

COMMENT

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Conflicting views in experimental carcinogenesis: a commentary on design and methodological deficiencies in the follow-up validation studies on radiofrequency radiation

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International Commission on the Biological Effects of Electromagnetic Fields

Abstract

Conflicting views in experimental carcinogenesis often arise due to differences in study design among reported studies. For carcinogenicity assessments, regulatory agencies, such as the US Food and Drug Administration (FDA), and intergovernmental advisory organizations, such as the Organization for Economic Co-operation and Development (OECD), specify the use of at least three dose levels plus control group for trend analyses, with the highest dose inducing a measurable toxic response. In addition, there needs to be a sufficient number of animals per group to have adequate power to detect a true carcinogenic effect. Departure from such recommendations can weaken the interpretations of study results. We examine here two recent carcinogenicity studies from Japan and Korea that were conducted following the positive carcinogenicity study of radiofrequency radiation (RFR) in experimental animals by the National Toxicology Program (NTP). The Japan and Korea follow-up studies used fewer animals per group, a single RFR exposure group, and a lower exposure level than the NTP study. Not surprisingly, while the NTP study revealed the carcinogenicity of RFR, the Japanese and Korean studies, which had reduced statistical power compared to the NTP study, issued conclusions conflicting with those of the more substantial NTP study on the health effects of RFR. In general, carcinogenicity studies with weaker doses, fewer exposure groups, and reduced statistical power should not be used to test the validity of more robust studies.

Keywords NTP Carcinogenicity Study, Japanese-Korean validation studies, Radiofrequency Radiation, Heart Schwannoma, Specific Absorption Rate

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Conflicting views on the interpretation of experimental carcinogenicity results have arisen frequently due to the importance and potential use of those results in setting regulatory exposure limits, e.g., glyphosate [1]. This circumstance, compounded with uncertainties of the magnitude of human health risks estimated from animal data, has created divisions between those who advocate for precautionary health measures when experimental data identify a carcinogenic effect versus those who argue against exposure reductions until adverse effects are clearly demonstrated in humans [2]. Factors related to study design and evaluation requirements necessary for reliable rodent carcinogenicity studies are major sources of conflicting views in experimental carcinogenesis; these include use of sensitive models, challenging doses and durations of exposure, sufficient numbers of animals per group to have adequate power to detect a true effect, multiple dose groups to characterize dose-response relationships, complete and peer-reviewed histopathological evaluations, and both pairwise comparisons and statistical analyses of trends [2]. Though these issues have impacted interpretations of chemical carcinogenesis studies, they also pertain to experimental carcinogenesis studies of physical agents.

This commentary addresses critical experimental design features in the recently published Japanese and Korean carcinogenicity studies of mobile phone radio-frequency radiation (RFR) [3, 4], which were conducted under the umbrella of “The International Validation Project of the NTP Study on the Carcinogenesis of Mobile-Phone RFR” [5]. The objective of those studies was “to evaluate the reproducibility of the NTP study results,” referring specifically to the positive outcomes observed in male rats exposed to Code-Division Multiple Access (CDMA)-modulated 900 MHz RFR [3–5].

However, the experimental design and exposure conditions in the Japan–Korea studies reduced the sensitivity of those studies compared to the NTP study [6] and had the practical effect of precluding the validation of the NTP findings. Instead of clarifying or validating the NTP results as intended, the design of the new studies (discussed below) resulted in data that appeared to create doubt about the carcinogenic effects of RFR in experimental animals.

