Bundesamt
für Strahlenschutz

Spotlight on EMF Research

Spotlight on "Effects of radiofrequency electromagnetic field (RF-EMF) exposure on male fertility: a systematic review of experimental studies on non-human mammals and human sperm in vitro" by Cordelli 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

In 2019, the World Health Organization (WHO) initiated an international project aiming at systematically reviewing the evidence regarding the association between exposure to radiofrequency electromagnetic fields (RF-EMF) and adverse health effects [2]. Within the project, several endpoints were prioritised by an expert group. These endpoints include reproductive health outcomes. Possible RF-EMF-induced adverse effects on fertility have been under discussion for years and have been investigated extensively in human epidemiological studies, experimental animal studies as well as in vitro studies on, e.g., human sperm. It is well known that heating affects sperm quality, but it is still unknown if RF-EMF may affect male fertility beyond heating effects. Data from experimental studies are inconsistent and controversial. In the systematic review by Cordelli et al. [1], the comprehensive data on the effects of RF-EMF on male fertility from experimental animal and in vitro studies were collected and evaluated. Potential adverse effects on pregnancy and birth outcomes were investigated in another review by the same authors [3] that is addressed in another spotlight [4]. In [5] we provide more information on the WHO initiative and the resulting systematic reviews.

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

The authors collected, assessed, and analysed all available evidence on the effects of exposure to RF-EMF on male fertility from peer-reviewed, experimental studies in non-human animals and in vitro studies on human sperm. A protocol for the present study was published beforehand [6] in which the search strategy, eligibility criteria, quality assessment and the approaches for the meta-analyses and evidence assessment were described in detail. The authors followed the guidelines for systematic reviews, which include an assessment of the study quality according to risk of bias (RoB) criteria defined in the *Handbook for Conducting a Literature-Based Health Assessment* [7]. As another potential source of bias, it was assessed whether studies had considered an RF-EMF-induced temperature increase, because this aspect is especially relevant in the case of RF-EMF exposure of reproductive organs. For the RoB assessment of RF-EMF effects on human sperm, some adaptations for in vitro studies were made, according to previous systematic reviews and protocols [8, 9, 10]. Based on the overall RoB ratings, study quality was categorised as “low concern”, “some concern”, or “high concern”.

For each eligible study, study characteristics were extracted, including outcome and exposure data. In terms of exposure data, reported whole body average SAR (wbSAR) values were extracted. If it was not reported, a wbSAR estimate was calculated based on other dosimetric information and biophysical assumptions, based on the recommendations by Durney (1986) [11]. For each endpoint, the average wbSAR across all studies was computed and a random-effects meta-analysis model was applied to the outcome data of the studies. For the random-effects model, DerSimonian and Laird between-study variants estimator was used. Depending on the extracted data, different risk estimates were calculated (e.g., odds ratio (OR) for binary data and mean difference (MD) or standardised mean difference (SMD) for continuous data).

For the final assessment of the certainty attributed to the body of evidence (i.e., GRADE assessment), a modified version of the GRADE approach, specified for experimental studies, was used [12]. According to the GRADE approach, every outcome was evaluated in five categories (RoB, inconsistency, indirectness, imprecision, and publication bias), resulting in high, moderate, low, or very low certainty of the evidence. Only studies with “low concern” or “some concern” RoB rating were considered for the GRADE assessment.

A total of 1335 papers reporting animal studies and 869 studies reporting human sperm were retrieved. After duplicate removal, title and abstract screening, and the check for eligibility, 117 papers reporting animal studies and 10 papers reporting human sperm were included in the systematic review.

In terms of quality, only very few studies were rated “low concern”, the majority were rated “some” or “high concern”. Main reasons for concern in animal studies and human sperm in vitro studies were the lack of blinding during the experimental procedure, poor characterisation of exposure and dosimetry, and low confidence in the outcome assessment, mostly due to lack of blinding during endpoint analysis.

None of the included studies provided an adequate temperature control (i.e., samples exposed to direct heating at a temperature comparable to that induced by RF-EMF). This would have provided a possibility to differentiate between "direct" RF-EMF effects and those mediated by tissue heating.

The authors defined four main outcome categories in non-human mammals (decrease of fertility, effects on semen quality, reproductive organ toxicity, and hormonal effects), each with several endpoints. For in vitro studies, semen quality was the main outcome category. For each endpoint, meta-analyses for studies rated "low" and "some concern" were performed separately from those categorised as "high concern". Only results for studies rated "low" or "some concern" are given in table 1.

