Summaries and assessments of selected studies

In the period from mid of April 2022 to mid of July 2022, 128 new publications have been identified, and four of these were discussed in depth by BERENIS. Based on the selection criteria, two of these publications were selected as the most relevant ones. Their summaries and assessments are provided below.

1) Experimental animal and cell studies

An international collaboration on carcinogenicity of radiofrequency electromagnetic field in experimental animals (partial replication of the NTP study in rats): introducing the project design (Ahn et al. *2022)*

In 2019, a partial replication of the NTP study (see special issue November 2018) was started in Asia, investigating effects of CDMA[1] (900 MHz) RF-EMF on carcinogenesis in experimental animals (rats), especially brain tumours (glioma) and cardiac schwannoma, as well as genotoxicity. The project will run for a total of five years, and the animal studies will be conducted in Japan as well as in South Korea. The authors stress the importance of identical exposure and environmental conditions of the animals to the NTP study. The exposure system was newly built and is therefore not identical to the one used in the NTP study. The number of animals is 70 per exposure group (sham, exposed, cage control) and per country, while in the NTP study there were 90 animals per group. The dosimetry accounts for the weight of the animals and the weight gain over the entire course of the study. Variations in the positioning of the animals as well as the weight influence the exposure and SAR values. However, it is reasonable to assume that the variability is approximately the same within all groups (RF-EMF- and sham-exposed animals). Another difference to the NTP study is the dose regime, namely, in the planned study only one exposure level (4 W/kg whole-body SAR) will be used, whereas the NTP study used three exposure levels (1.5, 3 and 6 W/kg SAR). Therefore, dose-response cannot be evaluated in the Asian study. The significant increase in malignant heart schwannoma as well as glioma in the brain, found in the NTP study at the highest exposure of 6 W/kg (whole-body SAR), cannot be followed up on in this study. Furthermore, the male rats used in the study originate from a different breeder, which means that the strain, the substrain and thus the genetic material of the animals is also not identical to that used in the NTP study. In the new study, only sham-exposed animals are used as controls. Historical controls are not included, probably because they are not available in the laboratories. In this context, it should be noted that sham controls are more relevant than historical controls which are predominantly used for rare tumors. However, in the case of an increased incidence of generally rare tumors such as heart schwannoma, historical controls can be beneficial, as these allow assessing the respective tumour incidence over several years in the rat strain and substrain, provided that the data were obtained in the same laboratory and over a time period of about five years. In practical terms, this means that in the case of an increase in such a tumour type, it is difficult to assess whether the effect is due to RF-EMF exposure.

Overall, there are differences between the NTP and the Asian replication study, although an exact replication of such animal experiments is virtually not feasible. A number of important parameters will complicate a comparative assessment of the results of the two studies, in particular the exposure at 4 W/kg (whole-body SAR), which is below the exposure level in which significant effects were found in

[1] CDMA = Code Division Multiple Access

the NTP study, namely for the incidence of schwannoma and glioma. In addition, the lack of a dose-response analysis, historical controls, and different origins and genetic disposition of the rats may prevent a direct comparison of the studies.

The influence of millimeter waves on gene activity and the secondary structure of DNA (Lawler et al. *2022)*

Non-thermal effects of RF-EMF in the range of millimeter waves (MMW) on biological systems have been sparsely studied so far. In order to identify possible biological effects of a 60 GHz RF-EMF, Lawler and colleagues (2022) conducted an *in vitro* study assessing genome-wide gene expression in human primary fibroblasts. A newly developed exposure system based on a beam continuously exposed cells in phases to minimise thermal effects. The power density of 2.6 mW/cm^2 was above the limit values (2 mW/cm^2 for 6 min and 1 mW/cm^2 for 30 min), and daily doses of 46.8 J/cm^2 were administered in a time window of 5 hours during 4 days.

The authors reported that the gene expression of about 250 genes was altered after MMW exposure. The cell response after exposure differed significantly from known expression changes caused by thermal and cytokine-induced (TGFβ) treatments and was also less pronounced. In addition, an increase in expression of genes involved in collagen production and the formation of extracellular collagen fibers was observed, which was confirmed in further investigations using immunofluorescence. Also, changes in the activity of genes that play a role in replication and in the structure of DNA and chromatin were frequently found. These structural changes are known to influence gene expression and could therefore be a possible cause of the effects. The authors indeed showed a reduction of secondary DNA structures (class G4 and iMotif) in exposed cells, which are enriched in the genes with altered activity. However, this is a correlation and the underlying biological mechanism remains unknown. Moreover, no evidence of DNA damage was found (detection of DNA double-strand breaks by immunofluorescence for γH2AX).

Due to the patchy nature of available data on the effect of MMW, the observations of Lawler *et al.* (2022) based on a hypothesis-free study design are difficult to contextualise but offer helpful starting points for further investigations. Furthermore, it should be noted that additional stress factors may have modulated the cellular responses. One needs to note that the exposure was carried out under non-physiological conditions (reduced proportion of serum, and outside the incubator), which is likely to alter the normal cellular response.

2) Information about other publications: Reviews

Report on the effects of non-ionising radiation on arthropods (Mulot et al. *2022)*

The Swiss Federal Office for the Environment (FOEN) has commissioned a review report on the effects of non-ionising radiation on arthropods, such as insects, which was prepared by the University of Neuchâtel. For this purpose, 127 studies were evaluated. The report has been now been published in both German and French on the FOEN website.[2]

[2] German: https://www.bafu.admin.ch/dam/bafu/de/dokumente/elektrosmog/externe-studien-berichte/wirkung-von-nichtionisierender-strahlung-auf-arthropoden.pdf.download.pdf/Auswirkungen_nichtionisierender_Strahlung_auf_Arthropoden.pdf,
French: https://www.bafu.admin.ch/dam/bafu/fr/dokumente/elektrosmog/externe-studien-berichte/wirkung-von-nichtionisierender-strahlung-auf-arthropoden.pdf.download.pdf/Effets_des_rayonnements_non_ionisants_sur_les_arthropodes.pdf

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Lawler NB, Evans CW, Romanenko S, Chaudhari N, Fear M, Wood F, Smith NM, Wallace VP, Swaminathan Iyer K (2022): **Millimeter waves alter DNA secondary structures and modulate the transcriptome in human fibroblasts.** Biomed Opt Express. 2022 Apr 28;13(5):3131-3144. https://pubmed.ncbi.nlm.nih.gov/35774325/

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

List of abbreviations (pdf)