Bundesamt
für Strahlenschutz

Spotlight on EMF Research

Spotlight on “A systematic review on the in vivo studies on radiofrequency (100 kHz-300 GHz) electromagnetic field exposure and co-carcinogenesis” by Pinto et al. in International Journal of Environmental Research and Public Health (2024)

Category [radiofrequency, review]

Spotlight - Sep/2025 no.1 (Eng)

Competence Centre for Electromagnetic Fields (KEMF)

1 Putting the paper into context by the BfS

The International Agency for Research on Cancer (IARC) classified radiofrequency electromagnetic fields (RF-EMF) as possibly carcinogenic in the year 2011. Since then, new studies have been conducted to elucidate the carcinogenic potential of RF-EMF. The current scientific state of knowledge is being summarised and assessed in systematic reviews coordinated by the World Health Organization (WHO) (see also Spotlight – Apr/2024 no.2 [2]). However, independent of the process coordinated by WHO, also other research groups are conducting systematic reviews on possible effects of RF-EMF exposure. For instance, Pinto et al. [3] recently published a systematic review on animal experimental studies. Their results provide low or inadequate evidence for an association between RF-EMF and cancer (see also Spotlight – Feb/2024 no.1 [4]). However, instead of being directly carcinogenic, RF-EMF could, in principle, also have a co-carcinogenic effect. This means that RF-EMF could intensify the effect of a known carcinogenic agent without being carcinogenic themselves. This can be investigated in co-exposure studies, where animals are exposed to both, RF-EMF and a carcinogenic agent.

2 Results and conclusions from the perspective of Pinto et al.

In this systematic review, the co-carcinogenic effect of RF-EMF exposure was assessed in experimental animal studies (mice and rats). The protocol, including all the criteria for eligible papers, the review design and analysis procedures, is part of the published comprehensive protocol [5] including also the criteria for the systematic review on the carcinogenic potential of RF-EMF [3], which was published by the same authors.

The risk of bias (RoB) was assessed for each eligible study following the criteria provided by the Office of Health Assessment and Translation (OHAT) [6]. Based on the RoB evaluation, each paper was assigned into one of three quality categories, i.e., “low quality”, “intermediate quality”, or “high quality”. The quality of the body of evidence was assessed for each tumour outcome following the guidelines set by OHAT and the WHO Handbook for Guideline Development [7], drawing on the guidance provided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. The final assessment of the level of evidence for health effects, i.e., the confidence in the association between RF-EMF co-exposure and an observed effect, followed the same guidelines.

From a total of 294 articles, 25 were included in the systematic review on co-carcinogenesis and 18 were included in the meta-analyses. Based on the RoB assessment, the studies were of overall good quality, with ten studies being of high, ten studies of moderate and only five studies of low quality.

In the meta-analyses, it was examined whether combined exposure to RF-EMF and a carcinogen increases the risk of tumour onset compared to exposure to a carcinogen along with a sham exposure to RF-EMF. This was represented in the form of the relative risk (RR). The results are summarised in Table 1. For example, in animals exposed to both a carcinogen and RF-EMF, a statistically significant 2.34-fold increase in the occurrence of malignant kidney tumours was observed, compared to animals exposed to the carcinogen with only sham exposure to RF-EMF.

In the subsequent subgroup-analyses, it was investigated whether the use of a specific carcinogen or of a particular animal species influences the relative risk of tumour onset. No statistically significant effects were observed that would suggest that the carcinogen or animal species played a role. Additionally, it was examined whether there was a relationship between the exposure level (dose) of RF-EMF and tumour onset. However, this analysis was conducted only for studies on brain cancer, where animals were treated with the carcinogen ethylnitrosurea (ENU, 9 papers), and for studies on breast cancer, where animals were treated with the carcinogen dimethylbenz(a)anthracene (DMBA, 4 papers). The results did not provide useful elements to define a dose-effect relationship, neither for brain nor breast cancer.

