

Summaries and assessments of selected studies

Between mid of January and end of April 2024, 84 new publications were identified, eight of which were discussed in depth by BERENIS. Of these, five were deemed most relevant based on the selection criteria. Their summaries and assessments are outlined below.

1) Experimental animal and cell studies

Millimeter wave electromagnetic fields and gene activities in skin cells (Martin et al. 2024)

In this in vitro study, gene activity profiles ("transcriptomics") of skin cells after exposure to RF-EMF in the millimeter wave range (60.4 GHz) were assessed by a refined version of global gene expression (Martin et al. 2024). Due to the low penetration depth of EMF in this frequency range, primarily the skin and eyes are targeted by millimeter wave exposure. Therefore, the authors of this study focused on keratinocytes, one of the cell types of the skin. They used an established cell line (HaCaT cells) as well as primary keratinocytes (HEK and NHEK cells) from donors, which exhibited distinguished gene activity patterns under sham exposure conditions. Out of the approximately 17,000 genes detected, between 200 and 1,100 (depending on the comparison) were altered more than 1.5-fold in a statistically significant manner. In contrast, exposure of the cells at 60.4 GHz EMF and 20 mW/cm² power density (corresponding to the ICNIRP limit for short-term occupational exposure) for 3 hours resulted in very few gene expression changes compared to sham exposure (14 in HaCaT cells, 4 in HEK cells, and none in NHEK cells). Most of these changes also occurred under control conditions, for which the temperature increase caused by the millimeter wave EMF (approximately 4.5°C) was simulated. In HaCaT keratinocytes, the same observations were also made in experiments with the lower exposure levels (5 and 10 mW/cm², corresponding to the ICNIRP limits for local exposure of the skin for the general population); the regulated genes and the activity profiles of thermally exposed cells and cells exposed to 60.4 GHz EMF were very similar. Furthermore, it was shown that a longer exposure time of 14 hours (10 mW/cm² in HaCaT keratinocytes) did not result in more pronounced changes in gene activity.

Based on their well-controlled and reproducible gene activity analyses, the authors concluded that there is no evidence of non-thermal effects due to millimeter wave EMF exposure in keratinocytes of the skin. The observed gene expression changes upon millimeter wave exposure can thus be explained mainly by the thermal effects. However, such observations in cultured cells cannot be directly transferred to organs or tissue such as the skin because neither thermoregulatory mechanisms nor the complexity and organization of the skin with its various cell types can be realistically reproduced in a simple cell model. In addition, the kind of thermal input into the cell cultures could also play a role and influence gene activity, for instance by differences in the dynamics of the temperature increase or the temperature gradient in the culture medium.

Genetic profile of brain tumors (gliomas) and heart tumors (schwannomas) in rats with lifetime radiofrequency electromagnetic field exposure (Brooks et al. 2023)

In the study by Brooks *et al.* (2024), genetic profiles of rare tumors such as gliomas and cardiac schwannomas were evaluated, which were already described in the Ramazzini study (see <u>newsletter</u> <u>15</u> and <u>special issue November 2018</u>). The aim of the current work was to analyze "mutation hot spots" in genes that are involved in the development of tumors in rats as well as those of humans. Genetic variants of these genes were also investigated. The researchers used 9-10 tumors as well as tumor-



free tissue of the corresponding organs, heart and brain. The occurrence of mutations was analyzed by sequencing the genome.

The results showed that gliomas in rats correspond to a stage referred to as "low grade" gliomas in humans. Mutations in the "hot spots" with homology to the associated genes in humans were not identified. In the positive controls (rats with chemical exposure), genetic alterations similar to a tumor type that occurs in humans were found. In the rat heart schwannomas, genetic changes, similar to a tumor type that occurs in humans, were obtained. However, no statements were made about differences between the genetic profiles of tumors from rats in the control group or rats exposed to RF-EMF. The data showed that sequencing of known genes involved in human carcinogenesis is an important tool to determine the translational relevance of tumors in experimental animals of such lifetime studies and thus to assess the applicability of the findings to human health.

Intestinal microbiota, neuronal cell death and anxiety-like behavior of mice exposed to 3.5 GHz radiofrequency electromagnetic fields (Zhou et al. 2024)

Zhou et al. (2024) investigated the possible relationship between effects of RF-EMF (3.5 GHz) on anxiety-like behavior and the gut microbiome ("gut-brain axis") in male mice (strain: C57BL/6J). The researchers were particularly interested in pyroptosis, a mechanism that is similar to apoptosis. Pyroptosis is an inflammatory form of cell death that also leads to the release of cytokines (cell messengers) that triggers inflammation. In neurological diseases such as, e.g., Alzheimer's disease, an inflammation of neurons occurs. The mice were exposed in a Plexiglas box to 3.5 GHz pulsed waves at 50 W/m², daily 1 hour for 35 days. The box was placed at a distance of 70 cm from the antenna. RF-EMF-exposed mice showed more anxiety-like behavior compared to control animals. This was linked to the occurrence of pyroptosis in the hippocampus, a region of the brain, which is dependent on the receptor NLR family pyrin domain containing 3 (NLRP3). NLRP3 is a component of the innate immune system and functions as a pattern recognition receptor recognizing pathogen-associated molecular patterns. The composition of the gut bacteria (microbiome) in mice exposed to RF-EMF was found to be markedly different from that of the control group. The differences mainly concerned the metabolic pathways glycerolphospholipide, tryptophan and other lipids. The protein gasdermin D (GSDMD), which plays an important role in the protection against pathogens and in danger signaling by initiating pyroptosis, was increased in the hippocampus of mice exposed to RF-EMF.

