Critique of the ICNIRP Note of September 4, 2018 Regarding
Recent Animal Carcinogenesis Studies

Ronald L. Melnick PHD
Senior Scientist (retired), National Toxicology Program, NIEHS, NIH

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The International Commission of Non-Ionizing Radiation Protection (ICNIRP, 2018) recently issued a report (dated September 4, 2018) that contains numerous false and misleading statements, particularly those about the toxicology and carcinogenesis studies on cell phone radiofrequency radiation by the US National Toxicology Program (NTP). This flawed analysis by ICNIRP served as the basis for ICNIRP to support their conclusion that existing radiofrequency exposure guidelines do not need to be revised despite new evidence showing that exposure to cell phone radiofrequency radiation (RFR) causes cancers in experimental animals. ICNIRP also does not take into account evidence on other harmful effects of cellphone radiation including damage to brain DNA, reduced pub birth weights, and decreased sperm quality.

There are numerous incorrect and misleading statements in this ICNIRP document, including the following:

1) The ICNIRP statement that "the NTP reports have not yet undergone full peer–review" is wrong; the NTP reports on cell phone RFR underwent multiple peer reviews, including an unprecedented 3-day independent review more than five months earlier in March 2018.

2) The ICNIRP statement that many endpoints presented in the NTP reports were not defined "a priori" is also wrong. All of the endpoints presented in the NTP reports were specified in the Statement of Work for the conduct of the NTP studies that was developed during my tenure at NTP.

3) ICNIRP incorrectly states many critical conclusions from the NTP studies (NTP 2018a, 2018b). The peer review panel in March 2018 (NTP 2018c) concluded that there was "clear evidence" of carcinogenic activity for heart schwannomas in male rats exposed to GSM- or CDMA-modulated RFR, "some evidence" of carcinogenic activity for brain gliomas in male rats (both GSM and CDMA), and "equivocal evidence" for heart schwannomas in female rats (both GSM and CDMA). These categories of evidence are defined in all NTP technical reports: some evidence of carcinogenic activity means that the test agent caused an increased incidence in neoplasms, but "the strength of the response was less than that required for clear evidence." Equivocal evidence of carcinogenicity means that there was "a marginal increase in neoplasms that may be test-agent related." Therefore, any analysis of the NTP data must include the brain gliomas and the heart schwannomas; the ICNIRP report excluded consideration of the RFR-induced gliomas.

4) The statement by ICNIRP that animals in the NTP study were exposed "over the whole of their lives" is incorrect. Surviving animals were killed at about 110 weeks of age; e.g., more than 70% of mice were still alive at the end of the study (NTP 2018a, 2018b).

5) The ICNIRP report criticized the exposure intensities used in the NTP studies as being "75 times higher than the whole-body exposure limit for the general public" and therefore "not able to inform on mobile-phone radiofrequency exposures." This issue had been raised before by others and is addressed in my paper (Melnick, 2018):

> "While the exposure limit to RFR for the general population in the US is 0.08 W/kg averaged over the whole body, the localized exposure limit is 1.6 W/kg averaged over any one gram of tissue (FCC, 1997); for occupational exposures, the limit is five times higher (0.4 W/kg and 8 W/kg, respectively). Thus, the whole-body exposure levels in the NTP study were higher than the FCC's whole-body exposure limits (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 RFR. When considering organ-specific risk (e.g., risk to the brain) from cell phone RFR, the important measure of potential human exposure is the local SAR value of 1.6 W/kg (the FCC's SAR limit for portable RF transmitters in the US, FCC 1997) averaged over any gram of tissue. In the NTP study in which animals were exposed to whole-body RFR at SARs of 1.5, 3, and 6.0 W/kg, exposures in the brain were within 10% of the whole-body exposure levels. Consider the converse scenario. If the brain and whole-body exposures were limited to 0.08 W/kg, then localized exposures in humans from use of cell phones held next to the ear could be 20 times greater than exposures to the brain of rats in the NTP study. Under this condition, a negative study would be uninformative for evaluating organ-specific human health risks associated with exposure to RFR. Therefore, exposure intensities in the brains of rats in the NTP study were similar to or only slightly higher than potential, localized human exposures resulting from cell phones held next to the head, and lower than the FCC's permissible localized limit for occupational exposures."

6) The claim by ICNIRP that the whole-body exposures in the NTP can produce adverse health effects is without foundation; the animals tolerated the exposure levels used in the NTP study without significant effects on body temperature, body weights, or induction of tissue damage (NTP 2018a, 2018b). The current RF exposure guidelines from the Federal Communication Commission, which are similar to those of ICNIRP, are based on a whole-body SAR of 4 W/kg, in order to 'protect' against adverse effects that might occur due to increases in tissue or body temperature of 1^{O}C or higher from acute exposures. The whole-body exposure limit of 0.4 W/kg SAR for occupational exposures and 0.08 W/kg SAR for the general public is based simply on dividing the 4W/kg value by 10 for occupational exposures and by 50 for the general public, while the exposure guideline limit for localized exposures in the US is 1.6 W/kg averaged over any one gram of tissue for the general population and 8 W/kg for occupational exposures (FCC, 1997) is based simply on multiplying the whole-body exposure limits by 20. For localized

exposures, the ICNIRP guideline is 2 W/kg averaged over any 10 grams of contiguous tissue for the general population, and 10 W/kg for occupational exposures. The NTP thermal pilot study showed that rats and mice could maintain body temperatures within $1^{O}C$ at 6 W/kg and 10 W/kg, respectively (Wyde et al., 2018). Thus, the exposures used in the NTP study are consistent with FCC and ICNIRP guidelines that limit whole body exposures to levels that do not cause any significant temperature increase. The 10x or 50x uncertainty factors applied to the 4 W/kg SAR are intended to protect against acute thermal effects, but do not address health risks from non-thermal or minimally thermal exposures. The ICNIRP report also criticized the use of subcutaneously implanted transponders to monitor the effects of RF exposure on core body temperature; however, Kort et al. (1998) showed that temperature changes recorded by the subcutaneous transponders did not differ significantly from rectal temperature measurements in rats or mice.

