



Bundesamt
für Strahlenschutz

Spotlight on EMF Research

**Spotlight on “Genotoxicity of
radiofrequency electromagnetic
fields on mammalian cells in vitro: A
systematic review with narrative
synthesis” by Romeo et al. in
Environment International (2024)**

Category [radiofrequency, review]

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Competence Centre for Electromagnetic Fields (KEMF)

1 Putting the paper into context by the BfS

Radiofrequency electromagnetic fields (RF-EMF) are ubiquitous in modern society, prompting concerns regarding possible adverse effects of RF-EMF exposures. While exposure limits recommended by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) provide protection against scientifically established effects, such as temperature increases, the question of possible long-term effects, like increased cancer risk from prolonged exposures below these limits, remains contentious. The International Agency for Research on Cancer (IARC) classified RF-EMF as possibly carcinogenic in 2011 [2]. Since then, new and extensive experimental studies have been conducted to elucidate the genotoxic (DNA-damaging) potential of RF-EMF, but their findings are still inconclusive [3]. Thus, the systematic review at hand [1] is the first attempt to systematically assess all available and eligible evidence on the potential effects of RF-EMF on genotoxicity in experimental mammalian *in vitro* studies.

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

Genotoxicity is a key characteristic of carcinogens and this systematic review examined the existing evidence concerning the DNA-damaging potential of RF-EMF from mechanistic *in vitro* studies. A protocol for the present study was published beforehand [4] describing in detail the search strategy, eligibility criteria, quality assessment, approaches for the planned data synthesis and evidence assessment. Following the guidelines for systematic reviews, the authors assessed the study quality according to the *Risk of Bias* (RoB) criteria defined in the *Office of Health Assessment and Translation (OHAT) Handbook for Conducting a Literature-Based Health Assessment* [5], after adapting them for *in vitro* studies [6]. Using a 3-tier stratification system, they classified studies according to their susceptibility to bias according to the OHAT recommendations [5, 7]: tier 1 studies represent low RoB and an overall high study quality, whereas tier 3 studies have a high RoB and an overall low study quality; studies not fitting tier 1 or tier 3 categories are rated as tier 2. In line with this procedure, the most important RoB questions were: (1) identical experimental conditions across study groups, (2) confidence in the exposure characterisation, (3) confidence in the outcome assessment, and (4) temperature monitoring and control (to distinguish thermal effects from non-thermal effects).

To assess the confidence in the evidence based on the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) approach, the authors followed the OHAT guidelines for animal studies [7] and adapted them to *in vitro* mechanistic studies. The degree of confidence was determined mainly on the basis of RoB tiering and indirectness, i.e., the likely biological relevance of the employed experimental model for humans, e.g., based on the reversibility of the detected DNA damage. Imprecision, inconsistency, and publication bias were not formally assessed.

After screening titles and abstracts of 7,750 unique records and assessing eligibility, $n = 159$ studies with $n = 1,111$ experiments were included in the systematic review. Most experiments were performed in human cells ($n = 838$, mostly in peripheral blood lymphocytes), fewer involved animal cells ($n = 273$, mostly rodent cells). Primary cells were used more often than cell lines (609 vs. 502). In terms of exposures, most experiments were performed applying frequencies associated with wireless technologies (10 MHz to 6 GHz), followed by frequencies above 6 GHz; exposures below 10 MHz were rare. Roughly 50% of experiments were performed with exposures below the ICNIRP reference levels for the general population, 34% were above and 18% were at or near the limits. Exposure durations were mostly long (72% >1h to <24h), followed by acute exposures (<1h, 22%), and a few experiments used chronic exposures (>24h, 7%).

In terms of study quality, 7% were classified as high quality (RoB Tier 1), 69% as medium quality (RoB Tier 2), and 7% as low quality (RoB Tier 3). The most frequent RoB issues were lack of blinding of research personnel, low confidence in the exposure and outcome assessment, and non-identical experimental conditions across study groups.

The authors decided to perform a narrative synthesis, following established guidance and tools [8, 9], mainly because of difficulties with extracting data reported in graphical form. Additionally, the included studies were very heterogenous in terms of study designs, exposure conditions, endpoints measured, and meth-

odological quality. Romeo et al. grouped included studies by endpoints and tabulated reported data for each experimental condition. Effects were assessed in terms of presence or absence of statistically significant changes in the exposed samples compared to the control samples. Further syntheses were performed, stratified by exposure condition and summary RoB tier. For the GRADE assessment, only studies reporting a statistically significant effect of RF-EMF exposure were considered for each body of evidence (Table 1).

