Bundesamt
für Strahlenschutz

Spotlight on EMF Research

Spotlight on “In Vivo Studies on Radiofrequency (100 kHz–300 GHz) Electromagnetic Field Exposure and Cancer: A Systematic Review” by Pinto et al. in International Journal of Environmental Research and Public Health (2023)

Category [radiofrequency, animal study]

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Competence Centre Electromagnetic Fields (KEMF)

1 Putting the paper into context by the BfS

The growing number of sources that emit radiofrequency electromagnetic fields (RF-EMF) has raised concern about its possible health effects. Extensive experimental and observational studies on the effects of EMF exposure on various biological endpoints have been conducted. To date, there is no substantiated scientific evidence for adverse health effects caused by RF-EMF. However, in 2011 the International Agency for Research on Cancer (IARC) classified RF-EMF as “possibly carcinogenic to humans”. This category is used for agents, mixtures and exposure circumstances for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals [2]. Investigations of RF-EMF exposure in animal models have analyzed its impact on the onset and disease relevant features of tumors. The often contradictory results point to the necessity of an overall assessment of the carcinogenic risk of RF-EMF. Systematic reviews such as the present paper are considered the gold standard for evaluating the scientific evidence for any effect of an environmental risk factor on a particular endpoint.

2 Results and conclusions from the authors‘ perspective

The authors conducted a systematic review to provide an update of the current scientific knowledge on the link between RF-EMF and cancer in experimental animal studies. The systematic reviewonly includes studies that investigated carcinogenesis. Studies on co-carcinogenesis will be dealt in another article. They quantitatively analyzed all relevant peer reviewed scientific papers to identify any relative change in tumor

incidence in RF-EMF exposed laboratory rodents. All criteria for eligible papers, the review design and analysis procedures were described in a published protocol beforehand [3]. SR

All studies were evaluated according to the risk of bias (RoB) and quality of evidence (NTP OHAT) criteria [4], and assigned to high, moderate or low quality [5].

From a total of 294 articles, 27 were included in the systematic review and 23 were included in the meta-analysis. Based on the RoB assessment, the studies were of overall good quality, with 16 studies being of high, nine studies of moderate and only two studies of low quality.

Most risk estimates from the meta-analysis were not statistically significant (n = 34 out of a total of n = 41 results), except for

- malignant tumors: in the central nervous system (CNS, increased risk), brain (increased risk), heart (increased risk) and intestine (decreased risk)
- benign tumors: CNS/brain (increased risk), male urogenital system (decreased risk) and kidney (decreased risk).

According to the authors, it was not possible to analyse the tumor incidence of all organs in relation to RF-EMF exposure, as only a few studies performed a comprehensive tissue pathology. In the subgroup analyses, no statistically significant differences in terms of risk estimates were found for animals with different genetic backgrounds. In contrast, when species (mice, rats) were included as a covariate, differences for malignant breast and spleen, as well as for benign tumors of the skin were statistically significant.

According to the authors, the results of the regression analyses do not provide useful information to define dose-effect or exposure duration relationships for the incidence of any of the analysed tumors. This can be attributed to a large variability of exposure duration in the included studies. Overall, there was no high or very high certainty in the evidence for an increased risk for malignant or benign tumors for any organ. For the statistically significant results observed in CNS, brain, heart and intestine, the quality of the evidence was low to very low. For the statistically significant results observed for benign tumors, the quality of evidence was moderate to very low.

The authors conclude that the overall low confidence ratings result in an inadequate or insufficient evidence for a definitive assessment of an association between RF-EMF exposure and carcinogenesis. Nonetheless, this systematic review updates the state-of-the-art research on in vivo RF-EMF experiments related to carcinogenesis. The insufficient health evidence does not warrant additional recommendations to current regulatory frameworks of radiation protection. Future studies with appropriate experimental design are needed.

3 Comments by the BfS

This systematic review summarizes and evaluates the available body of evidence concerning an association between RF-EMF exposure and cancer onset in animal studies. This is important from a radiation protection point of view and remains of interest to the general public.