The authors speculate about a possible mechanism with regard to the gut-brain axis: RF-EMF exposure induces neuronal pyroptosis in the hippocampus and a change in the gut flora, which could lead to metabolic diseases. This is an interesting finding, but much more research is needed to be able to make conclusive statements in this respect.



2) Epidemiological studies

Mobile phone use, brain tumour risk and headache - a prospective cohort study (COSMOS) (Feychting et al. 2024a, Traini et al. 2024)

The ongoing multi-national COSMOS study is thus far the largest prospective study on lifetime history of mobile phone use and its possible health effects. Participants of the cohort were recruited between 2007 and 2012, and two publications with results from the first follow-up (conducted in the years 2015-2018) were published on associations with headache (Traini *et al.* 2024) and on brain tumors (Feychting *et al.* 2024a).

The headaches paper (Traini *et al.* 2024) assessed weekly frequency of 1) headaches and 2) severe headaches, 3) daily frequency of headaches and 4) diagnosis of migraine at follow-up in the Netherlands and the UK. Call-time on mobile and cordless phones was analyzed, classified in four categories ranging from "very low" (less than 19.1 min/week) to "high" (more than 107.8 min/week). Use of hands-free devices was taken into account. The analysis adjusted for important confounders such as education, general health, and sleep disturbance. The study found significant adverse associations for (severe) weekly headache and migraine diagnosis, but these associations disappeared when the authors additionally adjusted for the number of text messages sent. Number of text messages was considered as an indicator for phone use (screen time) with negligible RF-EMF exposure. Since associations with the number of text messages were generally more robust than those with call time, the authors conclude that other factors than RF-EMF are likely responsible for the increased perception of headaches among mobile phone users.

Accurate assessment of RF-EMF exposure from mobile phones is extremely difficult in large cohorts. This was also the case in this largest prospective study into the relationship between mobile phone use and headaches. The prospective nature of the exposure assessment is a strength, but the authors acknowledge that the dose ultimately depends heavily on device output power, device characteristics, type of use, position of the device relative to the body and personal characteristics, none of which can realistically be taken into account in such large cohorts.

The brain tumors paper (Feychting *et al.* 2024a) with median follow-up period of seven years reported 149 glioma, 89 meningioma and 29 acoustic neuroma cases among 264,574 persons in five countries (Denmark, Finland, the Netherlands, Sweden and the UK) representing a total of 1,836,479 person years. Similar to the headaches paper, exposure was considered as a categorized number of cumulative hours of call time, ranging from "low" (less than 464 hours, the median) to "high" (more than 1062 hours, \geq 75th percentile). The study used Cox regression models, a typical statistical method to study the potential relationship between exposure and the time until the cancer diagnosis (if occurring at all). Analyses were adjusted for country, sex, educational level and marital status to account for possible differences, and also considered that age is generally a prime risk factor for cancer risk. No associations were found between moderate or high mobile phone use and the incidence of any of the cancer types.



This finding aligns with earlier studies on smaller cohorts^{1,2,3}, and also with general observations that there has been no trend towards an increase in brain cancer diagnoses since mobile phones have become ubiquitous. Findings also broadly align with the "Interphone" study, although an effect was found there for the highest exposure category, for which the exposure was greatly overestimated. The Feychting study was criticized in a letter to the editor by Moskowitz et al. (2024). One criticism was that no "non-exposed" control group was included, which Feychting et al. (2024b) deemed unfeasible because non-exposed persons would hardly constitute a representative group, since virtually the entire population is exposed. Moskowitz et al. also asked for personal study data to be disclosed, which is not possible due to data protection regulations. Moskowitz et al. however also point out (and Feychting et al. recognize) that the brain cancer types investigated in this study are extremely rare, and the exposure assessment is - almost inevitably, and similar to the headaches study - surrounded by a large amount of uncertainty. It is therefore unlikely that a significant relationship would be found even if a correlation existed. The authors point out that this is the first follow-up within the ongoing COSMOS study, and that statistical power to detect a relationship if one exists would be higher in future follow-ups. In summary, the burden of disease for the population as a whole due to these tumors is extremely low, as relatively few persons are affected, and the fraction that could be attributable to RF-EMF exposure would likely be negligible, especially if compared to other cancer types and their relation to environmental factors.

