Summaries and assessments of selected studies

In the period from October 2016 to January 2017, 83 new publications have been identified, and 15 of these were discussed in depth by BERENIS. Based on the selection criteria, six of these publications were selected as the most relevant ones. Their summaries and assessments are provided below.

1) Experimental animal and cell studies

Long-term exposure to RF-EMF induces hyperactivity, autophagy and demyelination in the cortical neurons of mice (Kim et al. *2017)*

This *in vivo* study assessed neuronal effects of radiofrequency electromagnetic fields (RF-EMF) on the cerebral cortex of the mouse brain. The cerebral cortex is important regarding sensory and cognitive functions such as hearing, smelling, orientation, movement, perception, and memory. Male C57BL mice were exposed for five hours per day during 12 weeks (835 MHz, SAR: 4 W/kg). The experiments were performed blinded and under controlled conditions (temperature, air, light). In addition to several behavioral experiments, a number of biomarkers for autophagy[1] and apoptosis (programmed cell death) were investigated. Furthermore, the amount of demyelination and myelin damage of nerve pathways, as commonly found in e.g. patients with multiple sclerosis, was studied. Myelin is essential for the development and function of the nervous system. The results showed increased autophagy following RF-EMF exposure, whereas no difference was found regarding apoptosis markers in exposed animals and controls. Exposed mice showed myelin damages and hyperactive behaviour. These neurological behavioural disorders were probably induced by the demyelination of the nerve fibres after 12 weeks of exposure. The authors interpret the increased autophagy as a protective pathway for the neuronal cell bodies in the cerebral cortex. A review article published in 2014[2] also describes myelination defects in rats after RF-EMF exposure.

Static magnetic fields and regulation of the photoreceptor cryptochrome in fruit fly larvae (Giachello et al. *2016)*

Cryptochrome (CRY) is a blue light sensitive protein, which has a key role in circadian photoreception. Many animals can sense the earth's geomagnetic field to enable behaviors such as orientation and navigation. CRY is also involved in non-circadian functions such as magnetoreception, modulation of neuronal firing, phototransduction and regulation of synaptic plasticity. It is proposed that the magnitude and direction of the geomagnetic field modulates the activity of CRY by influencing photochemical radical pair intermediates within the protein. The role of CRY as magnetoreceptor is still disputed, as experimental evidence for increased neuronal activity caused by magnetic field exposure is still lacking. This *in vivo / ex vitro* study investigated CRY-dependent effects of static

[1] Autophagy means “self-eating” and protects the cell from functional disorders by disintegrating defect or even damaging cell components or pathogens. They are isolated in specialised cell organelles, degraded and finally returned into the cell metabolism. Overly stressed or deficient autophagy can lead to diseases.

[2] Redmayne M, Johansson O (2014): **Could myelin damage from radiofrequency electromagnetic field exposure help explain the functional impairment electrohypersensitivity? A review of the evidence.** J Toxicol Environ Health B Crit Rev 2014; 17 (5): 247 – 258. http://www.ncbi.nlm.nih.gov/pubmed/25205214

magnetic fields (100 mT) on motoneurons of fruit fly larvae. A potentiation of neuronal activity of light-activated CRY was found after exposure of the fruit fly larvae to a magnetic field (100 mT). A region (C terminus) in CRY that is required for the potentiation could be identified. Thus, there is evidence that the biological activity of CRY is sensitive to magnetic fields, and that the external magnetic field can influence the behavior of animals via CRY. The results strengthen the evidence that magnetic fields modulate the neuronal activity of photo-activated CRY, and thus the orientation of animals.

Both exposure and experiments are well described, and therefore this study provides direct evidence that CRY is a magnetoreceptor in fruit flies.

Radiofrequency electromagnetic fields influence the dynamics and efficiency of DNA repair (Sun et al. *2016)*

