NOTE
ICNIRP NOTE ON RECENT ANIMAL CARCINOGENESIS STUDIES
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Two recent animal studies investigating the carcinogenic potential of long-term exposure to radiofrequency electromagnetic fields (EMFs) associated with mobile phones have been released: one by the U.S. National Toxicology Program (NTP 2018a, b) and the other from the Ramazzini Institute (Falcioni et al. 2018). These studies, among others, have been taken into account during revision of the ICNIRP radiofrequency exposure guidelines. However, both studies have inconsistencies and limitations that affect the usefulness of their results for setting exposure guidelines, and both need to be considered within the context of other animal and human carcinogenicity research. Overall, based on the considerations outlined below, ICNIRP concludes that these studies do not provide a reliable basis for revising the existing radiofrequency exposure guidelines.

Synopsis of NTP Reports

Although the NTP reports have not yet undergone full peer-review, they have been evaluated by ICNIRP as they report on a substantial national research project with potentially strong relevance to radiofrequency exposure protection. The NTP study exposed HSD:Sprague Dawley SD rats to 900 MHz GSM- or CDMA-modulated signals at whole-body specific absorption rates (SAR) of 1.5, 3 or 6 W/kg (NTP, 2018a), and B6C3F1/N mice to 1900 MHz GSM- or CDMA-modulated signals at whole-body SARs of 2.5, 5 or 10 W/kg (NTP, 2018b). Nine hours and 10 minutes of exposure per day was given (10 minutes on, then 10 minutes off, repeated for a total of 18 hours and 20 minutes), beginning in utero (gestation day 5) and continuing after birth for up to 107 weeks (rats), or beginning at 5-6 weeks of age and continuing for 106 and 108 weeks in males and females respectively (mice). Comparisons were then made to determine whether sham-exposed animals differed from animals exposed to each of the other SARs, and whether there was a trend with increasing exposure. Such comparisons were made for a number of biologically-relevant endpoints (e.g. pregnancy rates, pup numbers, body weights, pathologies), separately for mice and rats, males and females, GSM and CDMA exposures, at 14 weeks (for a subset of animals) and at the end of the study, and for total number of pathologies as well as pathologies per litter. None of these were defined a priori as primary endpoints.

Different results have been reported and/or emphasised in different NTP reports. As the final report has not been published, we here consider the most recent NTP conclusions, which are from Technical Reports TR595 and TR596 (NTP 2018a, b). These conclusions were largely made with reference to the NTP weight of evidence approach, whereby potential effects were described as being supported by ‘clear’, ‘some’, ‘equivocal’ or ‘no’ evidence (where a study was not adequate for comment on potential effects, it is described as an ‘inadequate study’). These reports make the following conclusions regarding carcinogenicity:

**GSM:** In terms of mice exposed to GSM, the NTP concluded there was “equivocal evidence of carcinogenic activity of male B6C3F1/N mice based on” 1/ “Combined incidences of fibrosarcoma,

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1 Note that as part of the NTP External Review in March 2018, recommendations were made to change some of the NTP weight of evidence descriptors (NTP 2018c). As it is not known how NTP will respond to those recommendations, we focus on the results as described in NTP (2018a, b).
sarcoma, or malignant fibrous histiocytoma in the skin”; 2/ “Incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in the lung”; and 3/ “Incidences of malignant lymphoma (all organs)”. No evidence of neoplastic lesions was noted in female mice.

In terms of rats exposed to GSM, the NTP concluded there is “some evidence of carcinogenic activity of male Hsd:Sprague Dawley SD rats based on incidences of malignant schwannoma in the heart”. NTP also concluded there is “equivocal evidence of carcinogenicity of male Hsd:Sprague Dawley SD rats” based on: 1/ “Incidences of adenoma or carcinoma (combined) in the prostate gland”; 2/ “Incidences of malignant glioma in the brain”; 3/ “Benign or malignant granular cell tumors in the brain”; 4/ “Incidences of adenoma in the pars distalis of the pituitary gland”; 5/ “Incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla”; and 6/ “Incidences of pancreatic islet cell adenoma or carcinoma (combined)”. NTP also reported that there was “no evidence of carcinogenic activity of female Hsd:Sprague Dawley SD rats”.