The NTP studies of RFR involved prenatal, lactational and 2-year exposures of male and female Harlan Sprague-Dawley rats ($N = 90$ per group) in specially designed and validated reverberation chambers to CDMA- and to Global System for Mobile Communications (GSM)-modulated 900 MHz RFR at whole-body specific absorption rates (SAR) of 0 (sham control), 1.5, 3.0, and 6.0 W/kg [6]. These studies provided “clear evidence” of malignant heart schwannomas in male rats with exposures to CDMA- or GSM-modulated RFR. For the CDMA exposures, there was a statistically significant increase in the

trend test for heart schwannomas, and the incidence in the 6 W/kg dose group was increased significantly compared to the sham control group. Additionally, the NTP reported “some evidence” of brain gliomas and adrenal medulla pheochromocytomas (the latter specifically from GSM exposure), as well as significant increases in Schwann cell hyperplasia in the heart endocardium (a putative preneoplastic lesion), right ventricle cardiomyopathy, and reduced pup birth weights with CDMA and GSM exposures; none of the latter adverse effects were addressed in the Japan-Korea “validation” studies. The terms “clear evidence” and “some evidence” are two of five categories of evidence of carcinogenic activity used in NTP Technical Reports to summarize the strength of evidence observed in each experiment. A 3-day external peer review of the NTP studies supported these levels of evidence (https://ntp.niehs.nih.gov/sites/default/files/ntp/about_ntp/trpanel/2018/march/peerreview20180328_508.pdf).

In contrast to the NTP, the studies conducted in Japan [3] and in Korea [4] involved exposure of male Harlan Sprague-Dawley rats in reverberation chambers to 900 MHz CDMA-modulated RFR only at a single SAR of 4 W/kg, plus sham control and cage control groups ($N = 70$ per group). To properly verify findings of rare tumors, such as malignant heart schwannomas and brain gliomas reported in rodent studies, follow-up studies must be designed with equal or greater sensitivity by substantially increasing the number of animals per group and including the highest exposure level used in the original study, as well as multiple dose groups. The studies by Imaida et al. [3] or Kim et al. [4] did not meet these obvious requirements. Simply claiming that the “overall design [was] closely linked to the NTP findings” [3] is not sufficient for a valid follow-up verification study. Excluding the 6 W/kg group is a critical deficiency in those studies, and the use of a single RFR exposure level eliminates the ability to analyze trends, which are *essential* for interpreting carcinogenicity data [7, 8]. In the WHO-sponsored systematic review on the effects of RF-EMF on cancer in laboratory animals, the authors [9] ascertained whether there was an effect of exposure if there was at least one exposure that showed an increase in cancer incidence or if there was a significant positive trend. In addition, the certainty of evidence is greater for increases in rare tumors, e.g., malignant heart schwannomas.

Imaida et al. [3] acknowledged the shortcomings of their studies: “the number of animals per group (70 males) and the use of a single exposure level (4 W/kg) inevitably limited the statistical power compared with the multi-dose design of the NTP study,” especially “to detect rare, low-incidence tumors.” The authors of the Japan and Korea validation studies should have performed power analyses when the studies were being designed to ensure

that their studies would have a sufficient number of animals per group to detect a significant response similar to the NTP study. For a follow-up validation study, a power value of at least 80% and preferably 90% should have been required. Linear interpolation of the heart schwannoma results from the NTP study yields an expected incidence of approximately 4.4% at 4 W/kg. A power calculation (<https://homepage.univie.ac.at/robin.ristl/samplesize.php?test=fishertest>) based on that value and an assumed incidence of 0.5% in the sham control group yields a required sample size of 258 animals per group for 80% power and 323 animals per group for 90% power. Thus, the Japan-Korea studies with only 70 animals per group did not have sufficient power to challenge the validity of the NTP carcinogenicity findings on RFR or to substantiate the authors' claim that their results show that CDMA-modulated 900 MHz RFR is non-carcinogenic at 4 W/kg. Even a combination of those studies ($N = 140$ per group) is greatly underpowered.

For carcinogenicity studies in experimental animals, the Food and Drug Administration (FDA), which provides scientific support to the Federal Communications Commission on RFR emissions from wireless devices in the US, as well as the Organization for Economic Cooperation and Development (OECD) guidelines specify the use of at least three dose levels plus a concurrent control group for trend analysis, with the highest dose being the maximum tolerated dose (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivc6-carcinogenicity-studies-rodents>; https://www.oecd.org/content/dam/oecd/en/publications/reports/2018/06/test-no-451-carcinogenicity-studies_g1gh2955/9789264071186-en.pdf). Thus, both the Japan and Korea single dose studies did not follow the FDA or OECD guidelines for the conduct of carcinogenicity studies in experimental animals.

