Bundesamt
für Strahlenschutz

Spotlight on EMF Research

Spotlight on “Effects of radiofrequency electromagnetic field exposure on cancer in laboratory animal studies : A systematic review” by Mevissen et al. in Environment International (2025)

Category [radiofrequency, review]

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Competence Centre for Electromagnetic Fields (KEMF)

1 Putting the paper into context by the BfS

It has long been hypothesized that radiofrequency electromagnetic fields (RF-EMF) are carcinogenic, i.e. have the potential to induce cancer. After the International Agency for Research on Cancer (IARC) classified RF-EMF as possibly carcinogenic to humans in 2011, new studies have investigated their carcinogenic potential in humans and animals. In 2019, the World Health Organization (WHO) launched an international project to systematically review the evidence for or against a possible link between exposure to RF-EMF and adverse health effects (see also Spotlight - Apr/2024 no.2 [2]). Two WHO-commissioned systematic reviews on possible associations between exposure to RF-EMF and cancer in observational studies have recently been published [3, 4]. The systematic review at hand by Mevissen et al. [1], also part of the WHO project, focusses on the evidence for cancer from animal experiments.

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

The objectives of the systematic review by Mevissen et al. were to evaluate whether exposure to RF-EMF increases the risk of cancer in experimental animal studies and to identify potential exposure-response and/or time-dependent relationships between the exposure and the outcome. Studies conducted on mice and rats exposed to RF-EMF in the frequency range 100 kHz to 300 GHz were eligible for inclusion.

The authors considered long-term carcinogenicity studies, initiation-(co-)promotion studies, studies on tumour-prone animals and studies in which cancer cells were implanted into animals prior to exposure. All studies were evaluated for potential risk of bias (RoB) and for factors that limit study sensitivity, i.e. the ability to detect a true effect. RoB assessment was conducted using the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) tool [5]. Study sensitivity was assessed using methods utilized by the NTP Report on Carcinogens [6].

Of a total of 4,350 publications, 52 were deemed eligible and included in the systematic review. Seven studies were rated as probably high RoB and 45 studies as definitely or probably low RoB. Regarding sensitivity, six studies were judged to have major or critical sensitivity concerns.

For analysis, the studies were grouped according to the organ system. If, for a specific organ system, at least one study reported a statistically significant harmful effect or if there was a statistically significant trend in the RF-EMF exposed groups compared to the control group, the authors of the systematic review assessed that there was an effect of the exposure, regardless of null results in other studies. For organ systems for which no study reported an increase in cancer-related outcomes, a brief description of the evidence was provided.

To assess the certainty of the evidence, the authors followed the approach of the “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) working group and the systematic review methodology developed by NTP for use in developing non-cancer and cancer assessments of environmental agents [5, 6, 7]. The authors noted that also other methods were used, when the application of the GRADE framework was unclear. Based on the OHAT handbook, they initially assigned a high certainty of evidence, which could then be downgraded if the authors identified factors that decrease the certainty in the evidence.

No or minimal evidence of RF-EMF exposure-related effects was detected for most cancer outcomes, more specifically in gastrointestinal/digestive, urinary, endocrine, musculoskeletal, reproductive, and auditory systems, as well as in kidney and mammary gland.

For each of the organ systems liver, lung, lymphatic system (focusing on the outcome lymphoma), adrenal gland, heart, and brain, at least one study reported a harmful effect of RF-EMF exposure. Therefore, the available data on those organ systems were fully assessed in the systematic review. The results are summarized in Table 1. No meta-analyses were conducted due to heterogeneity in study design, species, strain, sex, exposure characteristics, and cancer outcome.

The authors conclude that their findings indicate evidence that RF-EMF exposure increases the incidence of cancer in experimental animals, with the certainty of evidence being strongest for heart (malignant heart schwannomas) and brain tumours (gliomas). They further state that, despite the high level of certainty that evidence of carcinogenicity in experimental animals may predict a carcinogenic hazard to humans, extrapolation of risk from cancer bioassays to humans is particularly complex for RF-EMF. They note that malignant heart schwannomas and gliomas found in rodents are the same as those identified with limited evidence in humans by the International Agency for Research on Cancer (IARC) in 2013.