In the survival analysis, the data on the number of animals that were still alive at the end of the experimental period was processed. This means that it was examined, whether fewer or more animals were alive at the end of the study under combined exposure to RF-EMF and a carcinogen compared to exposure to a carci-

nogen along with a sham exposure to RF-EMF. The results of this meta-analysis indicate that there was no statistically significant difference in survival between the two differently exposed groups (12 papers, RR = 0.98, CI 95% = 0.96 — 1.01), independent of the used carcinogen.

Due to a low number of papers reporting on latency (the time elapsed between exposure and the onset of tumours) and because of the different metrics used to report latency, a meta-analysis was not possible. In five papers reporting on breast or brain tumours, no statistically significant differences in latency between groups that were sham-exposed to RF-EMF and treated with a carcinogen and those exposed to both, RF-EMF and a carcinogen, were reported. The two papers investigating latency in skin cancer reported a statistically significant acceleration of tumour growth in the groups exposed to a carcinogen along with RF-EMF exposure. However, both papers had very low quality.

Besides, the authors note that most co-carcinogenesis studies focused on chemical agents, while physical agents, like ultraviolet radiation (UV), were only scarcely investigated.

The authors conclude that the observed association between a combined exposure to RF-EMF and a carcinogen and the onset of kidney, liver and lung tumours cannot be considered definitively conclusive. The reasons they cite are the limited number of papers and individual comparisons of treated and sham-exposed animals within these papers, and the diversity of carcinogenic agents used. The same is concluded for benign skin cancers, where the meta-analysis resulted in no evidence for a health effect.

Tumour outcome	No. of studies per carcinogen	Relative risk [95% CI]	Quality of evidence	Health evidence
Kidney tumours (malignant)	2xENU, 1xMX, 1xRX	2.34 [1.35 — 4.03]	Moderate	Moderate for a health effect
Liver tumours (malignant)	2xENU, 1xMX, 1xRX	1.39 [1.08 — 1.8]	Moderate	Moderate for a health effect
Lung tumours (benign)	2xENU, 1xMX, 1xRX	1.65 [1.35 — 2.02]	Moderate	Moderate for a health effect
Skin tumours (benign)	1xUV, 1xMX, 1xRX	0.64 [0.39 — 1.05]	High	Evidence for no health effect
All other tumours (benign & malignant)	9xENU, 7xDMBA, 1xDMBA+TPA, 1xRX, 1xUV, 1xMX, 2xBaP, 1xDMH, 2xDEN	0.54 — 1.3 [0.12 — 2.81]	Low to moderate	Inadequate

Abbreviations: RR = Risk Ratio, CI = Confidence Interval, ENU = Ethylnitrosurea, DMBA = Dimethylbenz(a)anthracene, RX = X-Rays, UV = Ultraviolet Radiation, MX = 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone, TPA = Tetradecanoyl phorbol acetate, BaP = Benzo[a]pyrene, DMH = Dimethylhydrazine.

Table 1: Summary of the results of the meta-analysis regarding the incidence of tumours after combined exposure to RF-EMF and a carcinogen, as well as the quality of the body of evidence and the level of evidence for health effects.

3 Comments by the BfS

The human population is typically exposed to a mixture of different environmental factors, including known carcinogens like UV radiation. Therefore, it is important to investigate whether RF-EMF exposure could intensify the effect of such carcinogenic agents. Pinto et al. present the first systematic review on this relevant topic.

Although the authors published a protocol for the systematic review and followed established guidelines, the transparency of the process could still be improved in a few points. This applies in particular to the RoB assessment because the authors do not provide any content explaining the reasons for each study's RoB evaluation. That is why for some studies the given RoB evaluation is not entirely comprehensible. For example, the results of Tillmann et al. 2010 were included although the study lacks a combined sham-exposed and carcinogen-treated control group. Furthermore, in the same study, all results on liver were excluded from

interpretation by the authors of the study themselves, because of a helicobacter infection of the mice which could potentially have influenced liver tumorigenesis. Pinto et al. rated the study as a study of “intermediate quality”, but it is unclear whether these limitations have been taken into account, because downgrade was only applied for “evaluation of the experimental protocol”. In the publications by Heikkinen et al. 2001 and Heikkinen et al. 2006 there is no mentioning of blinding during the exposure phase, but this limitation was not considered in the RoB assessment.

