Summaries and assessments of selected studies

In the period from mid of January 2022 to mid of April 2022, 108 new publications have been identified, and six of these were discussed in depth by BERENIS. Based on the selection criteria, five of these publications were selected as the most relevant ones. Their summaries and assessments are provided below.

1) Experimental animal and cell studies

Indications for carcinogenic effects of RF-EMF exposure (Ding et al. *2022)*

The *in vitro* study of Ding *et al*. (2022) aimed at investigating in a cell culture model whether there are indications for carcinogenic effects of continuous and long-term RF-EMF exposure (1.8 GHz, 8 W/kg SAR, 4 h/day). The authors exposed murine embryonic fibroblasts (Balb/c-3T3 cells) for 40 or 60 days, and treated them additionally with a cancer-promoting compound (tetradecanoylphorbol acetate - TPA). While the authors found no colony formation of cells in sham-exposed controls, they observed several colonies in RF-EMF-exposed cultures. Classic tests for cancerous cells (migration, colony and tumour formation) as well as analysis of genome-wide gene activity were used to confirm that the cells with such an altered appearance were indeed malignant transformations.

Based on their findings, the authors conclude that high levels of RF-EMF exposure can potentially induce cancerous cell transformation, which is in line with observations from animal studies on carcinogenesis (see newsletter - special issue November 2018). However, the transferability and informative value of such cell culture models is limited. Further studies should include additional positive and negative control conditions as well as the investigation of dose-response relationship and controls for potential thermal effects.

Changed excitability of neurons after RF-EMF exposure (Echchgadda et al. *2022)*

In the *in vitro* study by Echchgadda *et al.* (2022), electrophysiological experimentations were used to investigate indicators for changes in cognitive function caused by RF-EMF exposure. For this purpose, the authors isolated primary rat hippocampal neurons and exposed them to RF-EMF for 60 minutes (3 GHz, E-field: 137 V/m, average SAR: 0.3 W/kg, maximum SAR: 0.8 W/kg). Analysis of the neurons was performed within 15-30 minutes of exposure. The authors observed that RF-EMF exposure reduced the amplitude of the induced action potential of the neurons by 10%, and prolonged the action potential peaks. Furthermore, the authors reported that the resting membrane potential of the cell was reduced and that this depolarization promoted neuronal excitability. According to the authors, this was due to increased calcium concentrations in the cells. This also affected the presynaptic release of excitatory and inhibitory neurotransmitters (glutamate, GABA), and led to increased spontaneous activations and altered amplitudes of postsynaptic neurons. Blocking voltage-gated sodium channels neutralized these effects.

Based on their observations, the authors concluded that there are indications for an influence of RF-EMF on neuronal activity, albeit their relevance for cognitive changes could neither be ruled out nor confirmed. Further experiments in respect to effect persistence and recovery , long-term effects and dose-response relationship are required. This well conducted study thus provides a good entry point for further investigations in this field.

Exposure to 1800 MHz RF-EMF under proinflammatory conditions decreases the response strength and increases the acoustic threshold of auditory cortical neurons in rats (Souffi et al. *2022)*

Microglia, the immune effector cells of the central nervous system, influences neuronal activity in the brain. Souffi *et al.* (2022) investigated the effects of RF-EMF exposure (LTE 1800 MHz, 0.5 W/kg brain SAR) on the microglia morphology in the rat brain and on neuronal cells activity after acoustic stimuli. The heads of the animals were RF-EMF- or sham-exposed for 2 hours. The neuronal activity as well as the microglia morphology in the auditory cortex (part of the brain) was analyzed 3-6 hours later. Preceding RF-EMF exposure, an inflammatory response was induced in one group (by intraperitoneal injection), which led to microglia activation, simulating the effects of viral or bacterial infections. Both groups were RF-EMF- or sham-exposed. In RF-EMF-exposed animals that received an inflammatory stimulus, the response (neuronal activity) to pure tones as well as natural vocalization was reduced, which was also associated with an increase in the acoustic threshold for low and medium frequencies (0.5-20 kHz). In the group without proinflammatory stimulus, no differences between RF-EMF- and sham-exposed animals were found.