The study was performed according to the high-quality standards for systematic reviews [6] with a pre-published protocol [3]. The authors provide detailed information on their study design, eligibility criteria and data extraction, as well as criteria for quality assessment. The eligibility criteria of this systematic review were not overly stringent in terms of animal populations and exposure conditions, with a wide range of exposure durations and specific absorption rate (SAR) values included. The RoB assessment graded the studies as being of good quality, although the reasoning behind individual RoB decisions lacks transparency. For a detailed description of the data analysis strategy, the authors refer to a book and

several articles which might not be readily available to everyone. For the purpose of transparency, a more detailed explanation in the systematic review itself would have been desirable.

In the main analysis, exposure was only considered as a binary factor (i.e., sham-exposed or exposed), because exposure duration and intensity were very heterogenous between studies. Nonetheless, the calculated risk estimates for each organ system are remarkably consistent and show no statistic heterogeneity (I2) within the individual meta analyses. However, most analyses provide wide confidence intervals of the risk estimates due to the low number of cases per individual result, so the robustness of the conclusion is limited. The main analysis has one serious limitation: from 23 included studies, just 10 studies contributed 44 out of a total of 61 sham vs. exposed comparisons. In those cases, only one or two animal groups served as controls for multiple exposed groups. Therefore, for the meta-analyses, the authors resorted to using some control groups repeatedly to calculate the exposure contrasts for several differently exposed experimental groups, leading to a “sham-shared bias”. Due to underestimation of the uncertainty of the results from controls, the shared-sham bias can lead to correlations and dependencies within the data and thus lead to unreliable estimates. For example: the observed significant effect on malignant tumours of the brain stems from 26 sham vs. exposed comparisons, with 23 of these derived from shared control groups. The authors stated that after exclusion of the NTP study [7], which contributed one control and six exposed groups, the risk estimate for brain tumours decreased and lost its significance. To address the insufficient study design of many of the included studies, the authors downgraded the quality of the evidence. Alternatively, to avoid the repeated use of shared control groups, the authors could have either split the sham-exposed groups into as many subgroups as there were matched exposed groups, or perform data aggregation, using only the largest exposure contrast per study. However, both of these strategies would have resulted in reduced sample sizes for many studies.

Overall, this systematic review provides a comprehensive and mostly transparent analysis of the current evidence for an association between RF-EMF exposure and cancer onset in experimental animal studies. From a radiation protection point of view, serious limitations in the quantitative analysis due to the low quality of the study design of the included studies, prevent a reliable conclusion for an association between RF-EMF exposure and cancer onset. Based on the low quality of the evidence, further research that meets high quality standards is needed.

References

[1] Pinto R, Ardoino L, Villani P, Marino C. **In Vivo Studies on Radiofrequency (100 kHz–300 GHz) Electromagnetic Field Exposure and Cancer: A Systematic Review**. *International Journal of Environmental Research and Public Health*. 2023;20(3):2071. https://doi.org/10.3390/ijerph20032071.

[2] International Agency for Research on Cancer (IARC). **Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans**. Lyon: IARC, 2006. https://monographs.iarc.who.int/wp-content/uploads/2018/06/CurrentPreamble.pdf.

[3] Pinto R, Ardoino L, Giardullo P, Villani P, Marino C. **Protocol for a systematic review of the in vivo studies on radiofrequency (100 kHz-300 GHz) electromagnetic field exposure and cancer**. *Syst Rev*. 2022;11:29. https://doi.org/10.1186/s13643-022-01898-4.

[4] National Toxicology Program (NTP), Office of Health Assessment and Translation (OHAT). **OHAT Risk of Bias Rating Tool for Human and Animal Studies**. 2015. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf.

[5] Balshem H, Helfand M, Schunemann HJ, et al. **GRADE guidelines: 3. Rating the quality of evidence**. *J Clin Epidemiol*. 2011;64(4):401-406. https://doi.org/10.1016/j.jclinepi.2010.07.015.

[6] National Toxicology Program (NTP), Office of Health Assessment and Translation (OHAT). **Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Intergration**. 2019. https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pubs/handbookmarch2019_508.pdf.

[7] Bundesamt für Strahlenschutz. **Long-term study in mice and rats at whole body exposure to cell phone radio frequency radiation (NTP study)**. https://www.bfs.de/EN/bfs/science-research/emf/statements/ntp-study/dossier-ntp-study.html.

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