7) Criticism by ICNIRP concerning the consistency between the NTP studies (NTP 2018a) and the Ramazzini study (Falcioni et al., 2018) is disingenuous. The fact that both studies carried out in independent laboratories in Italy and the U.S. found increased incidences of heart schwannomas and Schwann cell hyperplasias in Sprague-Dawley rats under different exposure environments and different RF intensity levels is remarkable. Without knowledge or analysis of the true dose-response relationship between RFR exposure and the induction of schwannomas and Schwann cell hyperplasias of the heart, it is unreasonable to expect a linear dose-response by combining data from these two separate studies.

8) The discussion by ICNIRP concerning the "expected ratio'" of about 30% for schwannomas to hyperplasias is based on the paper by Novilla et al., 1991, and is a misrepresentation of the data and its relevance to the NTP study on cell phone RFR. In the Novilla paper, there were zero hyperplasias and zero schwannomas among 100 male Sprague-Dawley rats (there was one hyperplasia and one schwannoma in female Sprague Dawley rats). Most of the spontaneous hyperplasias and schwannomas reported in that paper were observed in Wistar rats (ratio ~ 3). However, even if there had been a difference in the ratio of spontaneous hyperplasias to schwannomas in that study, it still would not reflect the impact of cell phone RFR on that ratio. The fact that Novilla et al. did not see either hyperplasias or schwannomas in male Sprague-Dawley rats lends further credibility to the absence of these lesions in the NTP study in Sprague-Dawley rats and the increased incidences of schwannomas in exposed rats being due to the exposures to cell phone RFR.

9) It is noteworthy that ICNIRP cites two reviews that conclude there is no association between RFR and acoustic neuromas, while ignoring any mention of the IARC monograph (IARC, 2013)) that reported positive associations between RFR from cell phone and glioma and acoustic neuroma in humans.

10) The issue raised by ICNIRP on the lack of cardiac schwannomas in control male rats in the NTP study and the expected incidence (0-2%) based on historical control rates had been raised before by others and is addressed in my paper (Melnick, 2018) for both schwannomas and gliomas:

"Gliomas and schwannomas of the heart are uncommon tumors that occur rarely in control Sprague-Dawley rats. It is not unusual to observe a zero incidence of uncommon tumors in groups of 50-90 control rats. In experimental carcinogenicity studies, the most important control group is the concurrent control group. As mentioned above, the uniquely designed reverberation chambers used in the NTP study were fully shielded from external EMFs, and the lighting source was incandescent instead of fluorescent light bulbs. The housing of rats in the RFR shielded reverberation chambers could affect tumor rates in control animals. No data are available on expected tumor rates in control rats of the same strain (Hsd: Sprague Dawley rats) held under these specific environmental conditions. Thus, historical control data from previous NTP studies are not reliably informative for comparison to the results obtained in the cell phone RFR study."

11) The hypothetical argument raised by ICNIRP about the effect of one additional schwannoma in the control group is nonsense; one must analyze the available data rather than inserting arbitrary values to downplay the significance of a true response.

12) The discussion in the ICNIRP report concerning survival differences between controls and exposure groups affecting the relative tumor response had been raised before by others and is addressed in my paper (Melnick, 2018)

"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), and (2) no glial cell hyperplasias (potential precancerous lesions) or heart schwannomas were observed in any control rat, even though glial cell hyperplasia was detected in exposed rats as early at week 58 of the 2-year study and heart schwannoma 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."

13) The issue in the ICNIRP report about the need for blind pathology to avoid biases related to exposure status is discussed in my paper (Melnick, 2018).

"The reviews of the histopathology slides and final diagnoses of lesions in the RFR studies by the pathology working groups were conducted similar 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 RFR. For anyone questioning the diagnosis of any tissue in this study, all of the slides are available for examination at the NTP archives."

Also, the designations 'test agent A' and 'test agent B' refer to the separate studies of GSM and CDMA exposures and not to exposure status within a study. Therefore, these designations would <u>not</u> "result in bias because perceived patterns within a group's samples can affect how subsequent samples are evaluated."

14) The issue of multiple comparisons leading to possible false positives (with a probability of 0.5) was addressed by the NTP in its release of the partial findings of the RFR study (NTP, 2016):

> "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 and in many instances statistically significant findings are not concluded to be due to the test agent. Many factors go in to 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)."

15) The conclusion in the ICNIRP report that the NTP study is not consistent with the RFR cancer literature is wrong, and the claim by ICNIRP that epidemiological studies have not found evidence for cardiac schwannomas neglects to note that no studies of cell phone users have examined relationships between RFR exposure to the heart and risk of cardiac schwannomas. While it is true that the NTP did not report an increase in vestibular schwannomas in rats, it must be recognized that the vestibular nerve was not examined microscopically. 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 concordance between rats and humans in cell type affected by RFR is remarkable and strengthens the animal-to-human association.

Based on numerous incorrect and misleading claims, the ICNIRP report concludes that "these studies (NTP and Ramazzini) do not provide a reliable basis for revising the existing radiofrequency exposure guidelines." The data on gliomas of the brain and schwannomas of the heart induced by cell phone radiation are suitable for conducting a quantitative risk assessment and subsequent re-evaluation of health-based exposure limits. The 'P' in ICNIRP stands for Protection. One must wonder who this commission is trying to protect – evidently, it is not public health.

Online link

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