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Methodologically solid and analytically rigorous: the evaluations of our systematic review on RF-EMF and animal cancer are reliable☆

To the Editors, Environment International

Response to: Karipidis et al.

Evidence on RF-EMF and cancer in animals misjudged: Methodological and analytical flaws in the Mevissen et al. systematic review.

Karipidis *et al.* claim that our systematic review (SR) on radiofrequency electromagnetic fields (RF-EMF) and cancer in animals (Mevissen et al. 2025) has serious methodological and analytical flaws. In our answer, we grouped topics that are related and given repetitively in various places in the letter by Karipidis *et al.*

1. Consistency across studies

The authors have mischaracterized our review as not considering the totality of the evidence. A critical aspect in our analysis when considering consistency across studies was to consider potential causes of inconsistency (i.e., species, strain, sex, life stage at exposure and assessment); exposure or treatment duration, level, or timing relative to outcome; study methodology (e.g., route of administration, methodology used to measure health outcome). We found considerable variation in study design that could potentially explain the inconsistent findings. According to the OHAT framework used in our analysis "*Generally, there is no downgrade when identified sources of inconsistency can be attributed to study design features such as differences in species, timing of exposure, or health outcome assessment*" (NTP, 2019). There is no downgrade for inconsistency in cases where the evidence base consists of a single study. In this case, consistency is unknown and is documented as such in the summary of findings table.

2. Why is a meta-analysis inappropriate for the RF−EMF animal cancer studies?

Karipidis et al. criticized that we did not perform a *meta*-analysis. Our previously published protocol clearly states under what conditions a meta-analysis would be performed (Mevissen et al., 2022). None of the collections of studies satisfied those conditions so we followed the protocol and did not conduct meta-analyses. Meta-analysis was considered inappropriate due mostly to methodological and biological differences related to the animal models being used (different species, genetically-modified animals, different feeds, different caging protocols, etc.), the exposure characteristics (far- near- field, modulation), and the experimental parameters (such as start of exposure, timing of exposure, duration of exposure, type of exposure system). In addition, reasons for not using a meta-analysis, including heterogeneity and biological inappropriateness, are given in the SR. We note that Karipidis *et al.* do not appear to have experience in the analysis of animal toxicology. Thus, they may not appreciate these considerations. Animal studies are typically much smaller in sample size compared to human studies, which is one reason researchers try to minimize variance by use of inbred strains, specific husbandry practices and experimental conditions. This can lead to greater differences between individual animal studies compared to what would be expected for epidemiological studies (Vesterinen et al., 2014).

Karipidis *et al.* emphasize that the SR by Pinto *et al.* has included a meta-analysis, resulting in negative findings. The meta-analyses performed by Pinto *et al.* make little biological or statistical sense. They combine different species, different strains, different sexes, pulsed fields with continuous fields, different frequencies, different study endpoints, different statistical analysis methods, etc. In addition, they treat individual groups from the same studies as independent when in fact there is a dependency based upon a common control group, violating one of the main assumptions of the meta-analytic methods they used. For example, if one study had 5 exposure groups, the study would enter 5 times into the meta-analysis as if they are independent studies rather than once (as would be appropriate) if they used the single p-value from a trend analysis.

Karipidis *et al.* seem to be under the impression that all bioassays in animals, regardless of design and toxicological target, are of equal value in determining if cancer can occur in animals for use in determining the risks of human cancers. This is simply not true. Chronic bioassays are considered the most meaningful assays regarding risk identification because of their nature (see respective textbooks for more details see guidelines by OECD (OECD 2014), EPA (EPA, 2005), IARC (IARC, 2019a), and the European Chemicals Agency (European Chemicals Agency, 2015). Initiation-promotion studies and studies in transgenic animals have serious limitations on their interpretation which limits their ability for making inference on the carcinogenicity of an agent to both laboratory animals and humans.

The protocol and the review by Pinto *et al.* (Pinto et al., 2022; Pinto et al., 2023) do not provide a transparent assessment of the risk of bias (RoB). They only state that they are using the methodology by OHAT, but no details are provided, nor are the assessments publicly available.

In summary, it would be inappropriate to draw conclusions from flawed meta-analyses, using studies that should not be combined, and it would be misleading to draw conclusions from such a meta-analysis in support of further risk assessment and decision-making activities.