The single 4 W/kg dose was selected by the authors because it "is a key reference point" in ICNIRP guidelines [10] for use in setting limits "to protect from adverse effects for acute exposure" [5]. However, a regulatory set-point should not be used as justification for conducting follow-up chronic studies with reduced sensitivity and at a single lower dose than the study that the investigators were attempting to verify. The FDA document noted above also states: "...the highest dose in a carcinogenicity study should not be selected so as to provide a pre-determined margin of safety over the maximum expected human exposure to the test substance, assuming that the results of testing at that dose will be negative." Yet, the choice of 4 W/kg seems aimed precisely at a data point inspired from the ICNIRP guidelines. The ICNIRP exposure limits are based on an acute threshold response to a single behavioral endpoint in 8 rats and 5 monkeys [11]. Consequently, the threshold dose derived from those

limited acute studies cannot be used to support the adequacy of a challenging dose for a chronic carcinogenicity study in experimental animals.

It is noteworthy that in the study by Kim et al. [4], the unadjusted rate of heart schwannomas was 3% in the RFR exposure group (versus 0/70 in both the sham and cage control groups, reflecting the rare occurrence of this tumor in unexposed rats), which is the same value as the unadjusted rate in the 3 W/kg dose group of rats exposed to CDMA-modulated RFR in the NTP study [6]. Interpretation of the Kim et al. [4] result is therefore severely compromised by the exclusion of the 6 W/kg dose group.

Despite the numerous limitations in their study design, the authors of the Japan-Korea studies concluded there is "no reproducible carcinogenic potential of mobile phone-type RF exposure in rats," and that alternatives to the ICNIRP "recommend[ed] exposure limits for RF radiation based on thermal effects" are inconclusive [3]. These statements reflect ideological support for ICNIRP's thermal-only mechanism of adverse effects and its repeated dismissal of the validity of the NTP carcinogenicity studies (e.g. [12]). The project's principal investigator is a member of ICNIRP, and the advisory committee that provided oversight and guidance throughout this project was heavily represented by current and past members of ICNIRP, suggesting a strong influence of ICNIRP in the design and interpretation of these studies.

In conclusion, methodological shortcomings due to the design choices in the Japan-Korea studies, specifically the restriction to a single exposure group of 4 W/kg of CDMA-modulated RFR and reduced statistical power, systematically biased the study toward null results and eliminated the possibility of detecting a positive trend. Consequently, these findings cannot be used to reasonably refute the peer-reviewed evidence of toxicity and carcinogenicity of CDMA- and GSM-modulated RFR in the NTP studies, nor to reinforce ICNIRP's thermal-based exposure limits. It is also important to note that the increases in schwannomas and gliomas reported in experimental studies of RF-EMF are of the same tumor types (glioma and vestibular schwannoma) that were increased in epidemiological studies in which brain cancer risk was increased among heavy users of mobile phones [13]. The example described in this commentary demonstrates how limited and divergent experimental designs and potential biases in the interpretation of experimental carcinogenicity results can lead to conflicting views on the health effects of RFR.

Reproducibility of experimental findings is a hallmark of scientific discovery. For meaningful comparisons of different results between studies, it is essential that the most relevant conditions in the original study be duplicated or have greater power (e.g., increased group size) in the follow-up study to verify or refute significant findings.

For experimental carcinogenesis studies, these factors include use of the same test agent, exposure environment, animal model, group size, diet, water purity, necropsy/histopathology procedures, diagnostic criteria, etc. For appropriate interpretation and validation of experimental carcinogenicity data, it is essential that the subsequent study(s) include doses at which tumor responses were significantly increased in the original study and that exhibited significant positive trends. Lastly, assertions that extend beyond actual findings should not be portrayed as established facts.

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Authors' contributions

RLM, JMM, and PH wrote the manuscript text. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

RLM led the design of the National Toxicology Program's studies on radiofrequency radiation. The other authors declare no competing interests.

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