The authors conclude, that the results of their systematic review and meta-analyses indicate a possible detrimental effect of RF-EMF exposure on pregnancy rate and sperm count, but no effect on litter size in experimental mammals. The decrease of pregnancy rate is consistent with the hypothesis of thermal effects. For all other endpoints, no general exposure-response relationship or minimum effective exposure level could be determined, so no recommendations on human exposure levels could be derived from this systematic review. The authors note, that average whole body exposure levels in the included studies were high with respect to those relevant for human exposure: 75–80% of the studies tested exposure levels above 0.4 W/kg (ICNIRP basic restriction for workers) and 46–53% tested exposure levels above 4 W/kg (an exposure level that may lead to exposure-induced body core temperature elevations of 1°C in humans at prolonged exposure duration [13]). Thus, the extent to which the conclusions of this systematic review can be applied to exposure levels that are relevant for humans is unknown. For future research, the authors recommend more focus on blinding during the experiment and endpoint assessment, as well as on exposure characterisation and dosimetry. The authors do not encourage further in vitro studies on human sperm samples, due to biological limitations considering the maturation process of human sperm, which cannot be considered in those experiments. Rather, they suggest semen quality analysis in humans by biomonitoring investigations on RF-EMF-exposed populations.

3 Comments by the BfS

This systematic review is important from a radiation protection point of view and provides a rich compilation of the available data. It is of interest to both the scientific community and the general public.

The study was performed according to the quality standards for systematic reviews [7]. The eligibility criteria were not too strict and include a wide variety of different exposure conditions (even electromagnetic pulses) and many different endpoints associated with male fertility. This approach increased the probability for a sufficiently large database to investigate all endpoints of interest.

The results of this systematic review are subject to numerous limitations. It needs to be considered that the average exposure levels used in the underlying studies exceed recommended exposure limits for humans (whole body average SAR = 0.08 W/kg) [13] by far and due to a lack of adequate temperature controls in the included studies it is not possible to differentiate between non-thermal RF-EMF effects (if they exist) and thermal RF-EMF effects, which are well-known to be detrimental for sperm and sperm maturation [14]. Due to the generally high exposures used, it cannot be determined at which threshold RF-EMF exposure might start to affect male fertility in experimental animal studies. In this context, it is important to emphasise that due to limitations in the underlying data base, all data were related to either reported or roughly approximated wbSAR. For a given wbSAR, the extent to which the body core temperature rises not only depends on exposure duration but also on the size and mass of the species and its thermoregulatory ability as well as whether the animal is restrained (e.g., in tubes) or free roaming and whether the animal is anaesthetised. If the observed effects are indeed mediated by body core temperature elevation, these factors might also be contributing factors for the observed heterogeneity in study results. Another limiting factor is the fact that the temperature in the testis is far more relevant for many parameters of male fertility (e.g., sperm count) than the temperature of the body core. This is also stated by the authors: "there is no clear relationship between testes temperature and average wbSAR". Also, if the observed effects are a direct effect of the RF-EMF in the testis (rather than thermally mediated), data on an exposure metric that is only averaged locally in the organ of interest would be needed to establish potential exposure-response relationships. In studies that used several exposed groups but only one control group, the authors decided to average exposures and effects to avoid a shared-sham bias. This might have led to diluting effects that only manifest at higher exposure levels. An alternative way to avoid a shared-sham bias would be using only the data from the largest exposure contrast from those studies that provided shared controls to enhance the probability for detecting a possible exposure-related effect in the meta-analysis.

Overall, the authors investigated fifteen different outcomes but for most of them the certainty of the evidence was very low and from a radiation protection point of view, no reliable conclusion can be drawn for the majority of them.

However, for three outcomes, the certainty of the evidence was at least low. The most robust result is a high certainty of the evidence that RF-EMF exposure decreases the rate of pregnancy. However, the authors emphasise that in the subgroup analysis only studies using exposures equal or higher than 5 W/kg provided a statistically significantly increased OR, the studies with exposures lower than 5 W/kg did not, suggesting that this effect only occurs at very high exposures that lead to temperature increases in the affected tissues. However, it is surprising that the results of the exposure-response analysis on sperm count, a crucial factor for male fertility, does not reveal a statistically significant increase of detrimental effects with increasing SAR values, a discrepancy the authors also note. If this discrepancy were not due to study limitations, this would raise questions about the underlying mechanism for the decreased pregnancy rate. For the endpoint sperm count itself, the meta-analysis resulted in a statistically significant decrease after RF-EMF exposure at high levels, but the certainty of the evidence is low. However, despite the substantial statistical heterogeneity, the majority of studies shows effects and the database is sufficiently large with 80 studies. On the other hand, there is a moderate certainty of the evidence that RF-EMF exposure had no effect on litter size, despite the very high exposures used in the included studies; the individual results consistently point to no effect. Also, the exposure-response analysis confirmed a lack of association between RF-EMF exposure and decreased litter size. These findings are somewhat inconsistent, which might be due to the fact that the underlying study base for the bodies of evidence is not identical. Overall, it is likely that there could be an effect of RF-EMF on pregnancy rate and sperm count at very high exposures in animal experiments that are most likely due to thermal effects, but should nevertheless be elucidated in future animal studies. For humans, the results of this systematic review do not provide evidence for possible effects within the recommended limits for whole body average SAR (wbSAR).

