Summaries and assessments of selected studies

In the period from early November 2018 to February 2019, 83 new publications have been identified, and nine 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

Influence of radiofrequency electromagnetic fields on brain tumors of rats (Ouadah et al. *2018)*

This animal study with male Wistar rats investigated the impact of a GSM 900 MHz EMF (pulse modulated at 217 Hz) on brain tumor growth (glioblastoma), animal survival, apoptosis, necrosis, proliferation, mitosis (cell division) of tumor cells and immune cell invasion. GSM or sham exposure of the rats (201 animals in total) was done in tubes/cylinders (adapted to the size of the animals) for 45 minutes, 5 days per week. The average SAR of the brain was 0.25 and 0.5 W/kg. Cage controls were also implemented. The endpoint of the experiment was either the natural death or day 65 after injection of C6 rat glioblastoma cells into the brain. From the time of injection, the mean survival time of exposed animals was 31 days and not different compared to sham-exposed animals. Similarly, no differences were found in tumor volume, mitotic index, vascularization (into the tumor), and rate of necrosis and cell division upon RF-EMF exposure. Among all the endpoints assessed, the invasion of immune cells into the tumor and the apoptosis rate (programmed cell death) of tumor cells were found to be reduced in RF-EMF-exposed rats in a dose-dependent manner. These data provide no evidence that GSM-modulated RF-EMF affects the progression of brain tumors in this glioblastoma rat model. The authors suggest that the observed reduced immune cell invasion is too weak to affect tumor development.

New evidence on the mechanism by which extremely low frequency magnetic fields can affect cell proliferation (Qiu et al. *2019)*

In line with findings of several previous studies, Qiu *et al.* (2019) found a slight change in cell proliferation upon ELF-MF exposure. The authors exposed human amniotic cells with an ELF-MF (0.4 mT, 50 Hz, 60 minutes) and observed increased cell proliferation compared to sham-exposed cell populations. This exposure effect was triggered by the stimulation of the central signaling cascade for cell proliferation (activation of the "MAP kinase pathway", i.e. phosphorylation of ERK1/2). Accordingly, the effect was neutralized by blocking this signaling pathway. Notably, the authors were able to connect the activation of the signaling cascade with the stimulation of the sphingolipid metabolism. Sphingolipids are polar lipids that have important structural but also signaling functions in the membranes. They showed that ELF-MF exposure led to an increase in certain ceramides and sphingosine-1-phosphate. When the authors blocked the enzyme responsible for the production of sphingosine-1-phosphate from sphingosine, the activation of ERK1/2 was inhibited and the effect of ELF-MF exposure on cell proliferation was reduced.

An activation of signaling cascades in connection with ELF-MF and RF-EMF exposure has been described repeatedly in recent studies. Although some open questions remain regarding molecular and functional interconnection, the work of Qiu *et al.* (2019) provides a new starting point for the understanding how MF may interact with cellular mechanisms. The cell membrane itself with all its polar lipids could act as a "receptor". By influencing the composition of the membrane, this could lead

either directly to the activation of signaling cascades or to altered reactions to additional external stimuli or cell communication signals.

2) Human experimental studies

Hardly any effects of evening exposure to electromagnetic fields emitted by 3G mobile phones (UMTS) on health and night sleep EEG (Lowden et al. *2019)*

Eighteen subjects (11 men, 7 women; aged 18–19 years) were exposed to electromagnetic fields from 3G mobile phones (UMTS, 1930-1990 MHz, SAR 1.6 W/kg) and a control condition (no field) for 3 hours in the evening before going to bed. The antennas were mounted on the right side of a helmet. Exposure had no effect on subjectively assessed health symptoms, fatigue and sleepiness, as well as on cognitive performance. Similarly, sleep architecture was not affected (sleep stages and latencies). The REM sleep EEG showed a reduction of the EEG power in the frequency range of the slow sleep spindles (11-13 Hz). However, this was not the case in the non-REM sleep EEG, where an increase would have been expected based on earlier studies which mostly used GSM exposure. Sleep spindles are characteristic of non-REM sleep.

Since no dosimetry is available, it is unclear which brain regions were exposed. It can be assumed that fewer brain regions were exposed compared to other studies that exposed the entire side of the head. Furthermore, the menstrual cycle was not considered in the participating women, which may have contributed to the fact that no effects on sleep spindles in non-REM sleep were found. Sleep spindles change systematically during the menstrual cycle. Previous studies revealed that pulse modulation is important for the occurrence of EEG effects. The UMTS signal used, which differs from the GSM signal previously used, may thus have had a smaller effect.