Outcome	No. of studies with significant effects	No. of experiments reporting significant effects vs. no effects	No. of studies with statistically significant effects by study quality (high/medium/low)	Final confidence rating
Primary Endpoints (irreversible damage)				
Mutations	1 von 3	1 vs. 9	0/1/0	Very low
Sister chromatid exchanges	1 von 16	4 vs. 32	0/1/0	Low
Spindle disturbances	4 von 4	8 vs. 1	0/4/0	Low
Aneuploidy	1 von 4	2 vs. 6	0/1/0	Low
Chromosomal aberrations	7 von 31	17 vs. 71	1/3/3	Very low
Micronuclei	15 von 55	54 vs. 211	1/11/3	Low
Secondary Endpoints (reversible damage)				
DNA strand breaks	24 von 89	101 vs. 544	5/18/1	Low
8-Oxoguanin adducts	3 von 4	8 vs. 6	1/2/4	Very low
Chromatin condensation	8 von 9	22 vs. 13	0/4/4	Very low

Table 1: Summary of findings. Results of the narrative syntheses and the GRADE assessment (confidence rating). Study quality in three tiers: high / medium / low.

The authors found that in about 80% of all experiments RF-EMF exposure did not induce statistically significant effects in the endpoints investigated (Table 1), independently of the exposure features, level, and duration. Noteworthy, experiments with the lowest exposure levels and durations yielded the highest rate of statistically significant outcomes, contrary to what is expected for a dose-response relationship (*Spotlight on EMF Research* editor's note: this holds for exposures above 10 MHz; for exposures below 10 MHz, figure 4a of Romeo et al. suggests an association between the rate of statistically significant results and increasing exposure level, although this impression is based on only 30 experiments). The authors noted that the absence of a statistically significant effect prevails among the high quality (RoB tier 1) and medium quality studies (tier 2), while for the low quality studies (RoB tier 3) the trend is reversed: only amongst the low quality studies (based on summary assessments of RoB) did the number of studies reporting effects exceed the number of studies reporting no effect. The certainty of the evidence is low or even very low for all endpoints investigated (Table 1). Overall, the authors conclude that the qualitative analysis of the studies included in the review at hand suggests that RF-EMF exposure probably does not increase the occurrence of genotoxic effects *in vitro*.

3 Comments by the BfS

Romeo et al. provide an extensive systematic review of the effects of RF-EMF exposure on genotoxicity in experimental *in vitro* studies, a topic of high relevance for radiation protection. The authors included a large number of mechanistic studies examining biological endpoints that comprehensively cover the overarching term “genotoxicity”. The authors’ differentiation between reversible and irreversible damage is biologically reasonable. How they reached their conclusions is described transparently. These conclusions, however, are based on a qualitative synthesis because limitations within the body of evidence precluded a more conclusive quantitative meta-analysis. The authors stated as the main reason that most included studies reported results in graphical form only (e.g., bar plots), and attempts to estimate data points from these graphs were inaccurate. In contrast, other systematic reviews on the effects of RF-EMF [10, 11] used digital rulers to extract graphical data, enabling meta-analyses. Furthermore, the authors had to contend with the lack of specific guidelines for systematic reviews of mechanistic evidence, such as that from *in vitro* studies, which further complicated the review process. Owing to the limitations inherent in narrative syntheses, the reviewers were constrained in the level of detail they could incorporate into their conclusions regarding the outcomes. Consequently, for each outcome, the key metric provided by this review is the correlation between studies reporting statistically significant effects and study quality.

To evaluate the certainty of the evidence for the outcomes investigated, the authors adapted the GRADE system to their narrative synthesis in two ways: i) they restricted the assessment to studies that show a statistically significant effect (instead of taking all studies for each outcome into account) and ii) they omitted the GRADE downgrade categories “inconsistency”, “imprecision” and “publication bias”, as well as the upgrade category “large magnitude”. As a result, for each outcome, the evidence assessment focuses on the quality of studies reporting a statistically significant effect rather than on the certainty of the overall body of evidence. The conclusion that confidence in studies reporting statistically significant effects is low to very low, combined with the identified relationship between RoB and significant effects, supports the primary conclusion of the review that RF-EMF exposure likely does not elevate the incidence of genotoxic effects *in vitro*, consistent with past narrative reviews [12, 13].

It is important to note that relying solely on studies with statistically significant results may overlook the combined impact of non-significant findings. A quantitative synthesis could reveal an overall significant effect that a purely narrative approach cannot detect. Therefore, considering the entire body of evidence, including non-significant studies is to be preferred for a comprehensive and unbiased assessment.

Despite the methodological shortcomings inherent to narrative syntheses discussed above, this systematic review is able to comprehensively present the current state of research on RF-EMF effects on genotoxicity. From a radiation protection point of view, the results of this systematic review do not provide reliable evidence for an association between RF-EMF exposure and genotoxic effects in experimental *in vitro* studies, which is consistent with the authors’ conclusion. This systematic review is one of the evidence streams included in a broader systematic review of scientific literature examining the potential carcinogenic effects of RF-EMF performed by several Italian public research agencies.

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