Overall, the authors provide a very comprehensive, diligent, and transparent work to analyse the research question in depth. From a radiation protection point of view, the limitations in the quality of the included studies and the resulting overall very low certainty of the evidence for most endpoints do not provide reliable evidence for or against a consistent RF-EMF effect on male fertility in experimental animal studies. However, the PECO elements for which high and low certainty of the evidence was concluded deserve further investigation, namely the RF-EMF-induced reduction in the rate of pregnancy and a decreased sperm count. In order to overcome the uncertainties in the previous studies, it would be desirable that future experimental animal studies include exposure-response analyses to detect possible thresholds for the occurrence of an effect (including exposures relevant to humans), proper dosimetry, temperature control, blinded experimental procedures and endpoint analyses.

Outcome	No. of studies	Mean exposure level (wbSAR)	Effect measure, effect size [95% Confidence Interval]	Interpretation of the effect estimate	Certainty of the evidence
Decrease of fertility (animal studies)					
Non-pregnant females over paired females*,†	9	∼24 W/kg	OR 1.91 [1.30 — 2.81]*	↓ Pregnancy rate	High*
Litter size†	16	∼24 W/kg	SMD 0.04 [-0.15 — 0.23]	No effect	Moderate
Rate of infertile males	4	∼0.4 W/kg	OR 1.38 [0.32 — 5.94]	No effect	Very low
Fertilisation rate in vitro	1	No assessment, only 1 study			
Effects on semen quality (animal studies)					
Sperm count	80	∼12 W/kg	SMD 0.74 [0.51 — 0.98]	↓ Sperm quantity	Low
Sperm morphology	65	∼14 W/kg	MD -0.94 [-1.28 — -0.59]	↑ Abnormal sperm	Very low
Sperm vitality	32	∼1.5 W/kg	MD -10.83 [-15.2 — -6.47]	↓ Sperm vitality	Very low
Sperm DNA alterations	6	∼1.6 W/kg	SMD -1.92 [-2.78 — -1.05]	↑ Markers for DNA alterations	Very low
Reproduction organ toxicity (animal studies)					
Testis-epididymis weight	55	∼4 W/kg	SMD 0.29 [0.10 — 0.47]	↓ Weight	Very low
Testis histomorphometry	24	∼2.5 W/kg	SMD 0.9 [0.32 — 1.49]	↓ Tubule diameter	Very low
Testis or epididymis histology	17	∼3 W/kg	MD 0.69 [0.45 — 0.92]	↑ Histological alterations	Very low
Testicular cell death	23	∼7 W/kg	SMD -1.18 [-1.82 — -0.54]	↑ Dead cells	Very low
Testicular sperm production	36	∼6 W/kg	SMD 0.87 [0.51 — 1.22]	↓ Sperm production	Very low
Hormonal effects (animal studies)					
Testosterone level	29	∼1 W/kg	SMD 0.87 [0.43 — 1.3]	↓ Testosterone level	Very low
Sperm quality (human in vitro studies)					
Morphology	1	No assessment, only 1 study			
Vitality	23	SAR not reported	MD -1.37 [-2.46 — -0.28]	↓ Vitality	Very low
DNA alterations	13	SAR not reported	SMD -0.17 [-0.48 — 0.13]	No effect	Very low

Abbreviations: OR = Odds Ratio, MD = Mean Difference, SMD = Standardised Mean Difference.

* In the original study [1], the analysis resulted in an OR = 2.42 [95% CI (1.68 — 3.50)] and a moderate certainty of the evidence [1]. In a corrigendum the authors corrected some errors in the analysis [15]. In the original analysis, a single study contributed ∼50% of the results in the meta-analysis (Saunders et al., 1983 [16]). In that study, a group of 24 exposed male mice, matched with a group of 18 sham-exposed mice, were mated repeatedly at different times after exposure for a total of 10 matings to groups of unexposed females. Thus, the experiments were not independent and had to be aggregated for the corrected analysis. This correction led to OR = 1.91 [95% CI (1.30 — 2.81)] and an increased certainty of the evidence from "moderate" to "high".

† In the original study [1], the analysis of the high concern studies included three results from one study, which were not independent (Goud et al. 1982, [17]). For the corrigendum [15], the results were aggregated and the analysis was recalculated. This had no impact on the certainty of the evidence.

Table 1: Summary of the results of the meta-analysis and GRADE assessment for each outcome category. The table includes the data from the corrigendum, published in 04/2025 [15].

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