CDMA: In terms of mice exposed to CDMA, the NTP concluded that there is: 1/ “Equivocal evidence of carcinogenic activity of male B6C3F1/N mice based on incidences of hepatoblastoma in the liver”; and 2/ “Equivocal evidence of carcinogenic activity of female B6C3F1/N mice based on incidences of malignant lymphoma (all organs)”.

In terms of rats exposed to CDMA, the NTP concluded that there is: 1/ “some evidence of carcinogenic activity of male Hsd:Sprague Dawley SD rats based on incidences of malignant schwannoma in the heart”; and 2/ “equivocal evidence of carcinogenic activity of male Hsd:Sprague Dawley SD rats” based on: 1/ “Incidences of malignant glioma in the brain”; 2/ “Incidences of adenoma in the pars distalis of the pituitary gland”; and 3/ “Incidences of adenoma or carcinoma (combined) in the liver”. NTP also concluded that there is: “Equivocal evidence of carcinogenic activity of female Hsd:Sprague Dawley SD rats” based on 1/ “Incidences of malignant glioma in the brain”; and 2/ “Incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla”.

Summary: According to the NTP weight of evidence descriptors, the strongest evidence of carcinogenicity (i.e. ‘some evidence’) was thus reported for male Hsd:Sprague Dawley SD rats, where incidences of malignant schwannoma in the heart (but not at other locations) increased with both GSM (0, 2, 1 and 5 cases for 0, 1.5, 3 and 6 W/kg respectively) and CDMA exposure (0, 2, 3 and 6 cases for 0, 1.5, 3 and 6 W/kg respectively). These exposure-response relations were reported to be statistically significant, as was the comparison between the 0 and 6 W/kg CDMA groups. As these represent the strongest findings from the NTP study, these are evaluated below. No evidence of increased rates of malignant schwannoma in the heart was reported for female rats or for male or female mice, from either the GSM or CDMA exposure groups.

Synopsis of Falcioni et al. (2018)

Falcioni et al. (2018) is the only other animal study that has assessed potential effects of radiofrequency exposure on schwannoma in the heart. It exposed Sprague Dawley rats to 1835 MHz GSM-modulated base station signals at whole-body SARs of 0.001, 0.03 or 0.1 W/kg. Rats were exposed continuously for 19 hours per day, beginning in utero (gestation day 12) and continuing until natural death. Of particular importance is that Falcioni et al. reported a significant increased incidence of schwannomas in the heart of male rats exposed at the highest SAR (0.1 W/kg), which was argued in the paper to be consistent with NTP (2018a). Increased incidence of heart Schwann cell hyperplasia (male and female) and malignant glial tumours (female only) were also reported, but as noted by the authors, these were not statistically significant.

Evaluation
There are many strengths to each of the NTP and Falcioni et al. studies. For example, both followed good laboratory practice (GLP), both used much larger numbers of animals than previous research, and both exposed animals over the whole of their lives. However, in determining the relevance of the results for human exposure guidelines, potential limitations need to be carefully considered, and whether any of the evidence regarding health effects in rodents is sufficiently strong and relevant to humans to serve as a basis for exposure guidelines.

