Bundesamt
für Strahlenschutz

Spotlight on EMF Research

Spotlight on “The effects of radiofrequency electromagnetic field exposure on biomarkers of oxidative stress in vivo and in vitro: A systematic review of experimental studies” by Meyer 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

The World Health Organization (WHO) has initiated an ongoing project to systematically assess the potential health effects of exposure to radiofrequency electromagnetic fields (RF-EMF) in the general and occupational populations. To this end, in 2018, the WHO conducted a comprehensive international survey among RF-EMF experts to prioritize the potential health effects according to their importance [2]. Key topics were identified for which the WHO has commissioned systematic reviews. More information on the WHO systematic reviews in general can be found in another Spotlight on EMF Research article (Apr/2024 no.2 [3]).

One of the prioritized topics is oxidative stress, which is defined as an imbalance between oxidants and antioxidants in favour of the oxidants, leading to damage to cellular structures [4]. It is well known that e.g. ionizing radiation causes oxidative stress, in fact, the majority of its induced cellular damage is indirect due to the formation of free radicals. Whether weak, non-ionizing RF-EMF could influence oxidative stress has been discussed for years, although there is no known mechanism of action to support this association. Oxidative stress is difficult to measure directly, thus damages or modifications on proteins, lipids and the DNA that are specific for oxidative stress are used as biomarkers [5].

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

This systematic review summarizes and evaluates all available eligible evidence on the effects of RF-EMF on biomarkers of oxidative stress from experimental cell culture and animal studies.

All methods, including eligibility criteria, literature search strategy, data extraction, data synthesis and a list of validated biomarkers for oxidative stress were summarized in a protocol published before the start of work on the systematic review [5]. The authors closely followed the Cochrane recommendations for conducting systematic reviews in toxicology and environmental health research [6]. The PECO (population, exposure, comparator, outcome) that formulates the research question was *"What is the effect of exposure to RF-EMF in the frequency range 100 kHz – 300 GHz (E) on the most important and best validated biomarkers for oxidative stress (O) compared to no exposure, sham exposure, or temperature-controlled no-exposure (C) in animals, humans, or cells (P)?"*.

Study quality was assessed by using an adapted version of the NTP OHAT risk of bias (RoB) rating tool for experimental studies and a 3 tier stratification system was employed to classify studies according to their susceptibility to bias according to the OHAT recommendations [7, 8]. In this system, 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 that did not fit in the tier 1 or tier 3 RoB categories were rated as tier 2. Blinding of research personnel and the confidence in an accurate outcome and exposure assessment were considered the most critical factors for overall study quality and were therefore used as key criteria for tier classification.

Data considered to be sufficiently similar to be combined (e.g. dealing with the same animal species or with cell lines from the same organ and the same biomarker) were analysed in a random-effects meta-analysis using Hedge's g effect size estimates. A pooled effect estimate was calculated, if the statistical heterogeneity (I^2) was lower than 75%. Subgroup analyses were performed for different species, cell types and for studies providing positive controls.

The certainty of the evidence for possible effects of RF-EMF exposure was rated according to the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) working group [9]. For this assessment, five factors (overall RoB, inconsistency, indirectness, imprecision and publication bias) were considered for every PECO element (combination of biomarker, organ and setting), leading to an overall certainty rating (very low, low, moderate or high certainty of evidence).

From a total of 27,845 publications, 56 studies met the inclusion criteria and results from 52 publications were included in the meta-analyses. The included studies were from 18 different countries and were conducted between 2004 and 2023. Three biomarkers (oxidized DNA bases, oxidized lipids and modified proteins) were analysed quantitatively in different organs and settings. From a total of 19 PECO elements

analysed quantitively, 11 meta-analyses were performed. The results are summarized in table 1.

Most of the studies included in the analysis demonstrated a generally high RoB and were thus classified as tier 3 (n= 38) or tier 2 (n= 17). Only a single high-quality study was identified (tier 1). Many studies were affected by high selection bias (no information on randomization), performance bias (no information on blinding of researchers), and detection bias (deficiencies in exposure and outcome characterization).

The quantitative analyses show that RF-EMF exposure could lead to an increase in biomarkers of oxidative stress in the plasma, testes and thymus of rodents. In the brain, liver, blood and female reproductive system of rodents, the analyses show either no or an inconsistent effect of RF-EMF with occasional increases or decreases in oxidative stress biomarkers. However, the confidence in the evidence is very low for all 19 PECO elements, i.e. RF-EMF may have no effect or an inconsistent effect on oxidative stress, but the certainty of the evidence is very low for either possibility.

