Summaries and assessments of selected studies

In the period from end of July to mid of October 2021, 82 new publications have been identified, and six of these were discussed in depth by BERENIS. Based on the selection criteria, three of these publications were selected as the most relevant ones. Their summaries and assessments are provided below.

1) Experimental animal and cell studies

Combined effect of environmental exposures: extremely low-frequency electromagnetic fields and plasticizer (Chen et al. *2021)*

In this *in vitro* study, Chen *et al.* (2021) investigated the interaction of two environmental factors on the proliferation of human amniotic cells. The cells were exposed to a 50 Hz ELF-MF for 1 or 24 hours, and to diethylhexyl phthalate (DEHP), an industrially used plasticizer. Single exposure of cells to either environmental factor at an exposure/dose of 0.4 mT ELF-MF or 1 µM DEHP resulted in a significant increase in cell proliferation by 10%. This effect was not detectable at lower exposures/doses of 0.2 mT ELF-MF or 0.1 µM DEHP. Yet, when the two lower exposures/doses were applied simultaneously, cell proliferation was again significantly increased, indicating an additive effect of the two environmental factors. Furthermore, the signaling cascade leading to this additive effect was identified by pharmacological inhibition and determination of activated signaling proteins. The authors showed that the sphingosine kinase 1 (SphK1) played a central role in this process. This kinase can modify sphingolipids (for example, ceramides), which are components of the cell membrane. The proliferation-promoting signaling molecules Akt and ERK are upstream and downstream of the SphK1 activation, respectively.

The study by Chen *et al.* (2021) showed that combined exposure to 50 Hz ELF-MF and DEHP enhanced cell proliferation at lower doses than single exposures. Interactions between EMF and other environmental agents with respect to biological effects have recently received increased scientific attention. Frequently, it has been observed that EMF exposure alone resulted in marginal effects, but may modulate cellular responses to a second environmental cue. Nevertheless, it remains to be clarified whether such additive effects, as found in this study, are limited to specific cell types or combination of environmental factors, or a more general phenomenon.

Induction of a transient mitochondrial stress by radiofrequency electromagnetic fields (Xie et al. *2021).*

In the *in vitro* study by Xie *et al.* (2021), the influence of an RF-EMF (unmodulated 900 MHz, 120 µW/cm², SAR according to the authors: 0.25 mW/kg) for 4 hours per day for 5 days on signs of mitochondrial stress was investigated. 30 minutes, 4 hours, and 24 hours after the last exposure of mouse bone marrow stem cells, the authors studied two parameters of mitochondrial stress response, namely, the formation of reactive oxygen species (ROS) and the misfolded protein response. X-ray exposure was used as a comparator. 30 minutes after RF-EMF exposure, the amount of ROS was slightly increased, and this increase was still detectable after 4 hours. The increase was less pronounced compared to the X-ray exposure. For both, the normal state was restored after 24 hours. The same temporal pattern was found when analyzing indicators of protein misfolding. The mitochondria-specific heat shock proteins HSP10 and HSP60, as well as the protease ClpP that

degrades such misfolded proteins, were temporally elevated. Moreover, the authors showed that this stress response was mediated by the Janus kinase JNK2.

Notably, these effects were observed at low exposure levels and were similar to the response to ionizing X-rays, used as a positive control. The results of this study indicate that RF-EMF-related mitochondrial stress is transient, even after multiple exposures over 5 days. However, weaknesses of this small study are that the exposure system was designed for animals rather than cell cultures, and that the description of the dosimetry is inadequate, and thereby difficult to replicate. Thus, these methodological uncertainties need to be eliminated by independent replications of the findings.

