the study was a significantly increased incidence of heart schwannoma in male rats exposed at the highest SAR (0.1 W/kg): 3/207 (1.4%) in exposed rats vs. 0/412 in the controls [47,48]. In females, there were no differences: 2/202 (1%) in exposed to 0.1 W/kg REF vs. 4/402 (1%) in controls. For both genders combined, the difference between exposed and control rats was not statistically significant. The results were deemed far from robust [49,56]. The studies [44,47,48] have been reviewed by the ICNIRP with a conclusion that substantial limitations make impossible any judgments on REF carcinogenicity [49,56]. It should be commented that the data from the NTP and Ramazzini Institute with exposures 9-19 hours/day are not directly extrapolable to MP users. The exposure of 6 W/kg [44] was three times higher than the local and 75 times higher than the whole-body exposure restriction set for the general public [56]. In particular, hotspots due to local tissue properties or wave interference must be more pronounced in motionless, sleeping animals. Such exposures do not usually occur in MP users. The problem of potentially damaging hotspots [53] in motionless biological objects should be studied in experiments imitating microwave diathermy of the head-and-neck area (discussed below) or such an “extreme” as a child sleeping with an emitting MP at his or her ear [57].

Finally, oxidative stress as a supposed damaging mechanism should be mentioned. Absorbed energy being equal, there are no reasons to expect more oxidative stress from REF than from infrared rays. Moreover, REF was reported to exert a protective action against oxidative and other cell damage [15,16,58]. Hyperthermia itself may lead to an increased production of reactive oxygen species [59,60]. The concept of oxidative stress seems to be generally overused [61].

Epidemiological studies

According to the IARC, there is limited evidence in favor of carcinogenicity of REF, although there was a minority opinion in the IARC Working Group that the evidence in humans is inadequate, permitting no conclusions on causality [33,52]. The “limited evidence” means that other explanations of the data are possible. Several epidemiological studies reported associations of REF exposures with glioma, acoustic neuroma, and other tumors [62-70]. Other research did not confirm

such associations or even found a reduced risk of brain tumors among MP users and workers exposed to REF [71-77]. In the large-scale INTERPHONE study, no increase in the glioma or meningioma risk in MP users was observed [77]. There have been suggestions of an increased glioma risk at the highest exposure levels, but possible bias prevented conclusions on causality [78]. Admittedly, at a re-analysis of the Canadian segment of the INTERPHONE cohort, positive results were obtained for glioma. Comparing the quartile with the highest MP use to those who were not regular users, the odds ratio was 2.2 (95% confidence limits: 1.3, 4.1). However, unlike the Canadian segment, the INTERPHONE multinational dataset demonstrated a diminished tumor risk in MP users. An elevated risk was found only in the highest decile of the MP use [79]. In sum, epidemiological data are heterogeneous and hardly suitable for cause-effect interpretations [42,50,80].

If carcinogenic effects of REF from MP had been substantial, the tumor incidence rates would be higher, especially in more developed countries. However, the incidence of glioma in the United States remained stable over the period 1992-2008 in spite of the rapid expansion of wireless communication [81,82]. No incidence increase of glioma during the last 30 years has been demonstrated in Sweden [83]. Age-standardized incidence rates of brain tumors were relatively stable over the period 1993-2007 in developed countries [84]. An increase in certain time periods, countries, age- and gender groups has been out of proportion to the rise in the MP use, being explainable by improving healthcare and imaging technologies [85,86]. According to the IARC, there has been no substantial increase in the incidence of brain tumors since the rapid expansion of wireless communication [33]. The SCENIHR stated that the epidemiological research generally does not indicate any risk elevation of brain tumors in MP users [19]. According to the ICNIRP, the accumulating evidence is increasingly against the hypothesis that MPs cause brain tumors [87]. Numerous studies found no associations between MP use and tumors of the brain and head area, referenced in [88]. ICNIRP has published REF exposure guidelines that are substantially lower than the lowest exposure level that science has found to cause harm [89].