**Exposure considerations:**

The degree to which the exposure conditions in each study are relevant to public health is an important consideration. In the NTP study, exposures were to the whole body and ranged from 1.5 to 6 W/kg for rats, and from 2.5 to 10 W/kg for mice, with 6 W/kg in rats the lowest exposure level reported to elevate malignant cardiac schwannoma incidence. ICNIRP (1998) has both local and whole-body exposure limits (basic restrictions). For the general public, local exposure is limited to 2 W/kg, averaged over any 10-g mass, and whole-body exposure is limited to 0.08 W/kg, averaged over the entire body. The NTP exposure of 6 W/kg is therefore 3 times higher than the local exposure limit and 75 times higher than the whole-body exposure limit for the general public. Local and whole-body exposures can produce very different effects, with the latter medically more serious, so whole-body exposure limits are 25 times lower than the equivalent local exposure limit. For any substantiated adverse health effects at the NTP exposure levels, it follows that they could be due to either the local or whole body exposure, and further research would be needed to determine which one. Further, when mobile-phones operate within the ICNIRP local and whole-body exposure limits, they cannot produce the 6 W/kg exposure condition of the NTP study reported to elevate malignant schwannoma incidence in male rats. So, the NTP study is not able to inform on mobile-phone radiofrequency exposures since NTP found effects occurring at levels substantially higher than ICNIRP’s general public whole-body basic restriction.

Falcioni et al. (2018) used whole-body exposures ranging from 0.001 to 0.1 W/kg, which would be similar to the local exposures of their rats. This would make all their local exposures within the ICNIRP (1998) exposure limits. Their whole-body exposures were within or similar to the exposure limits (0.1 W/kg only slightly exceeds the ICNIRP whole-body basic restriction of 0.08 W/kg for the general public). In terms of relevance to mobile-phones, if any adverse health effects were shown to be due to local exposures, then these could be highly relevant to mobile-phones. In assessing the consistency between the Falcioni and NTP rat studies, it should be recognised that the highest exposure in Falcioni et al. is lower (by a factor of 15) than the lowest exposure in the NTP study. Some consistency would be demonstrated if similar pathology was seen in the highest Falcioni et al. exposure condition (0.1 W/kg) and the lowest NTP exposure condition (1.5 W/kg).

**Biological interpretations of the studies’ data:**

For cancers that have benign tumour precursors, progression to cancer often involves a sequence from hyperplasias (proliferation of apparently normal cells), to dysplasia (cell abnormalities present), to cancer (a small percentage of these cells undergo malignant transformation) (Green et al, 2015; NCI, 2018). For schwannomas, less than 30% of hyperplasias progress to malignancy (Novilla et al. 1991), thus many more benign hyperplasias should be observed than malignant schwannomas. The NTP (2018a) study found approximately equal numbers of hyperplasias and malignant schwannomas, which is a large departure from the expected ratio of many hyperplasias to very few malignancies. These results suggest that for radiofrequency fields to be carcinogenic, they would need to affect the conversion rate from hyperplasias to malignancies in addition to potentially inducing hyperplasias. However, with very few cases with cardiac Schwann cell hyperplasia and schwannomas (e.g. none in the control group), it is difficult to interpret and accept this finding without further clarification. It is noted that Falcioni et al. also did not report the expected conversion rate; focusing on male rats, they
reported 3, 2, 1 and 5 cases of cardiac Schwann cell hyperplasia, and 0, 3, 1 and 3 cases of malignant cardiac schwannomas, for the 0, 0.001, 0.03 and 0.1 W/kg groups respectively.

ICNIRP has not found any studies that have specifically investigated malignant cardiac schwannomas, which are extremely rare tumours in humans, with only a few case reports describing such tumours (e.g. Morishita et al. 1988; Sirlak et al. 2003). Neither NTP (2018a) nor Falcioni et al. (2018) reported elevated rates of schwannomas of the auditory nerve in exposed rats, which are the more commonly found schwannomas in humans, or elevated rates of schwannomas overall. For example, in NTP (2018a), a range of other organs were examined for schwannomas in male rats, but no significant increases were found, and in the unexposed male rats (control group), malignant schwannomas were found in some other organs, but notably, no malignant schwannomas were found in the heart (NTP 2018a). Both studies considered the malignant schwannoma data to be particularly important given that some epidemiological case-control studies have reported an increased incidence of vestibular schwannoma, also called acoustic neuroma, which are benign and located on the eighth cranial nerve (e.g., Hardell et al 2005; Hardell and Carlbeg 2009; Hardell et al 2013). Other studies, however, have not reported any increase in these tumours (Schoemaker et al. 2005; Hours et al 2007; Takebayashi et al 2006), and these include the results from available cohort studies with prospectively collected exposure information (Schüz et al., 2011; Benson et al. 2014). Overall, detailed reviews of these data led to the conclusion that there is no association between exposure to radiofrequency EMF and the incidence of acoustic neuroma (e.g. SCENIHR 2015; HCN 2016).