However, the RF-EMF exposure is subject to some degree of uncertainty, as even small variations in the positioning of the animals' heads can lead to a variation in exposure. It is reasonable to assume, however, that the variability is similar in all groups. Compared to a previous study (GSM 1800 MHz) by the same research group, in which rats were RF-EMF- or sham-exposed at 1.55 W/kg (Occelli *et al.* 2018)[1], no differences in microglial morphology were found here. In the earlier study, increased branching and length of microglial protrusions was observed in RF-EMF-exposed animals. These findings indicate a dose-dependent response after an inflammatory stimulus with microglial morphology only being altered after RF-EMF exposure at a SAR of 1.55 W/kg, while RF-EMF exposure impacted neuronal activity in both studies.

2) Epidemiological studies

Mobile phone use and risk of brain tumors: update of the UK Million Women Study (Schüz et al. *2022).*

Schüz *et al.* (2022) provided an update on the results of a large ongoing prospective cohort study on brain tumor risk associated with mobile phone use. Between 1996 and 2001, 1.3 million women born 1935-1950 in the United Kingdom were recruited for the study. The participants were asked to fill questionnaires regarding mobile phone use in 2001 and again in 2011, inquiring about how many years a cell phone had been used and for how long per day. In the 2001 survey, the response options were "never," "less than once a day," and "every day", while the 2011 survey addressed the number of minutes per day. Cancer registry data were used to determine the incidence of benign and malignant tumors within the skull. Separate analyses were performed for gliomas, glioblastomas, acoustic neuromas, meningiomas, and pituitary tumors. All analyses were adjusted for socioeconomic status, smoking, alcohol intake, body mass index, menopausal hormone therapy, and strenuous exercise. During the 14-year observation period, 3268 brain tumor cases were registered among the approximately 780,000 women who had completed a questionnaire on mobile phone use in 2001. Brain tumor risk was not increased for mobile phone users compared to non-users (relative risk: 0.97, 95% confidence interval: 0.90 to 1.04), and also after 10 years of mobile phone use no increased risk was found (relative risk: 0.95, 95% confidence interval: 0.87 to 1.05). None of the tumor types in this study was associated with mobile phone use. Tumors did not occur more frequently in the strongly exposed head regions (temple). An analysis based on data from 430,000 women who provided

[1] https://doi.org/10.1016/j.neuroscience.2018.06.002

information on their mobile phone use in 2011 did not indicate an increased risk either. The authors consider their findings to be in line with those of other epidemiological studies, which also found no increased risk of brain tumors associated with typical mobile phone use in everyday life.

Strengths of the study are the prospective study design, the relatively large study population, and the adjustment for potential confounders. The main aim of the study was to investigate health effects of hormone replacement therapy in women. This explains the rudimentary assessment of mobile phone use, which comprises only two questions and has a low temporal resolution. As a result, errors in exposure assessment are unavoidable. However, because of the prospective approach, these errors are not associated with the disease and are therefore random (non-differential). Any risk that might exist would thus be underestimated. Without any validation data on the exposure assessment, it is difficult to quantify the potential degree of underestimation. It is likely that a small cancer risk would have been missed, while a substantial risk should still be detectable. The relevance as well as strengths and weaknesses of the study have been discussed in an independent editorial.[2]

3) Human experimental studies

No changes in brain network connectivity after 4G exposure (Yang et al. *2022).*

In this study, seventeen participants (right-handed, 9 males, 8 females) were exposed for 30 minutes to a 4G signal (LTE; 2.573 GHz; 1.22 W/kg peak SAR (averaged over 10 grams of tissue) or not exposed (control condition). A dipole antenna was placed 1 cm from the right ear. Functional magnetic resonance imaging (fMRI) was used to study the effect of radiation on network connectivity in the brain (static and dynamic connections). Fourteen networks were identified and analyzed. The exposure did not result in significant changes in connectivity. A comprehensive dosimetry was performed, and the applied signal characteristics were well documented. The authors concluded that short-term exposure was not sufficient to be detectable at the level of brain connectivity. However, it is questionable whether magnetic resonance imaging is a suitable measurement approach, since strong RF fields are applied during the scanning itself, which could mask the effects of the exposure.

4) Information about other publications

EU report on health risks of RF-EMF

Following a request from the European Commission, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) has prepared a report on health risks of RF-EMF. The preliminary report was published in August 2022, and made available for public consultation until end of September 2022.[3]

[2] https://doi.org/10.1093/jnci/djac043
[3] https://health.ec.europa.eu/consultations/scheer-public-consultation-preliminary-opinion-scientific-evidence-radiofrequency_en)

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BERENIS - Swiss expert group on electromagnetic fields and non-ionising radiation

List of abbreviations (pdf)