3) Further information

EU report on health risks of EMF in the frequency range 1 Hz to 100 kHz

At the request from the EU, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) has prepared a report on the health risk of EMF in the frequency range 1 Hz to 100 kHz. Following the preliminary version's public consultation period from November 2023 to January 2024,⁴ the full report is now available.⁵

References

Brooks AM, Vornoli A, Kovi RC, Ton TVT, Xu M, Mashal A, Tibaldi E, Gnudi F, Li JL, Sills RC, Bucher JR, Mandrioli D, Belpoggi F, Pandiri AR. **Genetic profiling of rat gliomas and cardiac schwannomas from life-time radiofrequency radiation exposure study using a targeted next-generation sequencing gene panel.** PLoS One. 2024 Jan 17;19(1):e0296699. <u>https://doi.org/10.1371/journal.pone.0296699</u>

¹ Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schüz J. Use of mobile phones and risk of brain tumours: update of Danish cohort study. BMJ. 2011 Oct 19;343:d6387. <u>https://doi.org/10.1136/bmj.d6387</u>

² Schüz J, Steding-Jessen M, Hansen S, Stangerup SE, Cayé-Thomasen P, Poulsen AH, Olsen JH, Johansen C. Long-term mobile phone use and the risk of vestibular schwannoma: a Danish nationwide cohort study. Am J Epidemiol. 2011 Aug 15;174(4):416-22. <u>https://doi.org/10.1093/aje/kwr112</u>

³ Schüz J, Pirie K, Reeves GK, Floud S, Beral V; Million Women Study Collaborators. Cellular Telephone Use and the Risk of Brain Tumors: Update of the UK Million Women Study. J Natl Cancer Inst. 2022 May 9;114(5):704-711. https://doi.org/10.1093/jnci/djac042

⁴ <u>https://health.ec.europa.eu/consultations/scheer-public-consultation-preliminary-opinion-potential-health-effects-exposure-electromagnetic_en</u>

⁵ SCHEER (2024): Potential health effects of exposure to electromagnetic fields (EMF): Update with regard to frequencies between 1 Hz and 100 kHz – final opinion. Scientific Committee on Health, Environmental and Emerging Risks. <u>https://health.ec.europa.eu/document/download/85ef39d5-49dc-4b5a-b875-</u> <u>54e578d1d2bc en?filename=scheer o 063.pdf</u>



Feychting M, Schüz J, Toledano MB, Vermeulen R, Auvinen A, Harbo Poulsen A, Deltour I, Smith RB, Heller J, Kromhout H, Huss A, Johansen C, Tettamanti G, Elliott P. **Mobile phone use and brain tumour risk - COSMOS, a prospective cohort study.** Environ Int. 2024a Mar;185:108552. Epub 2024 Mar 2. <u>https://doi.org/10.1016/j.envint.2024.108552</u>

Feychting M, Schüz J, Toledano MB, Vermeulen R, Auvinen A, Harbo Poulsen A, Deltour I, Smith RB, Heller J, Kromhout H, Huss A, Johansen C, Tettamanti G, Elliott P. **Response to the letter to the editor regarding "Mobile phone use and brain tumour risk - COSMOS, a prospective cohort study"**. Environ Int. 2024b Jul;189:108808. Epub 2024 Jun 8. <u>https://doi.org/10.1016/j.envint.2024.108808</u>

Martin C, Evrard B, Percevault F, Ryder K, Darde T, Lardenois A, Zhadobov M, Sauleau R, Chalmel F, Le Dréan Y, Habauzit D. **Transcriptional landscape of human keratinocyte models exposed to 60-GHz millimeter-waves.** Toxicol In Vitro. 2024 May;97:105808. Epub 2024 Mar 12. <u>https://doi.org/10.1016/j.tiv.2024.105808</u>

Moskowitz JM, Frank JW, Melnick RL, Hardell L, Belyaev I, Héroux P, Kelley E, Lai H, Maisch D, Mallery-Blythe E, Philips A; International Commission on the Biological Effects of Electromagnetic Fields. **COSMOS: A methodologically-flawed cohort study of the health effects from exposure to radiofrequency radiation from mobile phone use.** Environ Int. 2024 Aug;190:108807. Epub 2024 Jun 21. <u>https://doi.org/10.1016/j.envint.2024.108807</u>

Traini E, Smith RB, Vermeulen R, Kromhout H, Schüz J, Feychting M, Auvinen A, Poulsen AH, Deltour I, Muller DC, Heller J, Tettamanti G, Elliott P, Huss A, Toledano MB. **Headache in the international cohort study of mobile phone use and health (COSMOS) in the Netherlands and the United Kingdom.** Environ Res. 2024 Jan 25;248:118290. <u>https://doi.org/10.1016/j.envres.2024.118290</u>

Zhou GQ, Wang X, Gao P, Qin TZ, Guo L, Zhang ZW, Huang ZF, Lin JJ, Jing YT, Wang HN, Wang CP, Ding GR. Intestinal microbiota via NLRP3 inflammasome dependent neuronal pyroptosis mediates anxiety-like behaviour in mice exposed to 3.5 GHz radiofrequency radiation. Sci Total Environ. 2024 Jun 1;927:172391. Epub 2024 Apr 10. https://doi.org/10.1016/j.scitotenv.2024.172391

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



The Swiss expert group on electromagnetic fields and non-ionising radiation – BERENIS Newsletter Nr. 39 / December 2024

BERENIS newsletter search tool

List of abbreviations (pdf)