Another important issue is the relative inconsistency across the NTP (2018a) and Falcioni et al. (2018) studies. Although Falcioni et al. reported that their cardiac schwannoma results were consistent with those from the NTP study, they only reported a significant increase in male rats at 0.1 W/kg, whereas the NTP study did not report increased rates at the exposure level most closely matching that condition (1.5 W/kg), nor at the next highest exposure level (3 W/kg). Thus the two studies are clearly inconsistent in this respect. Further, as malignant cardiac schwannoma has not been assessed elsewhere, which is not surprising, given the extremely low incidence in humans, there is no other research to assess the relative consistency of these studies. Thus we are left with two mutually inconsistent sets of results, and no similar literature for comparison.

The distribution of malignant cardiac schwannomas across the experimental groups in the two studies also reduces confidence in the data. For example, in the Falcioni et al. (2018) study the number of cardiac schwannomas in the female rat controls was 3 times higher than the historical incidence rate; there were no cardiac schwannomas in the male rat controls while at least 2 would have been expected from historical control rates; the female group exposed at 0.01 W/kg had 4 times the number of schwannomas than those exposed at 0.1 W/kg; and overall, there were more schwannomas in female rats than in males. That is opposite to both what the NTP study found and what would be expected from the historical incidence rates. Although the NTP study (2018a) produced a more coherent set of cardiac schwannoma results, the absence of cases in the male control group also raises concerns. For example, although the failure to detect any cases is consistent with historical control rates (with a range of 0-2% cases expected), the very low numbers complicate the statistics, in that small variations can result in very different results. As noted by the internal NTP review process (NTP 2018d, Lee MP p. 64), if only one additional schwannoma had been found in the control group, the finding of an increased incidence in the 6 W/kg group of male rats would not be statistically significant, which would mean no statistically significant increase for schwannoma in any of the exposed groups. Further, overall survival was lower and mortality faster in the controls than in the exposed male rats (28% survival in controls, versus 50-68% and 48-62% in the exposed groups, for GSM and CDMA respectively). As it is difficult to control statistically for the better survival of the exposed rats (given the covariance between mortality and schwannoma incidence), this could have resulted in underrepresentation of late-developing schwannomas in the controls.
Although not relevant to the Falcioni et al. (2018) study due to the low exposure levels used, the role of body core temperature elevation in the NTP study (2018a, b) is important to consider when interpreting the results. This is because the exposures are sufficient to increase body core temperature appreciably, and thus there is the possibility that effects could occur due to temperature elevation. NTP measured subcutaneous temperature elevations during the 1-5 minute post-exposure interval of approximately 0.7 °C (in the 6 W/kg condition), and also that temperature reduced to baseline within 10 minutes of exposure cessation. A difficulty with this temperature measurement is that the rapid reduction of temperature to baseline makes the delay in measurement an underestimate of temperature during exposure, as the temperature would have already been reduced by the time the measurement was made. Since NTP measured superficial temperature rather than body core temperature, and as superficial temperature will fall far faster than body core temperature, body core temperature is unlikely to return to baseline within 10 minutes. Thus, superficial temperature measurement does not provide an indication of body core temperature elevation in rats from radiofrequency exposure. Given that high body core temperature elevations are known to lead to a range of adverse health effects, it would be important to consider the role of thermal mechanisms in any substantiated reports of health effects in the rats. ICNIRP guideline limits for the whole-body do not cause any significant temperature increase.

