Regarding ICNIRP'S Evaluation of the National Toxicology Program's Carcinogenicity Studies on Radiofrequency Electromagnetic Fields

Dear Editor:

In the International Commission on Non-Ionizing Radiation Protection (ICNIRP) note (ICNIRP 2019) on the evaluation of the recent carcinogenicity studies of radiofrequency electromagnetic fields (RF-EMF) in experimental animals, the authors made several incorrect statements that appear to be written to justify retaining exposure standards that were established more than 20 y ago. In fact, the ICNIRP note concludes, "…if the research was shown to have relevance to humans, this would represent a crucial issue for ICNIRP to incorporate into the advice and guidance that it provides to the community through a range of formats, such as its RF EMF exposure guidelines." This correspondence focuses on correcting ICNIRP's false claims about the methodology, interpretation, and relevance of the National Toxicology Program studies on cell phone RF radiation (NTP 2018a and b). Several issues raised in the ICNIRP note were addressed by Melnick (2019) and in the NTP response to the initial reviews of the cancer findings in rats that are included in the NTP report of partial findings of the carcinogenesis studies of cell phone radiofrequency radiation (Wyde et al. 2016) but were ignored in the ICNIRP note.

ICNIRP wrongly claims that methodological issues "preclude drawing conclusions about carcinogenicity" from the NTP studies on RF radiation

Pathology review procedures

The NTP has provided results on the carcinogenicity of approximately 600 environmental and occupational agents. These results have been used by IARC (International Agency for Research on Cancer) and other public health agencies throughout the world to assess human risk and set health-protective exposure standards. The three-tier pathology review process is the most rigorous approach used by any research organization to identify neoplastic and non-neoplastic lesions associated with exposure to a test agent. The ICNIRP note claims that because the initial pathology examination was not blinded as to the dose group in which slides were read, there were biases in these histopathological evaluations. However, the NTP's pathology review process involves much more than "samples where pathology was found (i.e., only a few percent of the total number) were then analyzed by another pathologist who was partially blind to the exposure status." For all NTP studies, an independent quality assessment pathologist (second tier) reviews all lesions identified by the laboratory pathologist plus 10% of all remaining tissues. The reviews of the histopathology slides and final diagnoses of lesions in the RF radiation studies were made by pathology working groups (third tier involving over 30 pathologists). The latter reviews were conducted similarly to all other NTP studies in that the pathologists did not know whether the slides they were examining came from an exposed or an unexposed animal (Maronpot and Boorman 1982). In fact, the reviewing pathologists didn't even know that the test agent was RF radiation. The assertion by ICNIRP, which has never been made in the 40-y existence of the NTP, impugns the validity of all 600 bioassays performed by this program. However, for anyone questioning the diagnosis of any tissue in this study, unlike most other institutional studies, all of the slides from the NTP studies are available for examination at the NTP archives.

Rat survival rates

The ICNIRP note states "…that survival was lower and mortality faster in the male rat controls than in the exposed groups" and, therefore, "There remains a strong possibility that the decrease in survival resulted in underrepresentation of late-developing tumors in the controls that importantly affected the statistical results." However, as explained by Melnick (2019), this comment is an inaccurate portrayal and interpretation of the data for at least two reasons: (1) there was no statistical difference in survival between control male rats and the exposure group with the highest rate of gliomas and heart schwannomas (CDMA-exposed male rats, SAR = 6.0 W kg^{-1}), and until week 93 of the 2-y study, survival was greater in control male rats than in the 6 W kg^{-1} CDMA-exposed male rats [the mean survival for male rats in the 6 W kg^{-1} CDMA exposure group (637 d) was actually 5 d less than that for control male rats (642 d) (NTP 2018a)]; and (2) no glial cell hyperplasias (potential precancerous lesions that can progress to a malignant glioma) or heart schwannomas were observed in any control rat, even though glial cell hyperplasia was detected in exposed rats as early as week 58 of the 2-y study, and heart schwannoma

The author declares no conflicts of interest.

0017-9078/20/0

DOI: 10.1097/HP.0000000000001268

was detected as early as week 70 in exposed rats. Thus, survival was sufficient to detect tumors or pre-cancerous lesions in the brain and heart of control rats.

