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The Systematic Review on RF-EMF Exposure and Cancer by Karipidis et al. (2024) has Serious Flaws that Undermine the Validity of the Study's Conclusions

To the Editors, Environment International

We write as members of the ICBE-EMF, an international non-profit group of independent multidisciplinary scientists from backgrounds relevant to the safety of radiofrequency electromagnetic fields (RF-EMF) from wireless telecommunication devices and systems (https://icbe-emf.org). We recently completed a detailed analysis, including an assessment of the epidemiological methodology used, of the systematic review (SR) and *meta*-analysis by Karipidis et al. (2024). That review concluded there is "moderate certainty evidence" that exposure to such telecommunications-related EMFs "does not increase the risk of glioma, meningioma, acoustic neuroma, pituitary tumours, salivary gland tumours or paediatric brain tumours" (Karipidis et al., 2024).

We disagree with that conclusion because the Karipidis et al. (2024) review *does not provide a scientifically valid assessment of the evidence* on the risk of these tumors associated with use of mobile phones or other wireless devices, due to critical methodological flaws. These flaws combine to make the conclusions of this review biased, in a direction that systematically understates the potential for causation.

Although Karipidis and his co-authors declared no competing interests, it should be noted that some of them had linkages to the telecommunications industry and/or were members of ICNIRP, a self-selected organization that promotes its own RF-EMF radiation protection guidelines based on self-referencing authorships and had previously declared there is no evidence of increased cancer risk from exposure to RF-EMF (Hardell and Carlberg, 2020; Nordhagen and Flydal, 2022; Nyberg et al., 2023).

Five key weaknesses of the Karipidis et al. (2024) SR:

1. Basing conclusions on studies with Flawed Designs

The authors included several major studies in their *meta*-analysis which have been shown in peer-reviewed publications to have serious design flaws. In particular, the Interphone case-control studies (Interphone Study Group, 2011) have been found by independent reviewers (e.g. Choi et al., 2020) to have biased controls' selection, with over-representation of cell phone users compared to the general population, leading to systematic underestimation of the actual strength of association between RF-EMF exposure and cancers, to the extent that most Interphone studies found such exposures to be protective against cancer risk – a hypothesis with no scientific justification.

Two major cohort studies, the Danish cohort study and the Million Woman Study, had serious design flaws. In its assessment and classification of brain cancer risk from exposure to radiofrequency radiation, the International Agency for Research on Cancer (IARC, 2013) downplayed the value of the Danish cohort and its updated studies (Frei et al., 2010, 2011; Schüz et al., 2006a,b) because they relied on subscriptions to mobile phone providers as a surrogate for mobile phone use: the study "lacked information on level of mobile-phone use and there were several potential sources of misclassification of exposure"– which will always underestimate the strength of association in cohort studies. The Million Women Study (Schüz et al., 2022) not only had poor exposure assessment, it suffered from high participant attrition and was underpowered (Moskowitz, 2022).

2. Excessive Reliance on RF-EMF exposure Categories that do not reflect extent of exposure

In their assessment of potential biases in the primary studies which they included in their *meta*-analyses, Karipidis et al. (2024) were too lenient in including studies with major weaknesses in their measurement of RF-EMF exposures. In their *meta*-analysis depicted in Figure 2, no less than three cohort studies and ten case-control studies were included which employed the use of overly simplistic "dosage" measures for actual phone use, such as "ever" versus "never," and "time since start of use." Because this approach does not use actual measures of exposure, it would be expected to create exposure misclassification, which, as already noted, tends to obscure any actual dose–response relationships that might have been observed, again reducing the strength of the evidence for causation (Hill, 1965; Carlberg and Hardell, 2017).

Additionally, Karipidis et al. (2024) use complex biostatistical models – for which critical information is not provided (such as goodness-of-fit to empirical data in the primary studies) – to estimate the dose–response relationship between cumulative call-time (CCT), a better estimate of actual RF-EMF dosage. However, their graphs of these models' outputs (e.g., Figure 6 for gliomas) show that the primary studies had little statistical power to inform the models' estimates of relative risks at high CCT levels. A newly-published *meta*-analysis (Moon et al., 2024) employs better epidemiological methodology, and – based on almost exactly the same primary studies – finds (in Figure 2) that higher levels of CCT (greater than 896 h) are associated with a statistically significantly higher relative risk of brain tumors (OR 1.59, 95 % CI 1.25–2.02).