**Methodological considerations**

In experimental radiofrequency EMF studies, blinding is used to ensure that biases related to exposure status and to the determination of outcomes do not affect results. However, the NTP study was only partially blinded. That is, in regard to outcomes the initial pathology was performed unblinded, and samples where pathology was found (i.e. only a few percent of total number) were then analysed by another pathologist who was partially blind to the exposure status (they were told that samples were from ‘test agent A’ or ‘test agent B’ (NTP, 2018d). This does not follow best-practice data analysis protocol and gives substantial potential for biases in the original pathology assessment to affect the study outcomes (e.g. Landis et al., 2012; Bello et al., 2014). Similarly, as noted by the NIH reviewer Dr Lauer (p.50, Appendix G1, NTP 2018d), identifying samples as being from ‘test agent A’ or ‘test agent B’ can also result in bias because perceived patterns within a group’s samples can affect how subsequent samples are evaluated. Falcioni et al. (2018) stated that their study was blinded, but they also stated that it was conducted “in compliance with the most recent NTP recommendations and the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) guidelines” (page 6), which raises similar questions about their assessment of pathology outcomes.

The above-described inconsistent pattern of results may also relate to the choice of analyses used in both the NTP (2018c) and Falcioni et al. (2018) studies. That is, a large number of comparisons were conducted in each study without controlling for multiple comparisons. The actual number of analyses is not provided in either the NTP (2018a, b) or Falcioni et al. (2018) studies. Although sufficient detail to estimate the number of comparisons has not been provided in Falcioni et al. (2018), from consideration of the NTP (2018a, b) reports, it can be seen that a range of endpoints have been assessed (i.e. > 200), for males and females (i.e. 2), GSM and CDMA (i.e. 2), interim and 2-year intervals (i.e. 2), overall and as a litter ratio separately (i.e. 2), comparing control to each of the 3 exposure groups as well as the trend over exposure (i.e. 4 comparisons). This amounts to over 12,800 comparisons, with many hundreds expected to be significant by chance alone; no primary endpoints were described as a priori hypotheses. According to Li et al. (2017), this makes the results useful as ‘exploratory’ analyses only, but not as tests of any particular set of hypotheses. This is because, as the number of comparisons increase, the probability of positive findings becomes more and more likely, even if there is no effect of radiofrequency exposure; once there are approximately 14 such comparisons, what is reported as having a probability of 0.05 is actually about 0.5, and no more remarkable than guessing the ‘toss of a coin’ correctly. As currently presented, there is no indication from the NTP study that any of the results are significant in a statistical sense.
Conclusion

Although the NTP (2018a, b) and Falcioni et al. (2018) studies used large numbers of animals, best laboratory practice, and exposed animals for the whole of their lives, consideration of their findings does not provide evidence that radiofrequency EMF is carcinogenic. NTP reported that their strongest findings were of increased malignant cardiac schwannoma in male rats, however that is not consistent with the results of Falcioni et al. (2018), is not consistent with the NTP female rat nor male or female mouse results, and is not consistent with the radiofrequency EMF cancer literature more generally. While results from epidemiological studies suggest vestibular schwannoma is an outcome of interest, this is not true for malignant cardiac schwannoma. NTP found no increase in schwannoma overall or for vestibular schwannoma. Further, as multiple comparisons were not controlled for in the NTP study, there is no indication that the increased incidence of malignant cardiac schwannomas in male rats was more than what would be expected by chance alone. ICNIRP considers that the NTP (2018a, b) and Falcioni et al. (2018) studies do not provide a consistent, reliable and generalizable body of evidence that can be used as a basis for revising current human exposure guidelines. Further research is required that addresses the above limitations.

References


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NTP (2018a). Technical report on the 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. National Toxicology Program; NTP TR 595.

NTP (2018b). Technical report on the 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. National Toxicology Program; NTP TR 596.


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