In this innovative *in vitro* study, Sun *et al.* (2016) report remarkable observations regarding the effect of RF-EMF on the genome and its control mechanisms. The authors exposed murine connective tissue cells (embryonic fibroblasts) to a modulated RF-EMF (1800 MHz, SAR 4 W/kg, 5/10 min on/off), mimicking a GSM signal. After 1, 12, 24 and 36 hours of exposure, the amount of single- and double-strand breaks in the DNA as well as biomarkers for DNA repair activities and cell proliferation were analysed and compared to control cell cultures. The same analyses were also performed in cells lacking the ATM protein. This protein is central for recognising and repairing genome damage, and for triggering signaling cascades that counteract fatal consequences such as carcinogenic mutations. A rare congenital disease in humans, known as Louis-Bar syndrome or *Ataxia-telangiectasia,* is caused by mutations in this gene. The lack of the important regulating control function of the ATM protein leads to a multitude of symptoms in patients, such as neurodegeneration, reduced immune competence, and increased cancer risk. Cells lacking the ATM protein typically have an increased basal level of DNA damage, higher mutation rates and an altered cellular response to genotoxic treatments. In normal cells, the authors found a transient increase of single-strand breaks after one hour of exposure, which was not detectable anymore after 12 and 24 hours, and even significantly decreased after 36 hours. No differences were observed for double-strand breaks. In the mutated ATM cells, however, no differences between exposed and control cells were observed after one hour of exposure, but a temporary increase of single-strand and double-strand breaks after 12 and 12/24 hours, respectively, alongside with increased signs of DNA repair activities. This indicates a delayed cellular response to the exposure, which finally led to reduced DNA damage after 36 hours of exposure. The authors speculate that these findings point to hormesis, a non-linear response to the cumulative dose. This specific kind of adaptive cell response to external influences has also been described for drugs, genotoxic chemicals and slightly increased radioactive radiation; however, it has not yet been fully established at least for the latter. Such a reduction of cellular effects is commonly explained by the activation of certain compensation mechanisms (in this case increased DNA repair activities) by weak exposure. This leads to decreased sensitivity of the cells to higher doses, or to cells reacting faster and more efficiently, causing an attenuation or even overcompensation of the response. In order to confirm the hormesis effect of RF-EMF exposure, the authors performed the same experiments with low doses of known genotoxic chemicals (4-nitroquinoline 1-oxide, hydrogen peroxide) in both cell types, and found comparable overcompensations.

Based on such an *in vitro* study, it is difficult to judge whether this has positive or negative implications on human health in the long term. In addition, the SAR value investigated in this study was relatively high, and it thus remains open whether hormesis could also be observed in more relevant exposure scenarios.

2) Epidemiological studies

Radiofrequency electromagnetic field exposure of adolescents in Switzerland (Roser et al. *2017)*

Adolescents belong to the heaviest users of wireless communication devices, but only little is known about their RF-EMF exposure. In this study (Roser *et al.* 2017), personal RF-EMF exposure of 90 adolescents aged 13-17 years living in Central Switzerland was measured during 48 to 72 hours using a portable measurement device (Expom-RF) between May 2013 and April 2014. Participants carried the measurement device for two to three days with them and filled in an activity diary. Geographic location (GPS) was also recorded by the Expom-RF. Mean personal RF-EMF exposure was 0.15 V/m (max: 0.51 V/m). The strongest exposure contributors were emissions from mobile phone handsets (67%, both own and other mobile phones) and mobile phone base stations (20%). WLAN contributed 3.5% to the average RF-EMF exposure. Exposure was highest in cars (total: 0.56 V/m, contribution of mobile phone base stations: 0.10 V/m), buses (0.50, 0.15 V/m) and trains (0.45, 0.18 V/m). Mean exposure at home was 0.11 V/m (contribution of mobile phone base stations: 0.06 V/m), 0.15 V/m in schools (0.04 V/m), and 0.24 V/m outdoors (0.14 V/m). In order to calculate the average absorbed radiation, these measurements were combined with data on average wireless device use of the sample. According to these dose calculations, exposure from own devices contributes 94% of the total RF-EMF absorbed by the brain, and 91% of the total RF-EMF absorbed by the whole body.

This study demonstrates that most of the RF-EMF exposure is “self-made”, mostly from mobile phones. Apart from the duration of use, connection quality is an important factor determining the cumulative RF-EMF dose. The better the connection, the less the EMF emission by mobile phones.