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3. Biostatistics

As for the comment regarding biostatistics used, especially pairwise comparisons versus trend tests, we would refer the reader to the Preamble to the IARC Monographs, the OECD Guidelines (OECD, 2014), EPA Risk Assessment Guidelines (EPA, 2005) and other references (Haseman, 1984), all of which point out that a positive result in either test should be considered as a rejection of the null hypothesis of no effect. The paper by Nead *et al.* (Nead et al., 2018) cited by Karipidis *et al.* discuss the use of "trends" toward significant p-values when pairwise comparisons are all non-significant. This approach is statistically very different from our analyses employing statistical tests for trend, and it is not supported by any guidelines and was not used by the NTP. Knead *et al.* do not discuss the statistical trend tests (Armitage linear trend test, poly-K test) as used by the NTP. In statistical terms, these tests represent the uniformly most powerful unbiased methods for formally testing against linear trends in binomial data (Bailer and Portier, 1988) and are robust to deviations from the core assumptions in the test.

4. The NTP study – appraisal of study design and rigor?

Karipidis *et al.* only repeat their own previously published but unjustified criticisms (ARPANSA, 2019; ICNIRP, 2020) of the NTP (National Toxicology Program 2018a; b) and the Ramazzini study (Falcioni et al., 2018), and pointed out that we did not consider various flaws in our RoB assessments.

The NTP is the largest toxicology program in the world, and they plan, perform and analyse their studies using state-of-the-art designs, methods and procedures in a transparent process. The studies performed by the NTP, including the cancer bioassays have a very rigorous reviewing process including external experts with everything being publicly available. The NTP performed the statistical analyses that corrected for differences in survival. This is clearly stated in their reports. The NTP review panel has concluded there is clear evidence of carcinogenicity from long-term RF exposure in rats. The experimental procedures and the analyses are described in detail in the preliminary technical reports provided by the NTP (National Toxicology Program, 2018a; 2018b) with all data and details being accessible to all. Comments from the public hearing have been posted on the NTP website as well. The procedure and study results have been reviewed by an independent review panel consisting of experts from various areas including pathology and dosimetry in March 2018 (NTP, 2018a). On 1. November 2018, after accounting for the reviewers' comments, the NTP has published the final technical reports (NTP 2018d, 2018e). No such information and transparency in the process are available for any of the other studies. In comparison to many other studies published, the NTP study multiple dose groups (SAR or incident field), allowing for the formal evaluation of dose–response trends. The animals were exposed in cages, hence, such stress effects that might be a problem in carousel exposure can be ruled out in the NTP study and the study by Falcioni *et al.* (Falcioni et al. 2018; National Toxicology Program, 2018a; 2018b).

The authors criticizing the NTP study that was highlighted by Karipidis *et al.* (ARPANSA, 2019; FDA, 2020; International Commission on Non-Ionizing Radiation, 2020) have never criticized a negative finding in any study nor the conclusions drawn from negative findings; this suggests the potential for bias in these reviews.

In this response, we can only give some examples, demonstrating that basic knowledge in toxicology is necessary. For example, the increase in heart schwannomas with dose was seen in both male and female rats but only reached statistical significance in the male animals. The argument that this might point to random findings is seriously counter-intuitive. However, differences between gender, and especially an increase in tumors only in male animals are frequently reported in toxicological animal studies (IARC, 2019b; Kadekar et al., 2012). Therefore, the fact that the statistically significant increase in schwannomas was only found in male rats is not a reason to question this result *per se*. as already described in the BERENIS newsletter of the Swiss Federal Office for the Environment (FOEN) in 2018 (BERENIS Newsletter, 2018).

5. Flawed RoB assessment?

The critique that our RoB assessment is flawed is not justified. In fact, the use of historical controls and blinding of the histopathological evaluations are scientifically correct. Analyses in the NTP studies were performed using the concurrent controls. Historical controls were only used when and where appropriate (EPA, 2005; Haseman et al., 1997; Haseman et al., 1984; IARC, 2019a; OECD, 2014). The publication cited by Karipidis and colleagues by Angelos is an opinion piece in the "*Annals of Emergency Medicine*" (Angelos, 2000); it cites a single example where the study had no concurrent control group and only used a single control group from a previous study (historical control). However, the use of a historical controls is not in line with guidance documents for cancer bioassays *(IARC, EPA, OECD)*, defining that the "*use of a historical control group may be justified in a situation in which laboratories have a long experience with a particular model group may be justified in a situation in which laboratories have a long experience with a particular model*" (Angelos, 2000). The NTP has long experience with the use of historical data, and they are not substituted into the evaluation (only concurrent controls are used) but are used as a guidance to be certain the concurrent controls are not unusual relative to historical incidence. For example, historical controls of the specific strain of rats used in the NTP study showed a tumor incidence for heart schwannomas of 0.8 % for male and 0.3 % for female rats and thus seeing 0/90 animals with the tumor in males and females is normal.

In the NTP study, 5.6 % and 6.7 % (5/90 and 6/90) of male rats exposed to the highest dose (6 W/kg) of Global System for Mobile Communication (GSM) and Code Division Multiple Access (CDMA), respectively, developed malignant heart schwannomas. Based on historical controls, one would have expected to observe zero to maximum two cases in any group of male rats if there was truly no effect. However, even if such a case had occurred, the observed number of 5 and 6 cases in the highest GSM and CDMA exposure groups are substantially higher when compared with the historical incidence.