In their draft of this note that was posted last year (https://www.icnirp.org/cms/upload/publications/ICNIRPnote2018.pdf), ICNIRP cited a paper by Novilla et al. (1991) on the prevalence of spontaneous endocardial proliferative lesions in rats. The fact that Novilla et al. did not see either hyperplasias or schwannomas in 100 control male Sprague-Dawley rats lends further credibility to the absence of these lesions in the NTP study in Sprague-Dawley rats and supports the increased incidences of cardiac schwannomas being due to exposures to cell phone RF radiation. In addition, survival-adjusted overall primary tumor rates were greater in male rats exposed to GSM or CDMA RFR compared to concurrent control rats, with statistical significance observed in the 1.5 W kg^{-1} (CDMA) and in the 3.0 W kg^{-1} (GSM and CDMA) exposure groups (NTP 2018a; Lin 2019).

Multiple comparisons

Because of the large number of statistical comparisons, the ICNIRP note claims that by "…using a significance level of $p < 0.05$, many hundreds are expected to be significant by chance alone," and "It is therefore not possible to determine whether any of the results are due to RF-EMF exposure, as opposed to chance." This issue came up in the peer review of the NTP report of partial findings from the carcinogenesis studies of cell phone RF radiation (Wyde et al. 2016) and was addressed in the NTP's response to the reviewer's comments: "Although the NTP conducts statistical tests on multiple cancer endpoints in any given study, numerous authors have shown that the study-wide false positive rate does not greatly exceed 0.05 (Fears et al. 1977; Haseman 1983; Office of Science and Technology Policy 1985; Haseman 1990; Haseman and Elwell 1996; Lin and Rahman 1998; Rahman and Lin 2008; Kissling et al. 2014). One reason for this is that NTP's carcinogenicity decisions are not based solely on statistics. Many factors go into this determination, including whether there were pre-neoplastic lesions, whether there was a dose-response relationship, biological plausibility, background rates and variability of the tumor, etc. Additionally, with rare tumors especially, the actual false positive rate of each individual test is well below 0.05 due to the discrete nature of the data, so the cumulative false positive rate from many such tests is less than a person would expect by multiplying 0.05 by the number of tests conducted (Fears et al. 1977; Haseman 1983; Kissling et al. 2015)" (Wyde et al. 2016). Gliomas and heart schwannomas, which were found in the NTP studies on RF radiation, are uncommon tumors that occur rarely in control Sprague-Dawley rats.

Additional incorrect statements and misinformation in the ICNIRP critique that aim to undermine the utility of the NTP studies for assessing human health risks

1. One reason given by the ICNIRP Commission for dismissing the carcinogenic effects of RF-EMF in experimental animals is "...because there is currently no verified mechanism that would predict that RF EMFs would be carcinogenic." However, there is no requirement to establish a verified mechanism before accepting the carcinogenicity results of an agent in experimental studies. For most or perhaps all of the NTP studies that demonstrated carcinogenic activity, no verified mechanism had been identified when the studies had been completed. With respect to RF-EMF, Yakymenko et al. (2016) reported that evidence of oxidative stress was observed in 93 of 100 studies dealing with oxidative effects of low intensity RF radiation. Furthermore, oxidative stress can lead to mutations, chromosomal translocations, and genetic instability (Smith et al. 2016), and DNA damage was observed in brains of rats and mice exposed to RF radiation in the NTP studies (NTP 2018a and b; Smith-Roe et al. 2019). Oxidative stress caused by EMFs is thought to be due to the altering of recombination rates of short-lived radical pairs leading to increases in free radical concentrations (Barnes and Greenebaum 2015). Thus, oxidative stress leading to DNA damage may be involved in the induction of tumors from exposure to RF radiation (Lai and Singh 1997).
2. The ICNIRP Commission claims that "none of the compared pathologies were specified a priori as primary end points." This is wrong; all of the endpoints in the NTP study were specified in the NTP Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals, and in the Statement of Work for the conduct of the studies on RF radiation prior to the start of these studies.
3. In their evaluation of the carcinogenic potential of RF-EMF, the ICNIRP note failed to recognize that focal hyperplasias (proliferative lesions) of glial cells in the brain and of Schwann cells in the heart are putative preneoplastic lesions that may progress to malignant glioma or to cardiac schwannoma, respectively. In fact, the term hyperplasia is not present in the ICNIRP note.
4. While the ICNIRP note focused on the carcinogenicity of RF-EMF from animal studies, it neglected to point out that other adverse effects were observed in the NTP studies, including reduced birth weights, DNA strand breaks in brain cells (which is supportive of the cancer findings), increased incidences of

proliferative lesions (tumors and hyperplasia) in the prostate gland, and exposure-related increases in the incidence of cardiomyopathy of the right ventricle in male and female rats. In addition, other studies have reported adverse effects on male and female reproduction and neurobehavioral effects resulting from exposure to low intensity non-ionizing radiation (Belpomme et al. 2018).