3 Comments by the BfS

Mevissen et al. provide an extensive systematic review on the effects of RF-EMF exposure on cancer incidence in experimental animal studies, a topic of high relevance for radiation protection. They included all relevant studies we are aware of and are mostly transparent in describing how they reached their conclusions. However, the approach used by Mevissen et al. raises some questions, which are addressed below.

Consistency across studies: An important criterion when assessing the strength of evidence is consistency across multiple studies. This is in contrast to the approach of Mevissen et al.: They judge that there is a harmful effect of RF-EMF exposure for any organ system or tumour type as long as there is at least one study or experiment that reports statistically significant increases or trends in tumour rates. This judgement remains regardless of null results in other studies with high sensitivity and quality. The weakness of such an approach is illustrated by the endpoint liver, where RF-EMF was classified has having a moderate certainty of evidence for carcinogenicity, with hepatoblastoma being the most informative outcome for this conclusion. However, only one of five chronic bioassays and none of the 11 studies of the other study types, all with sufficient quality and sensitivity, reported statistically significant increases of hepatoblastoma. Regarding other liver tumour types, three studies reported adverse effects, while three studies reported beneficial effects (i.e. a decrease of incidence). For most other endpoints for which at least one study or experiment showed a statistically significant adverse effect, the majority of the included studies did not report effects. Therefore, not all the available information has been considered by the authors when integrating the evidence, although a systematic review of the literature should take all relevant evidence into consideration.

Multiple testing: Besides neglecting information that comes from other studies, the chosen approach suffers from incorporating a multiple testing problem directly into the conclusions of the review, because the probability that at least one study or experiment randomly shows a statistically significant effect increases with the number of studies/experiments and outcomes included. This approach therefore enhances the chance that the conclusion of the review is impacted by false positive findings.

Assessing RoB: As a result, the conclusions for all cancer outcomes are mainly driven by the findings of three of the few studies reporting effects: the two NTP studies on mice and rats and the study by Falcioni et al. [8, 9, 10]. Those studies were rated by the authors as having definitively or probably low RoB in most domains and not having sensitivity concerns. This rating can be challenged, because both NTP studies and the Falcioni study have limitations in the study design [11, 12, 13, 14]. In this context, it is noticeable that for their risk of bias assessment, Mevissen et al. appear to have applied the rigour of the RoB criteria inconsistently across various studies without providing a clear rationale for a different weighting. For example, no reporting of blinding during exposure phase was rated as probably high RoB in 23 studies, but not, e.g. in the NTP or Falcioni studies, where a blinding was also not mentioned in the report.

Historical control data: The use of historical control data instead of original data in the statistical reanalysis of specific tumour results also raises questions. The authors stated in the protocol [15] that they will use historical controls as comparators for rare tumours ($\leq$ 1–3%) or when the incidence in concurrent controls is abnormal. However, neither in the published systematic review nor in the protocol it is specified why and how exactly historical control data is used to replace the originally published control group data and what statistical approach is applied. Mevissen et al. explicitly use historical controls only once: as the reference group for reanalysing the data by Anderson et al. [16]. They calculated a statistically significant positive trend for oligodendroglioma, a brain tumour. However, it is unclear which historical controls were used and how

many animals and cases the historical controls represented. This is problematic, since Mevissen et al. base their conclusion of high certainty of evidence for an increased risk of gliomas on this reanalysis of the Anderson et al. study. However, the protocol's criteria for using historical control data as comparator appears to be met also for the lymphoma data. Nevertheless, Mevissen et al. did not reanalyse the data for lymphoma risk and did not offer any explanation for this decision. They only mention that the incidence of malignant lymphoma in the sham exposed animals (2%) of the NTP mouse study [11] was significantly lower compared to the respective historic controls (mean 16%, range 10–36%). Here, the historical control data might have been informative, since the incidences of lymphoma in all RF-EMF exposed groups in the NTP study were within the range observed in overall historical controls. In the assessment carried out by the NTP, these considerations reduced the confidence that the increased incidences of lymphoma were attributable to RF-EMF exposure and the evidence was classified as equivocal [10]. In contrast, Mevissen et al. conclude a moderate certainty of evidence, downgrading only one level for unexplained inconsistency because statistically significant increases were only seen at lower doses in this NTP study.