In the INTERPHONE and some other studies, glioma tended to be more frequent on the side of the head where MP had been used [72,77]. However, the ipsilateral effect found in low exposure groups suggested that cancer patients tend to overestimate the use of MP on the tumor side [78]. Bias is known to occur in the epidemiologic research: dose-dependent selection, recall and observation bias [90], for ionizing radiation discussed previously [2]. It can be reasonably assumed that a cumulative duration of MP use roughly correlates (or did so in the recent past) with personal income [91], the latter correlating with diagnostic quality, which may explain reported associations between the time of MP use and various health risks.

Therapeutic use of REF

Supposed MP-related risks in humans are from REF of subthermal intensity. The ultra high frequency (UHF) therapy of thermal intensity (diathermy) has been widely used for the treatment of inflammatory otorhinolaryngological conditions in children and adults in the former Soviet Union (SU) since the 1960s [92]. Extremely high-frequency waves have been used for respiratory and allergic conditions in children, while the absence of contraindications was pointed out [93]. No associations of the UHF therapy with glioma or other tumors have been reported. The output power recommended for the head and neck area has been 15-40 W, but UHF devices with the output power up to 500 W were used [93,94]. An overexposure of ocular and cerebral tissues is possible if certain output power levels are exceeded [41,95]. The same considerations pertain to magnetic resonance imaging (MRI) associated with REF exposure, which is regarded to be a safe procedure [96].

The UHF therapy and MRI cause short-term exposures. The total absorbed energy in MP users may be higher, but current knowledge does not suggest any accumulation of REF effects [19]. Lifetime

studies of REF-exposed animals have shown no cumulative adverse effects. In the absence of significant heating or electric currents, the cardiovascular system and blood pressure regulation were not affected [29]. No correlations between total exposure duration and cellular responses in vitro have been found [25]. In the INTERPHONE study, the increased risk of glioma for cumulative call time was restricted to the top decile. The risk did not increase with the time since the first exposure or with total exposure duration. By analogy with known carcinogens, the lack of a consistently increasing risk with dose and/or exposure duration witness against the causality [77]. Admittedly, other studies reported correlations of glioma risk with the time since the first MP use or with the cumulative call time [62,65,66]. Considering potential bias in the epidemiological research, cumulative effects should be verified by large-scale animal experiments. Analogously to infrared radiation, no plausible mechanisms of accumulation of non-thermal REF effects are conceivable. Apparently, only special kinds of thermal damage, e.g. lens opacity, can accumulate. Cataracts develop after professional exposures >1000 W/m^2 [87], that is, much higher than in MP users.

Discussion

A long list of positive findings obtained in experiments of questionable reliability may appear impressive in a review and yet mean little [97]. As discussed above, high-quality REF research tended to be associated with negative results. The doses (SAR values) in experiments were generally higher than those in MP users [41], while some observed effects may be thermal. Theoretically, REF with certain characteristics may produce non-thermal effects in the nervous system [97], where moving electric potentials participate. Certain functional effects were probably caused by hotspots in the brain, retina or cochlea [98,99]. Exposures with high peak power pulses may influence behavior of animals, if the focally absorbed energy per pulse exceeds a threshold for perception. The hearing effect, phosphenes, and other transient phenomena are not considered health hazards, although they may be disturbing [19,100]. These and other functional phenomena are difficult to relate to mechanisms linking REF effects to health [29,43,101]. Being highly variable in the natural environment, REF may influence living organisms as the weather does, not necessarily causing harm. Accordingly, the ICNIRP guidelines are not intended to protect against biological effects as such, unless there is an associated adverse health effect [98]. Phosphenes and other functional phenomena have thresholds, and are avoidable by adhering to existing exposure limits. Avoidance of retinal phosphenes is expected to protect against all effects on the nervous system [19,100,101]. The same pertains to the supposed association between REF and tinnitus [102,103]. Tinnitus and hearing loss did not correlate with the average MP call time per week [103]. The last systematic review concluded that exposures below guideline values do not cause tinnitus, migraine or any non-specific symptoms [104].