Karipidis *et al.* criticized that we did not downgrade for non-blinding of the histopathological assessment. For nontargeted or screening-level histopathology outcomes often used in guideline studies, blinding during the initial evaluation of tissues is generally not recommended as masked evaluation can make "*the task of separating treatment-related changes from normal variation more difficult*" and "*there is concern that masked review during the initial evaluation might result in missing subtle lesions*." Generally, blinded evaluations are recommended for targeted secondary review of specific tissues or in instances when there is a predefined set of outcomes that is known or predicted to occur (Crissman et al., 2004). In summary, the use of masked analysis can have a negative effect on histopathological evaluation because it is important for the pathologist to compare treated groups to the concurrent controls, which would not be possible in a blinded evaluation. Therefore, the NTP supports an informed approach to histopathological evaluation in its toxicity and carcinogenicity studies (Sills et al., 2019). This has been performed in both the NTP and the Falcioni studies.

Our RoB assessment was performed using the OHAT guidelines with 3 team members evaluating every single study but also considering expertise in dosimetry for the exposure and dosimetry-related domain and associated issues. Hence, it was performed in a systematic and transparent manner by experts with strong subject matter of expertise with all results shown on the "Health Assessment Workspace Collaborative" (HAWC) (Health Assessment Workspace Collaborative (HAWC) which, in comparison to many other of the SRs initiated by WHO, is publicly available. The confidence of the evidence (CoE) assessment was considering the weight of the study design, and as noted earlier, cancer bioassays are more useful in interpreting positive findings in terms of

carcinogenicity to humans than initiation promotion studies and studies using transgenic mice. The approach used was consistent and implemented during all stages of the systematic review process. Therefore, as stated in Annex 1, high CoE requires evidence from long term cancer bioassays. More details are given in our SR. None of this weighting is new. Most human cancer hazard evaluations performed by national and international expert consensus evaluations are primarily based on chronic cancer bioassays. This also extends to the assessment of tumor concordance between experimental animals and humans (Baan et al., 2019; Krewski et al., 2019).

The statement by Karipidis *et al.* that our conclusions on different animal models did not warrant a downgrade in the CoE, and that a meta-analysis should not be conducted over different animal models, are contradictory and clearly displays their lack of understanding of the toxicological literature being reviewed. Mice do not always respond like rats, who do not always respond like humans. Even in one species, two strains do not always respond in the same way. Basically, while all of these mammals are similar, they still harbour significant biological differences that cannot be ignored. For this reason alone, it is biologically consistent to consider a negative response in one species/strain/sex as not downweighing a positive response in a different sex/species/strain AND combining results seen from different sex/species/strain experiments should be done judiciously. This is specifically spelled out in many of the guidelines cited earlier and was outlines in our published study protocol.

6. Task of this SR

The paragraph in the letter by Karipidis *et al.* referring to translation of animal results to humans is irrelevant. The task of this review did not include risk assessment in humans based on the findings in animals. The task was to determine if RF-EMF exposures could cause cancer in laboratory animals. The interpretation Karipidis *et al.* added to their letter regarding how CoE should be handled is not at all related to any statements in our SR.

Section 4 of the letter by Karipidis *et al.* provides no detail and vague criticisms on what is flawed. The analysis of the data giving statistically significant trends for certain neoplasms and preneoplastic lesions, e.g., glial-cell-derived tumors, heart schwannomas, are not deviating from the protocol. However, it is difficult to figure what the authors are referring to.

7. Conclusions

In conclusion, the concerns raised by Karipidis *et al.* reflect certain gaps in the application of toxicological principles, particularly with respect to risk identification and contemporary methodologies in experimental carcinogenesis. The methodology used in our evaluation of the data has been applied appropriately.

CRediT authorship contribution statement

Meike Mevissen: Writing – original draft, Conceptualization. **Angélique Ducray:** Writing – review & editing. **Jerrold M. Ward:** Writing – review & editing. **Annette Kopp-Schneider:** Writing – review & editing. **Tania M. Rivero:** Writing – review & editing. **Kurt Straif:** Conceptualization.

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Declaration of competing interest

KS has been the Head of the IARC Monographs program until his regular retirement (11/2018). Since 10/2019, he is a member of the International Scientific Advisory Committee of the Ramazzini Institute. This involves one 3 h advisory group meeting per year. He does not receive remuneration for his advisory activity.

MM is a member of the scientific advisory board of The Swiss Research Foundation for Electricity and Mobile Communication (FSM) at the ETHZ in Zurich that receives research money from commercial entities. Her partner does consulting relating to cell phone safety.

Data availability

No data was used for the research described in the article.

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