5. In their attempt to downplay the concordance between schwannomas observed in animal studies and in human studies on cell phone radiation, the ICNIRP Commission claimed that an increased incidence of vestibular schwannoma (also called acoustic neuroma) from mobile phone use was reported "mainly by one research group" (Hardell et al. 2005, 2013). This statement is wrong since the INTEPHONE Study group (2011) reported that the odds ratio (OR) for acoustic neuroma after ≥10 y of mobile phone use was 2.79 (95% confidence interval: 1.51-5.16) for ≥1,640 h of cumulative call time. In addition, there were significant increases in the incidence of acoustic neuroma for ≥10 y use and on the same side of the head as reported phone use among the North European countries that participated in the Interphone study (Lönn et al. 2005; Shoemaker et al. 2005). The fact that "malignant cardiac schwannomas are extremely rare tumors in humans" and have not been investigated in epidemiological studies of RF-EMF does not detract from the concordance in cell type affected in animals and humans. The NTP findings of significantly increased incidences and/or trends for gliomas and glial cell hyperplasias in the brain and schwannomas and Schwann cell hyperplasias in the heart of exposed male rats are most important because the IARC classified RFR as a "possible human carcinogen" based largely on increased risks of gliomas and acoustic neuromas (which are Schwann cell tumors on the acoustic nerve) among long-term users of cell phones.

The hypothetical argument raised by ICNIRP about the effect of one additional cardiac schwannoma in the control group on *p* values lacks scientific credibility; one must analyze the available data rather than insert arbitrary values to downplay the significance of a true response. As noted above, carcinogenicity evaluations by the NTP are not based solely on statistics; other factors such as the presence of preneoplastic lesions and the rarity of the tumor also impact the evaluation of carcinogenic activity.

6. The ICNIRP note claims that, "The exposure levels used in NTP would indeed have raised body core temperature substantially," which "would have put them [male rats] under greater metabolic stress due to their greater thermoregulatory requirements." The main reason for this claim is that the "NTP measured superficial temperature rather than the body core temperature." However, there is no evidence to support the claim of substantial elevation of core temperature or that the rats were under metabolic stress. The NTP study used subcutaneously implanted transponders to monitor the effects of RF exposure on core body temperature; this approach was chosen because Kort et al. (1998) had shown that temperature changes recorded by the subcutaneous transponders did not differ significantly from rectal temperature measurements in rats or mice. In addition, it is clear that animals tolerated the exposure levels used in the NTP study, as there were no significant effects on body temperature, body weights in the 2-y study, induction of tissue damage in the 28-d study, nor exposure-related clinical observations.
7. The ICNIRP note claims that the "NTP exposures are not directly relevant to those encountered in the community" because "the NTP exposure of 6 W kg^{-1} is therefore 3 times higher than the local exposure restriction and 75 times higher than the whole-body exposure restriction for the general public." While the exposure limit to RF radiation for the general population in the US and Europe is 0.08 W kg^{-1} averaged over the whole body, the localized exposure limit is 1.6 W kg^{-1} averaged over any 1 g of tissue in the US (FCC 1997) and 2 W kg^{-1} averaged over any 10 g of tissue in Europe; for occupational exposures, the limit is five times higher (0.4 W kg^{-1} for whole-body exposures in the US and Europe, and 8 W kg^{-1} and 10 W kg^{-1} for localized exposures in the US and in Europe, respectively) (FCC 1997; ICNIRP 1998). Thus, the whole-body exposure levels in the NTP study were 19 to 75 times higher than the FCC's and ICNIRP's whole-body exposure limit for the general population and only 3.8 to 15 times higher than the occupational whole-body exposure limit. Whole-body SAR, however, provides little information about organ-specific exposure levels (IARC 2013). When an individual uses a cell phone and holds it next to his or her head, body tissues located nearest to the cell phone antenna receive much higher exposures than parts of the body that are located distant from the antenna. Consequently, the localized exposure level is more important for understanding and assessing human health risks from cell phone RF radiation. When considering organ-specific risk (e.g., risk to the brain) from cell phone RF radiation, the important measure of potential human exposure is the local SAR value of 1.6 W kg^{-1} (US) or 2 W kg^{-1} (Europe). In the NTP study in which animals were exposed in