There were several issues that impaired the certainty of the evidence: The RoB was high across studies, and the results were imprecise due to low sample sizes and large confidence intervals that often included large positive and negative effects. Many PECOs were subject to unexplained inconsistency, with varying effect estimates and high statistical heterogeneity that could not be explained by additional subgroup analyses.

Overall, the results provide no robust indication for an association between exposure to RF-EMF and changes in biomarkers of oxidative stress.

3 Comments by the BfS

For the publication presented here, BfS employees have participated as authors. As a result, we are refraining from providing a detailed evaluation and commentary on the content and significance of this publication.

Outcome	No. of studies	Study quality	Effect size (SMD), [95 % CI]	Certainty of the evidence
In vivo studies				
Oxidized DNA bases in the brain of rodents	5	2nd tier: 2 3rd: 3	Varies from -3.40 [5.15, -1.64] to 2.20 (0.78, 3.62)	Very low
Oxidized DNA bases in the brain of rabbits	2	2nd tier: 2	Varies from -1.06 [-2.13, 0.00] to 5.94 [3.14, 8.73]	Very low
Modified proteins in the brain of rodents	15	2nd tier: 3 3rd tier: 12	Varies from -6.11 [-8.16, -4.06] to 5.33 [2.49, 8.17]	Very low
Oxidized lipids in the brain of rodents	1	3rd tier: 1	Varies from -4.10 [-5.48, -2.73] to 1.27 [0.45, 2.10]	Very low
Oxidized DNA bases in the liver of rodents	2	3rd tier: 2	Varies from -0.71 [-1.80, 0.38] to 1.56 [0.19, 2.92]	Very low
Oxidized DNA bases in the liver of rabbits	2	2nd tier: 2	Pooled effect size: 0.39 [-0.79, 1.56]	Very low
Modified proteins in the liver of rodents	6	3rd tier: 6	Pooled effect size: 0.55 [0.06, 1.05]	Very low
Oxidized DNA bases in the blood of rodents	4	3rd tier: 4	Varies from -1.14 [-2.23, -0.06] to 1.71 [-0.1, 3,53]	Very low
Modified proteins in the blood of rodents	3	3rd tier: 3	Pooled effect size: -0.08 [-1.32, 1.16]	Very low
Oxidized DNA bases in the plasma of rodents	2	3rd tier: 2	Pooled effect size: 2.25 [1.27, 3.24]	Very low
Oxidized DNA bases in the testis of rodents	2	2nd tier: 1 3rd tier: 1	Pooled effect size: 1.60 [0.62, 2.59]	Very low
Modified proteins in the ovary of rodents	2	3rd tier: 2	Varies from 0.24 [-0.74, 1.23] to 2.08 [1.23, 2.94]	Very low
Oxidized DNA bases in rodent cells	1	3rd tier: 1	Pooled effect size: 2.49 [1.30, 3.67]	Very low
Oxidized lipids in rodent cells	1	3rd tier: 1	Pooled effect size: 0.34 [-0.62, 1.29]	Very low
Modified proteins in the thymus of rodents	1	3rd tier: 1	Pooled effect size: 6.16 [3.55, 8.76]	Very low
In vitro studies				
Oxidized DNA bases in human cells	3	2nd tier: 2 3rd tier: 1	Varies from 0.01 [-0.59, 0.62] to 7.12 [0.06, 14.18]	Very low
Modified proteins in human cells	1	3rd tier: 1	Pooled effect size: 1.07 [-0.05, 2.19]	Very low
Oxidized DNA bases in rodent cells	3	1st tier: 1 2nd tier: 2	Pooled effect size: 2.07 [-1.38, 5.52]	Very low
Modified proteins in rodent cells	2	2nd tier: 1 3rd tier: 1	Pooled effect size: 0.56 [-0.29, 1.41]	Very low

Table 1: Summary of findings. Results of the quantitative analysis and the GRADE assessment (certainty of the evidence). A positive effect estimate indicates an increase in biomarkers of oxidative stress upon RF-EMF exposure, a negative effect estimate indicates a decrease. A pooled effect estimate was only calculated, if the statistical heterogeneity (I^2) was lower than 75%. Otherwise, the minimum and maximum SMDs are shown. SMD: Standardized mean difference; CI: Confidence interval; Study quality – tier 1: low RoB, tier 2: medium RoB, tier 3: high RoB.

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