One especially useful aspect of dose–response studies involves separately analysing tumors which are ipsilateral, versus contralateral, to the side of the head that the cancer patient normally has held his/her phone. Moon et al.'s (2024) sophisticated analysis reveals that over two dozen primary studies, when pooled, have found a consistently higher odds ratio of 1.40 (95 % CI 1.21–1.62) for ipsilateral tumors than for contralateral ones (OR 1.04, 95 % CI 0.93–1.16). Karipidis et al. (2024) fail to make full use of these studies, again reducing their analysis' capacity to identify important dose–response relationships strongly

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suggestive of causation in environmental health (Hill, 1965).

In addition to the recent study by Moon et al., several previously published *meta*-analyses of case-control studies that were based on cumulative call time found significant increases in brain tumor risk associated with heavy and long term use (greater than 10 years) of mobile phones, and the risk was greatest on the side of the head in which the user had held their mobile phone (Wang and Guo, 2016; Bortkiewicz et al., 2017; Carlberg and Hardell, 2017, Prasad et al., 2017; Yang et al., 2017; Choi et al., 2020).

3. Mischaracterization of the evidence on brain cancer Time-Trends

The authors claim that their time-trend simulations provided an external validation of their "moderate" rating of the certainty of the brain cancer evidence. However, cancer time trends do not capture the unique use and exposure characteristics of the groups in which brain tumor risks were increased in the case-control studies, such as tumor risks in the areas of the brain (temporal lobe) with the highest absorption of RF radiation emitted from a mobile phone held next to the head. Critically, key studies finding recent increases in population-level incidence for such brain cancers were omitted by Karipidis et al. (Philips et al., 2018; Hardell and Carlberg, 2017; Zada et al., 2012; Defossez et al., 2019; Davis et al., 2020).

4. Understatement of the Considerable uncertainty about cancer risk after longer latent periods following exposure

Several authors of this review had previously written that some uncertainty remains regarding long latency periods greater than 15 years for cancer development (as would be expected by cancer experts). Those uncertainties were not resolved, nor even fully cited, in Karipidis et al. (2024). Furthermore, the authors do not give recognition to the evidence we already have that is highly suggestive of causation over long latencies (Hardell et al., 2013; Hardell and Carlberg, 2015; Carlberg and Hardell, 2017) – e.g. for total wireless phone use, the highest risk, while imprecisely estimated (and therefore requiring independent replication), was calculated for the longest latency time, >20 years (OR 4.4, 95 % CI 2.2–9.0) (Hardell et al. 2013).

The studies cited by Karipidis et al. lacked sufficient follow-up time to detect and diagnose late-developing cancers. The International Agency for Research on Cancer Monographs (IARC, 2013) preamble states "experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; therefore, latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.".

5. Failure to follow widely used scientific guidance for systematic Reviews and Meta-Analyses

The authors failed to follow standard guidance for pooling the results of primary studies. They ignored high levels of inconsistency (despite the fact that they document and quantify these inconsistencies across the studies' results —- for example, an I-squared value of over 61 % across all the primary studies in their Figure 2, and even higher I-squared values in their Figure 3). Such inconsistency is usually considered a contraindication to pooling the results across the primary studies (Ioannidis, 2018). They also proceeded in some of their *meta*-analyses to pool the results of fewer than five primary studies on a given research question, in contravention of widely cited statistical guidance (Valentine et al., 2017). These failings all have the effect of making the scientific certainty of their conclusions appear much greater than it actually is.

Conclusion

Considering these methodological flaws, we find that few, if any, of the RF-EMF exposure/tumor associations examined by Karipidis et al. have been the subject of sufficiently replicated, high-quality primary studies, of adequate power and follow-up time, to warrant any legitimate scientific certainty about the absence of causation, especially when accounting for the animal studies of RF-EMF carcinogenicity (Falcioni et al., 2018; National Toxicology Program, 2018a, 2018b). The overall GRADE recommendations in this paper appear to reflect biases of the authors. In contrast to the authors' rating of the evidence for RF-EMF exposures NOT causing these tumors as being of "moderate certainty," we contend there is no scientific justification for concluding there is any certainty that RF-EMF exposures do not cause cancer.

CRediT authorship contribution statement

John W. Frank: Writing – original draft, Conceptualization. **Joel M. Moskowitz:** Writing – review & editing, Conceptualization. **Ronald L. Melnick:** Writing – review & editing, Conceptualization. **Lennart Hardell:** Writing – review & editing. **Alasdair Philips:** Writing – review & editing. **Paul Héroux:** Writing – review & editing. **Elizabeth Kelley:** Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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