



Effects of radiofrequency electromagnetic field exposure on cancer in laboratory animal studies, a systematic review[☆]

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ABSTRACT

Background: More than ten years ago, the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) published a monograph concluding there was limited evidence in experimental animals for carcinogenicity of Radio Frequency Electromagnetic Field (RF EMF).

Objective: The objective of this review was to systematically evaluate the effects of RF EMF exposure on cancer in experimental animals.

Methods: Eligibility criteria: Based on pre-established Populations, Exposures, Comparators, Outcomes, and Study Type (PECOS) criteria, studies in experimental animals of the following study types were included: chronic cancer bioassays, initiation-(co-)promotion studies, and studies with tumor-prone animals.

Information sources: MEDLINE (PubMed), Science Citation Index Expanded and Emerging Sources Citation Index (Web of Science), and the EMF Portal.

Data abstraction and synthesis: Data are publicly available online as interactive visuals with downloadable metadata. We adapted the risk-of-bias (RoB) tool developed by Office of Health Assessment and Translation (OHAT) to include considerations pertinent to the evaluation of RF EMF exposure and cancer bioassays. Study sensitivity was assessed with a tool adopted from the Report on Carcinogens (RoC). We synthesized studies using a narrative approach. Effect size was calculated as the 1% Bayesian Average benchmark dose (BMD) of a respective study when dose-response or a trend was identified (see BMDAnalysisSupplementaryMaterial) (Supplement 1).

Evidence Assessment: Certainty of the evidence (CoE) was assessed using the Grading of Recommendations, Assessment, Developing and Evaluations (GRADE) approach, as refined by OHAT. Evidence from chronic cancer bioassays was considered the most directly applicable to evaluation of carcinogenicity.

Results: We included 52 studies with 20 chronic bioassays. No studies were excluded based on risk of bias concerns. Studies were not considered suitable for meta-analysis due to heterogeneity in study design, species, strain, sex, exposure characteristics, and cancer outcome. No or minimal evidence of RF EMF exposure-related cancer outcomes was found in most systems or organs in any study (these included gastrointestinal/digestive, kidney, mammary gland, urinary, endocrine, musculoskeletal, reproductive, and auditory).

For lymphoma (18 studies), with 6 chronic bioassays (1,120 mice, 1,780 rats) inconsistency between two chronic bioassays was not plausibly explainable, and the CoE for lymphoma was rated 'moderate'.

For brain tumors (20 studies), including 5 chronic bioassays (1,902 mice, 6,011 rats), an increase in glial cell-derived neoplasms was reported in two chronic bioassays in male rats. The CoE for an increased risk in

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glioma was judged as high. The BMD analysis was statistically significant for only one study and the BMD was 4.25 (95% CI 2.70, 10.24).

For neoplasms of the heart (4 chronic bioassays with 6 experiments), 3 studies were performed in rats (~2,165 animals), and 1 in mice (~720 animals). Based on 2 bioassays, statistically significant increases in malignant schwannomas was judged as high CoE for an increase in heart schwannomas in male rats. The BMDs from the two positive studies were 1.92 (95 %CI 0.71, 4.15) and 0.177 (95 %CI 0.125, 0.241), respectively.

Twelve studies reported neoplasms in the adrenal gland (5 chronic bioassays). The CoE for an increased risk in pheochromocytoma was judged as moderate. None of these findings were dose-dependent when compared to the sham controls.

Sixteen studies investigated tumors of the liver with 5 of these being chronic bioassays. The CoE was evaluated as moderate for hepatoblastomas.

For neoplasms of the lung (3 chronic bioassays), 8 studies were conducted in rats (~1,296 animals) and 23 studies in mice (~2,800 animals). In one chronic bioassay, a statistically significant positive trend was reported for bronchoalveolar adenoma or carcinoma (combined), which was rated as moderate CoE for an increase in lung neoplasms with some evidence from 2 initiation-(co-)promotion studies.

Discussion: Meta-analysis was considered inappropriate due to the heterogeneity in study methods. The GRADE/OHAT CoE framework has not been frequently applied to animal studies and experience to date suggests refinements are needed. We referred to standard methods in environmental health where CoE is framed in the context of strength of the evidence providing positive support for carcinogenicity. High CoE can be interpreted as the true effect is highly likely to be reflected in the apparent relationship. Moderate CoE indicates the true effect may be reflected in the apparent relationship. Cancer bioassays conducted in experimental animals are commonly used to identify potential human carcinogens. We note that the two tumor types with high CoE in animals in this systematic review are the same as those identified with limited evidence in humans by the IARC Working Group. However, even in cases where the animal evidence demonstrates high CoE, the extrapolation of risk from cancer bioassays to humans is particularly complex for RF-EMF. Without a better understanding of the mechanism of the carcinogenicity of RF-EMF, the choice of exposure metric for risk extrapolation (whole body versus localized), intensity or cumulative exposure, whether or not a monotonic dose-response holds for carcinogenic effects, and whether SAR is the appropriate dose metric for adverse effects induced by RF-EMF, may be critical.

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