Following the GRADE approach, there was a moderate evidence for an enhancement of the carcinogenic effect by RF-EMF regarding the onset of liver, lung and kidney tumours. However, the whole evidence is based on only four studies, and in case of kidney tumours, on very few tumour bearing animals in all studies. Both limitations lower the precision of the results. For the assessment of the quality of the body of evidence, the authors stated that they would downgrade the evidence for imprecision when most of the studies show imprecise ratio measures. In particular, they would downgrade if the ratio of the upper to lower 95% confidence interval (CI) is ≥ 10 for most studies. This is the case for all studies on malignant kidney tumours and, in case of lung and liver, for the two studies by Heikkinen et al. However, downgrade for imprecision was not applied.

Therefore, from the perspective of the BfS, the conclusion of a moderate evidence for the onset of malignant liver and kidney tumours, as well as benign lung tumours following combined exposure to RF-EMF and a carcinogen is not entirely comprehensible. In fact, the authors themselves noted that the limited number of eligible papers and individual treated-sham-comparisons, as well as the use of different carcinogens would not establish a robust foundation for assessing a moderate level of evidence for health effects for all three tumour types.

Overall, this work contributes to an important area that is highly relevant in the context of radiation protection and public health. Several methodological questions remain open, particularly regarding the risk of bias (RoB) assessment. Nevertheless, the BfS is pursuing indications of a possible increased cancer risk following combined exposure to RF-EMF and a carcinogen by allocating further research projects.

References

[1] Pinto, R, Ardoino, L, Giardullo, P, Villani, P, Marino, C. A systematic review on the in vivo studies on radiofrequency (100 kHz-300 GHz) electromagnetic field exposure and co-carcinogenesis. *International Journal of Environmental Research and Public Health*. 2024; 21(8):1020.
DOI: https://doi.org/10.3390/ijerph21081020.

[2] Kompetenzzentrum Elektromagnetische Felder (KEMF), Bundesamt für Strahlenschutz (BfS). Spotlight on "WHO assessment of health effects of exposure to radiofrequency electromagnetic fields: systematic reviews", eine Sonderreihe in Environment International. *Spotlight on EMF Research*; Spotlight - Apr/2024 no.2.
URL: https://nbn-resolving.org/urn:nbn:de:0221-2024042443254.

[3] 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.
DOI: https://doi.org/10.3390/ijerph20032071.

[4] Kompetenzzentrum Elektromagnetische Felder (KEMF), Bundesamt für Strahlenschutz (BfS). 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). *Spotlight on EMF Research*; Spotlight - Feb/2024 no.1.
URL: https://nbn-resolving.org/urn:nbn:de:0221-2024021441649.

[5] 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. *Systematic Reviews*. 2022; 11:29.
DOI: https://doi.org/10.1186/s13643-022-01898-4.

[6] National Toxicology Program (NTP). *Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration*. National Institute of Environmental Health Sciences, 2019.
URL: https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pubs/handbookmarch2019_508.pdf.

[7] World Health Organisation (WHO). *WHO handbook for guideline development*. 2nd ed. Geneva, 2014.
URL: https://www.who.int/publications/guidelines/handbook_2nd_ed.pdf.

Impressum
Bundesamt für Strahlenschutz
Postfach 10 01 49
38201 Salzgitter

www.bfs.de

Tel.: +49 30 18333-0
Fax: +49 30 18333-1885
E-Mail: spotlight@bfs.de

Please always use the following URN when citing this document:
urn:nbn:de:0221-2025090854656

Spotlight - Sep/2025 no.1 (Eng)