reverberation chambers to whole-body RF radiation at SARs of 1.5, 3, and 6.0 W kg^{-1}, exposures in the brain were within 10% of the whole-body exposure levels. Thus, with respect to dosimetry in the brain, the exposures in the brain were similar to or only slightly higher than the localized exposure limits set by the FCC and ICNIRP for the general population (1.6 and 2 W kg^{-1}, respectively), and lower than the localized limits for occupational exposures of 8 and 10 W kg^{-1} (FCC 1997; ICNIRP 1998). Consider the converse scenario. If the brain and whole-body exposures were limited to 0.08 W kg^{-1}, then localized exposures in humans from use of cell phones held next to the ear could be 20 to 25 times greater than exposures to the brain of rats in the NTP study. Under this condition, a negative study would not be informative for evaluating organ-specific human health risks associated with exposure to RF radiation. The ICNIRP statement, "Research using substantially lower exposure levels would be required in order to determine whether there was a risk to the public," is contradictory with methodologies used to assess population-based human cancer risk (US EPA 2005).

8. The NTP cancer study was 2 y in duration; animals were not exposed "over the whole of their lives." Surviving animals were killed at about 110 wk of age; e.g., more than 70% of mice were still alive at the end of the study (NTP 2018a and b).

CONCLUSION

ICNIRP's misrepresentation of the methodology and interpretation of the NTP studies on cell phone RF radiation does not support their conclusion that "limitations preclude drawing conclusions about carcinogenicity in relation to RF EMFs." In contrast to the ICNIRP evaluation, a 3-d independent peer-review of the NTP studies concluded that there was *clear evidence of carcinogenic activity* in male rats exposed to RF radiation (NTP 2018c). In addition, the dosimetry issue raised in the ICNIRP note falsely portrays the relevance and utility of the NTP cancer data for assessing human cancer risks. After all, it was the US Food and Drug Administration that requested the NTP studies of cell phone radiation in experimental animals to provide the basis to assess the risk to human health. The NTP studies show that the assumption that RF radiation is incapable of causing cancer or other adverse health effects other than by tissue heating is wrong. If ICNIRP's goal is truly aimed at protecting the public from potential harm, then it would be appropriate for this group to quantify the health risks associated with exposure to RF-EMFs and then develop health-protective guidelines for chronic exposures, especially for children, who are likely to be more susceptible than adults to adverse effects of RF radiation. At the very least, ICNIRP should promote precautionary advice for the general public rather than trying to justify their decision to dismiss findings of adverse health effects caused by RF-EMFs and thereby retain their 20+ y-old exposure guidelines that are based on protection against thermal effects from acute exposures.

Acknowledgments—The author led the design of the NTP studies on cell phone RF radiation during his tenure in the NTP.

RONALD MELNICK

Ron Melnick Consulting
North Logan, UT

REFERENCES

Barnes FS, Greenebaum B. The effects of weak magnetic fields on radical pairs. Bioelectromagnetics 36:45–54; 2015.

Belpomme D, Hardell L, Belyaev I, Burgio E, Carpenter DO. Thermal and non-thermal health effects of low intensity non-ionizing radiation: an international perspective. Environ Pollut 242(Pt A):643–658; 2018.

Federal Communications Commission. Evaluating compliance with FCC guidelines for human exposure to radiofrequency electromagnetic fields. OET Bulletin 65. Washington, DC: Federal Communications Commission Office of Engineering & Technology; 1997. Available at ***https://transition.fcc.gov/Bureaus/Engineering_Technology/Documents/bulletins/oet65/oet65.pdf***. Accessed 10 October 2019.

Hardell L, Carlberg M, Hansson Mild K. Case-control study on cellular and cordless telephones and the risk for acoustic neuroma or meningioma in patients diagnosed 2000–2003. Neuroepidemiol 25:120–128; 2005.

Hardell L, Carlberg M, Hansson Mild K. Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiol 20:85–110; 2013.

International Agency for Research on Cancer. IARC monograph on the evaluation of carcinogenic risks to humans: non-ionizing radiation, part 2: radiofrequency electromagnetic fields. Lyon, France: IARC; Volume 102; 2013.