When considering all included studies, regardless of whether they show harmful effects or not, and taking into account the additional concerns mentioned above, the conclusions of Mevissen et al. regarding the classification of confidence in the evidence are not fully conclusive. From the BfS's point of view, the results do not provide a sufficient foundation to justify a high certainty of evidence for an increased risk of heart schwannomas and gliomas or a moderate certainty of evidence for an increased risk of the other analysed cancer types in animals due to RF-EMF exposure. However, there are some indications of potentially adverse effects in rats at very high whole-body exposures, mainly as a result of the NTP study. These results have still to be verified or falsified, as for example by an ongoing replication study conducted in Japan and Korea [17].

Outcome and study design	No. of studies	Statistically significant increase(s) / decrease(s) (↑ / ↓) or trend(s) (↗ / ↘) and studies of origin	Factors decreasing / increasing (↑ / ↓) the certainty of evidence	Certainty of evidence
Heart				
Chronic bioassay	3	↗ 1 study (NTP rat [8][†]), ↑ 2 studies (NTP rat [8], Falcioni et al. [9])	(↑ rare outcome)	**High** (for heart schwannomas in male rats)
Initiation-(co-)-promotion study	1			
TP animals	none			
Brain				
Chronic bioassay	5	↗ 2 studies (NTP rat [8], Anderson et al. [16])	(↑ dose response)	**High** (for glioma)
Initiation-(co-)-promotion study	10			
TP animals	5			
Lymphoma				
Chronic bioassay	6	↑ 1 study (NTP mouse [10])	(↓ unexplained inconsistency)	Moderate
Initiation-(co-)-promotion study	4	↑ 1 study (Lerchl et al. [18])		
TP animals	7	↑ 1 study (Repacholi et al. [19])		
Adrenal gland				
Chronic bioassay	5	↑ 1 study (NTP rat [8])	(↓ unexplained inconsistency)	Moderate (for pheochromocytoma)
Initiation-(co-)-promotion study	2	↓ 1 study (Heikkinen et al. [20])		
TP animals	5			
Liver				
Chronic bioassay	5	↑ 1 study (NTP mouse [10]), ↓ 1 study (NTP mouse [10]), ↘ 2 studies (NTP rat [8], Tillmann et al. [21])	(↓ unexplained inconsistency)	Moderate (for hepatoblastoma)
Initiation-(co-)-promotion study	6	↑ 1 study (Lerchl et al. [18])[‡]		
TP animals	5	↗ 1 study (Oberto et al. [22])[§]		
Lung				
Chronic bioassay	2	↗ 1 study (NTP mouse [10])	(↓ unexplained inconsistency)	Moderate (for bronchioalveolar adenoma or carcinoma)
Initiation-(co-)-promotion study	4	↑ 2 studies (Lerchl et al. [18], Tillmann et al. [23])		
TP animals	5			

Spotlight authors' notes:

[†] Mevissen et al. only report a statistically significant trend at CDMA modulation, but NTP reported a statistically significant trend also at GSM modulation in male rats.

[‡] Mevissen et al. do not mention the statistically significant increase of hepatocellular adenoma in the RF-EMF+ethylnitrosourea exposed group compared to the ethylnitrosourea-only group in Tillmann et al. [23].

[§] The statistically significant trend is not reported by Oberto et al. and it is not specified by Mevissen et al., whether and how this trend was calculated by them in the systematic review.

Table 1: Summary of study results. TP animals = Tumour prone animals.

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