Mobile phone use in England from 1985-2014 and incidence of selected brain tumour types (de Vocht 2016)

The use of mobile and cordless phones has become very common in the last two decades. Thus, if wireless phone use were a risk factor for developing a brain tumour, one would expect to observe an increase in the incidence during the last decade. In order to evaluate such a link, de Vocht (2016, plus corrigendum) analysed the incidence of selected brain cancer subtypes in England between 1985 and 2014 using a Bayesian structural time series approach. Annual case numbers of the following subtypes were considered: unspecified malignant neoplasm of the brain, glioblastoma multiforme, malignant neoplasms of the temporal lobe and malignant neoplasms of the parietal lobe, obtained from the Office of National Statistics. The effect of mobile phone use on the change in brain cancer incidence was inferred from differences between recorded and modelled time series. The modelled number of cases included incidence of all type of cancers, population size, median age of the population, prevalence of cigarette smokers, urbanization rate and a quality measure for the cancer coding. Temporal changes in unspecified malignant neoplasms of the brain and glioblastoma multiforme incidence were not related to the increase in mobile phone subscriptions. Malignant neoplasms of the parietal lobe were negatively correlated with time trends of mobile phone subscriptions. For malignant neoplasms of the temporal lobe, time series indicated a risk increase of 1.35 (95% CI: 1.09-1.59) with a 10 year latency but not with a 15 years latency. The temporal lobe is mostly exposed when using wireless phones. The observed risk increase corresponds to 188 additional cancer cases in England each year.

Limitations of this simple ecological analysis include lack of individual exposure data and selective reporting of outcomes. It remains unclear why only unspecified diagnoses have been considered.

These diagnostic groups are strongly affected by changes in diagnostic and coding practices. With the introduction of improved diagnostic techniques in the last 20 years, coding of location information may change over time, possibly affecting the analyses. It seems implausible that an increased risk is restricted to a latency period of 10 years only. This may indicate bias from other secular time trends, for example increasing life expectancy of the population. For instance, median age does not accurately represent population growth in older age groups with the highest risk for developing brain tumours. In general, the study would have been more informative if results had been shown for all subtypes of brain tumours to enable systematic evaluation of the time trend patterns with respect to the exposure of various brain areas.

Personalised exposure tests for electromagnetically hypersensitive individuals (van Moorselaar et al. *2016)*

In this study, van Moorselaar *et al*. (2016) tested a new approach to treat electromagnetically hypersensitive (EHS) individuals. The authors conducted repeated individualised provocation testing of EHS individuals at their home to overcome limitations of previous research in this population group. In total, 42 persons with a mean age of 55 years were included in the study. They reported perceiving or reacting to either radiofrequency or extremely low frequency fields within minutes of exposure. The participants were tested at home with a mobile custom-made exposure unit. First, the type of exposure (frequency) and duration that the participants responded to were determined together with the participants in open provocations. This means the participants were informed about the respective strength and frequency of the exposure device signal. After that, 10 double blind tests were conducted with 3 to 7 randomly selected true exposure situations, and a maximum of 15 minutes per exposure situation. The participants had to identify presence or absence of EMF exposure. The results were communicated to the study participants immediately after the double blind testing. 38 participants requested RF testing with an electric field that ranged between 0.2 and 6 V/m (median: 0.44 V/m). Four participants preferred an ELF-MF test at levels between 0.15 and 6.6 µT. None of the participants was able to identify when they were being exposed in double blind testing. On average, the test persons correctly assessed the exposure in 48% of the tests. Four months after the testing self-reported EHS levels were unchanged, but certainty to react to EMF within minutes was decreased in the study participants. Further, the number of symptoms and severity score of the symptoms was significantly lower than at the beginning of the study. This may indicate that a subgroup of persons profit from a personalised EMF testing procedure.

A strength of this study is the verification of an individualised testing signal together with the study participant. This could be achieved by a mobile testing system which was able to generate a wide range of EMF signals. Since there was no control group, it cannot be proven whether the observed symptom reduction within four months was the consequence of study participation or not. Nevertheless, this seems to be a very innovative approach to help EHS individuals who report to react to EMF exposure within a short time. It would thus be useful to collect more experience how helpful such an individualised testing is in the long run, and for which subgroup of EHS individuals.

The BERENIS group emphasises the importance of identifying and evaluating diagnostic and treatment approaches for EHS individuals, in addition to research on causal links. The degree of suffering in EHS individuals is very high, and medical consultation is vital. Since 2001, comprehensive medical, psychological assessments are available in Switzerland. From 2008-2011, a group of medical doctors in Switzerland (Ärztinnen und Ärzte für Umweltschutz, www.aefu.ch) has performed environmental medical assessments that were integrated in physician's everyday practice, and has then started to offer an environmental medical counseling service for affected individuals. In the

view of BERENIS, it is necessary and important to be in a position to offer evidence based therapeutic support to electromagnetically hypersensitive individuals.

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

List of abbreviations (pdf)