International Commission on Non-Ionizing Radiation Protection. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). Health Phys 74:494–522; 1998.

International Commission on Non-Ionizing Radiation Protection. ICNIRP note: critical evaluation of two radiofrequency electromagnetic field animal carcinogenicity studies published in 2018. Health Phys. 118: [online]; 2020. Available at ***https://www.icnirp.org/cms/upload/publications/ICNIRPnote2019.pdf***. Accessed 10 October 2019.

INTERPHONE Study Group. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Cancer Epidemiol 35:453–464; 2011.

Kort WJ, Hekking-Weijma JM, TenKate MT, Sorm V, VanStrik R. A microchip implant system as a method to determine body temperature of terminally ill rats and mice. Lab Anim 32:260–269; 1998.

Lai H, Singh NP. Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells. Bioelectromagnetics 18:446–454; 1997.

Lin JC. The significance of primary tumors in the NTP study of chronic rat exposure to cell phone radiation [health matters]. IEEE Microw Mag 20:18–21; 2019.

Lönn S, Ahlbom A, Hall P, Feychting M, Swedish Interphone Study Group. Long-term mobile phone use and brain tumor risk. Am J Epidemiol 161:526–535; 2005.

Maronpot RR, Boorman GA. Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Tox Pathol 10:71–80; 1982.

Melnick RL. Commentary on the utility of the National Toxicology Program study on cell phone radiofrequency radiation data for assessing human health risks despite unfounded criticisms aimed at minimizing the findings of adverse health effects. Environ Res 168:1–6; 2019.

National Toxicology Program. Toxicology and carcinogenesis studies in Hsd:Sprague Dawley SD rats exposed to whole-body radio frequency radiation at a frequency (900 MHz) and modulations (GSM and CDMA) used by cell phones. Research Triangle Park, NC: National Toxicology Program; NTP TR-595; 2018a.

National Toxicology Program. Toxicology and carcinogenesis studies in B6C3F1/N mice exposed to whole-body radio frequency radiation at a frequency (1900 MHz) and modulations (GSM and CDMA) used by cell phones. Research Triangle Park, NC: National Toxicology Program; NTP TR-596; 2018b.

National Toxicology program. Peer review of the draft NTP technical reports on cell phone radiofrequency radiation. March 26-28, 2018 [online]. 2018c. Available at ***https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2018/march/peerreview20180328_508.pdf***. Accessed 10 October 2019.

Novilla MN, Sandusky GE, Hoover DM, Ray SE, Wightman KA. A retrospective survey of endocardial proliferative lesions in rats. Vet Pathol 28:156–165; 1991.

Schoemaker MJ, Swerdlow AJ, Ahlbom A, Avinen A, Blaasaas KG, Cardis E, Christensen HC, Feychting M, Hepworth SJ, Johansen C, Klaeboe L, Lonn, S, McKinney PA, Muir K, Raitanen J, Salminen T, Thomsen J, Tynes T. Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. Br J Cancer 93:842–848; 2005.

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect 124:713–721; 2016.

Smith-Roe SL, Wyde ME, Stout MD, Winters JW, Hobbs CA, Shepard KG, Green AS, Kissling GE, Shockley KR, Tice RR, Bucher JR, Witt KL. Evaluation of the genotoxicity of cell phone radiofrequency radiation in male and female rats and mice following subchronic exposure. Environ Mol Mutagen 61:276–290; 2020.

US Environmental Protection Agency. Guidelines for carcinogen risk assessment. Washington, DC: US EPA; EPA/630/P-03/001F; 2005. Available at ***https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf***. Accessed 15 October 2019.

Wyde ME, Cesta MF, Blystone CR, Bucher JR, Elmore SA, Foster PM, Hooth MJ, Kissling GE, Malarkey DE, Sills RC, Stout MD, Walker NJ, Witt KL, Wolfe MS. Report of partial findings from the National Toxicology Program carcinogenesis studies of cell phone radiofrequency radiation in Hsd: Sprague Dawley® SD rats (whole body exposures). BioRxiv 055699 (preprint 26 May 2016) [online]. 2016. Available at ***https://www.biorxiv.org/content/biorxiv/early/2016/05/26/055699.full.pdf***. Accessed 10 October 2019.

Yakymenko I, Tsybulin O, Sidorik E, Henshel D, Kyrylenko O, Kyrylenko S. Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. Electromagn Biol Med 35:186–202; 2016.

■■