Several studies have shown that REF may influence brain activity, e.g. modifying the waking but not sleeping electroencephalogram [105,106]. This indicates bias due to subjects' awareness of the procedure. There was little evidence in favor of any significant association between the use of MP and cognitive function in school children [107]. Results of a meta-analysis suggested that REF may have a mild impact on human attention and working memory [108,109], although some experts regard such effects to be unproven or insignificant [100,107,110]. A recent systematic review and meta-analysis found only a few studies that provided low certainty evidence of little to no association between REF exposures and memory, attention and executive functions [111]. Another review found evidence that short-term REF exposures do not reduce cognitive performance [112]. An improvement of cognition and other favorable effects of the transcranial magnetic stimulation have been reported [113,114]. Transcranial stimulation with extremely low frequency REF was found to be useful for the treatment of certain neurodegenerative disorders. Mechanisms of the neuroprotective action of REF (if any) are unclear; the induction of antioxidant pathways has been suggested [16,58].

The concept of non-thermal effects and their supposed accumulation served as a ground for strict exposure limits in the former SU compared to the United States: in the 1970s, the difference was ~1000 times. Considerable international differences in exposure limits are remaining [115-117]. Some data about the non-thermal effects of REF have not been validated [118-120]. Certain experiments were not informative [119]. For example, hen eggs in an incubator were exposed to REF emitted by an MP. The call mode was activated for 1.5 min, then switched off for 0.5 min; the cycle was repeated uninterruptedly for 21 days. An increase in embryonic mortality was recorded and conclusions made about damaging impact of REF on human embryos and newborn infants. However, the experimental conditions did not rule out heating as a cause of the embryonic mortality. The temperature in the incubator was reportedly 37 ± 1 °C, but inside the eggs it was elevated by REF. The embryos were static and thermally insulated [57]. Temperature changes around 1°C have a significant impact on the mortality rate of chicken embryos [121]. The heating of immobile eggs from the stationary MP could have been uneven with damaging hotspots. Apart from the exposure duration, conclusions regarding human fetuses and newborns are unfounded in view of the temperature leveling in the latter due to their mobility, blood circulation, and convection of amniotic fluid. The number of publications is growing, and it is difficult to distinguish between reliable and unreliable papers. It has been noticed that genotoxicity of REF was more frequently detected in studies of lower quality [25,26]. The research quality should be taken into account defining inclusion criteria into meta-analyses and reviews.

Conclusion

There is neither compelling evidence nor theoretic plausibility of cause-effect relationships between REF and cancer. Epidemiological data should not be dismissed, but more attention must be given to bias. Large samples and statistical precision do not protect from bias in epidemiological research. To confirm causality, verification by independent studies and understanding of mechanisms is generally needed. Reliable evidence could be obtained from large-scale animal experiments. To make experiments less expensive, it is unnecessary to examine the animals for tumors and perform necropsies. It would suffice to maintain large animal groups and to record life duration. Life span is known to be a sensitive endpoint attributable to radiation exposures. Necropsies and histological examinations are time-consuming and potentially susceptible to subjectivity. Various tests incur expenditures that could be used to increase the quantity of animals and hence statistical power. Thermometry is the single most important test in REF research. Further research could quantify effects of heating by REF for different animal species, enabling more precise extrapolations to humans. The doses (SAR values) and exposure duration must be comparable to those in humans to enable extrapolations.

As discussed above, the average life span in the NTP experiments tended to be longer in some exposed groups of rats than in controls [44], indicating net benefit according to the concept of hormesis. The net harm or benefit reflected in the life duration is obviously more important than rare age-related lesions. Regulatory agencies should take the life duration data into account. In the authors' opinion, current limits for public and professional exposures to REF are exceedingly restrictive in some countries. Unrealistic laws and regulations are often violated, which contributes to disrespect for the law in general. International harmonization must be based on reliable evidence and accompanied by measures that would guarantee adherence to the regulations.

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