3) Epidemiological studies

Changes in diagnostic and coding procedures affect reported incidence time trends of brain tumors (Karipidis et al. *2018)*

Today, a large majority of the population has been using mobile phones regularly for years. Therefore, one would expect a relevant brain tumor risk to be reflected in an increase in case numbers (incidence), and to be visible accordingly in cancer registry data. In this regard, several studies have already been published, some of which found indications of an increase for certain diagnostic groups. Previous BERENIS newsletters featured analyses based on data from Sweden and New Zealand (Newsletter 3 / September 2015) and from England (Newsletter 10 / June 2017). Karipidis *et al*. (2018) conducted in-depth analyses of Australian Cancer Registry data from 1982 to 2013. The authors divided the time span into three periods: 1982-1992 (representing increased CT and MRI use), 1993-2002 (representing advances in MRI) and 2003-2013 (representing substantial and increasing mobile phone use; more than 65% of the population). No increase in glioma was observed for the latter period (annual percentage change in incidence: -0.6% [95% confidence interval: -1.4% to 0.2%]). Furthermore, taking into account various risk scenarios, the authors have concluded that an excess risk of at least 50% with a latency period of 15 years would have been observable in their analysis of brain tumor rates. However, for latency periods of 20 years and longer, the cancer registry data are not yet informative.

In principle, the results are not new. It is interesting to note that trends were presented separately for different tumor types and for tumors at different locations in the head. The authors show that there are shifts between the different diagnostic groups over time. For example, the increasing use of

imaging techniques (MRI and CT) has led to a sharp decrease in tumors with unknown anatomical location, and an increase in tumors with known location over time, with an approximately constant total number of cases. This implies that subgroup analyses are vulnerable to bias and it is important to consider changes in coding practice when interpreting temporal trends in incidence. Therefore, if an increase of tumors in the temporal lobe is reported, it has to be crosschecked whether this might be due to a better availability of such location information in more recent times. If this explanation can be ruled out, an increase of tumors in the head region most heavily irradiated by mobile phones would be indicative for a tumor risk caused by mobile phone radiation.

Large multinational study investigating occupational exposure to extremely low-frequency magnetic fields and electric shocks with regard to risk of amyotrophic lateral sclerosis (Peters et al. *2019)*

In a pooled case-control study of data from Ireland, Italy and the Netherlands, Peters *et al.* (2019) investigated whether occupational exposure to extremely low-frequency magnetic fields (ELF-MF) or electric shocks increases the risk of amyotrophic lateral sclerosis (ALS). ALS is an incurable degenerative disease of the motor nervous system with largely unknown causes. The included cases were diagnosed between 2010 and 2015. Controls of the same age, sex and geographic location were randomly selected from the population. Lifetime occupational histories were obtained using questionnaires. Job exposure matrices were used for assigning occupational exposure levels to ELF-MF and likelihood for electric shocks. The clinical diagnosis was verified on the basis of hospital records. A total of 1,323 ALS cases and 2,704 controls were included in the analysis. The statistical analysis was adjusted for age, sex, study center, education, smoking, and alcohol consumption. Persons who were ever occupationally exposed to ELF-MF or who had an increased risk of electric shock were found to have an increased ALS risk, with a statistically significant risk increase of 16% and 23%, respectively. However, the results were not consistent between the three study centres/countries, and showed no dose-response relationship with respect to cumulative exposure. Exclusion of cases with a genetic predisposition to ALS resulted in the same findings.

The results of this study suggest that both occupational ELF-MF exposure and electric shocks independently increase the risk of ALS. Previous studies have often found an increased risk for one of the two factors, but not for both at the same time. Strengths of the study include the relatively large number of cases for this rare disease, as well as the thoroughly conducted process of data collection. Nevertheless, it is unclear whether a control selection bias occurred, as there is no information on how the controls were selected, and the participation rate is not reported. The authors state that control subjects on average had a higher education level than cases, which might be an indication of selection bias. If controls have been chosen selectively with a lower probability of electric shocks and/or exposure to ELF-MF, this would lead to an overestimation of ALS risk in this study.

References

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Correction: Karipidis et al. **Mobile phone use and incidence of brain tumour histological types, grading or anatomical location: a population-based ecological study.** BMJ Open, 2019. 9(1): p. e024489corr1. https://doi.org/10.1136/bmjopen-2018-024489corr1

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

List of abbreviations (pdf)