2) Epidemiological studies

Extremely low frequency magnetic fields in residential buildings and skin cancer (Khan et al. *2021a), brain tumors and leukemia (Khan* et al. *2021b)*

Khan *et al.* (2021a) conducted a cohort study on ELF-MF exposure from residential transformers and skin cancer in Finland. To some extent, the study was motivated by recent reports about possible effects of ELF-MF on photoinduced radical reactions at high exposure levels. The study included 225,492 individuals living in buildings with transformer rooms, with a mean follow-up period of about 15 years. Based on a dataset of buildings in Finland with indoor transformer stations, 8617 individuals who had lived in an apartment directly above or next to the transformer room for at least six months were classified as 'exposed'. They all lived on either the first floor or the ground floor. The remaining residents of the first and ground floors (n=46,169) and the upper floors (n=170,706) served as the reference group. The Finnish Cancer Registry was used to determine whether study participants had been diagnosed for skin cancer (melanoma and squamous cell carcinoma) at 18 years of age or older. Analysis of the data accounted for age at start of residence, sex, and year of birth. Overall, there was no increased risk for exposed individuals, with 559 cases of melanoma and 355 cases of squamous cell carcinoma evaluated. However, among exposed individuals who lived in the apartments before they reached 15 years of age, the relative risk was increased by approximately a factor of 2.5 (95% confidence interval 1.15 to 5.69). This increased risk was mainly due to exposure before the age of 10 years. However, this result is based on only seven exposed and 42 unexposed melanoma cases.

Overall, the study results do not indicate an association between residential ELF-MF exposure and skin cancer. However, it cannot be ruled out that ELF-MF exposure in childhood might, in very rare cases, favor the development of melanoma later in life. A similar conclusion was drawn with regard to leukemia and brain tumors in the same cohort: overall, no association was found, although a subgroup analysis based on four exposed cases in childhood showed a significantly increased risk of acute lymphoblastic leukemia (Khan *et al.* 2021b).

The study approach is innovative since it did not require any contact or interaction with the study participants, and thus no selection bias could have occurred. Moreover, a strength of the study is the exposure assessment, as it is well documented that ELF-MF exposure is substantially increased in apartments located close to transformers.[1] The analyses only accounted for few confounders. However, as it is unlikely that there are systematic differences regarding residential location and transformer room location for residents of the same house, this study design implicitly controls for many potential confounders. The most critical confounder is UV exposure, and it cannot be completely ruled out that children who live on the ground floor and thus are more likely to be near a transformer

[1] See measurements in Switzerland: Röösli M, Jenni D, Kheifets L, Mezei G (2011): **Extremely low frequency magnetic field measurements in buildings with transformer stations in Switzerland.** Science of the Total Environment, 2011, 409 (18): 3364-3369.

are also more likely to spend time outdoors. However, a sensitivity analysis limited to study participants living on the first and ground floor found no evidence for such type of confounding. The main limitation of the study is the small sample of participants exposed during childhood, so that this evaluation requires confirmation from additional studies.

References

Chen L, Ye A, Liu X, Lu J, Xie Q, Guo Y, Sun W (2021): **Combined effect of co-exposure to di (2-ethylhexyl) phthalates and 50-Hz magnetic-fields on promoting human amniotic cells proliferation.** Ecotoxicol Environ Saf. 2021 Aug 26;224:112704. https://pubmed.ncbi.nlm.nih.gov/34455183/

Khan MW, Juutilainen J, Naarala J, Roivainen P (2021a): **Residential extremely low frequency magnetic fields and skin cancer.** Occup Environ Med. 2021 Sep 30:oemed-2021-107776. https://pubmed.ncbi.nlm.nih.gov/34593542/

Khan MW, Juutilainen J, Auvinen A, Naarala J, Pukkala E, Roivainen P (2021b): **A cohort study on adult hematological malignancies and brain tumors in relation to magnetic fields from indoor transformer stations.** Int J Hyg Environ Health. 2021b Apr;233:113712. https://pubmed.ncbi.nlm.nih.gov/33601135/

Xie W, Xu R, Fan C, Yang C, Chen H, Cao Y (2021): **900 MHz Radiofrequency Field Induces Mitochondrial Unfolded Protein Response in Mouse Bone Marrow Stem Cells.** Front Public Health. 2021 Aug 26;9:724239. https://pubmed.ncbi.nlm.nih.gov/34513791/

Contact

Dr Stefan Dongus
BERENIS Secretariat
Swiss Tropical and Public Health Institute
Department of Epidemiology and Public Health
Environmental Exposures and Health Unit
Kreuzstrasse 2, CH-4123 Allschwil, Switzerland
Tel: +41 61 284 8111
Email: stefan.dongus@swisstph.ch

Additional information:

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

List of abbreviations (pdf)