Comments on the NTP technical reports:

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

TOXICOLOGY AND CARCINOGENESIS STUDIES IN B6C3F1/N MICE EXPOSED TO WHOLE-BODY RADIO FREQUENCY RADIATION AT A FREQUENCY (1,900 MHz) AND MODULATIONS (GSM AND CDMA) USED BY CELL PHONES

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Summary

NTP conducted extensive studies in rats and mice to obtain more insights in the potential health risks associated with exposure to RF-EMF at GSM and CDMA modulations (technologies used in 2G and 3G cell phones; CDMA being similar to the European UMTS).

On November 1, 2018, the NTP published the two final reports of their studies. The reports present the results of animal exposures for 28 days and two years. According to the authors, these final reports reflect the consensus of the NTP and a group of external scientific experts who reviewed the studies in March 2018 after the publication of the draft reports in February 2018.

NTP experts concluded that high exposure to RFR used by mobile phones was associated with:

- *Clear evidence of tumors in the hearts of male rats. The tumors were malignant schwannomas.*
- *Some evidence of tumors in the brains of male rats. The tumors were malignant gliomas.*
- *Some evidence of tumors in the adrenal glands of male rats. The tumors were benign, malignant, or complex combined pheochromocytoma.*

For female rats, and male and female mice, it was unclear if tumors observed in the studies were associated with RFR used by cell phones. This is also known as equivocal evidence[1]*.*

Note: Results are expressed based on the four categories of NTP evidence of cancer: clear evidence (highest), some evidence, equivocal evidence, no evidence (lowest).

Study design

Whole body exposure of rats and mice was performed in exposure chambers especially designed for this study, which have the advantage that the animals could move freely. RFR field strengths were monitored in real time by E- and H-field probes and were adjusted throughout the studies to maintain specific exposure levels. Moreover, air flow, temperature, humidity and light were also monitored in each chamber.

Characteristics of the exposure system and the protocol are summarized in Appendix 1. Rats and mice were exposed to respectively 900 and 1900 MHz GSM and CDMA to obtain a comparable energy

[1] https://ntp.niehs.nih.gov/results/areas/cellphones/index.html (consulted November 16, 2018)

absorption in their body (Gong et al., 2017). Exposure levels were selected based on the outcome of thermal pilot studies (Wyde et al., 2018) which indicated that an elevation in body temperature of 1°C occurred in adult rats when exposed to > 8 W/kg. In mice, sporadic elevations in body temperature were observed starting from exposure levels of 12 W/kg. However, due to technical constraints, exposure levels in mice could not exceed 15 W/kg, preventing the precise definition of the SAR inducing an elevation in mean body temperature of 1°C in mice. Consequently, 9 W/kg and 15 W/kg were selected as highest exposure levels for the 28 day study in rats and mice, respectively. The differences in exposure levels between rats and mice related to the characteristics of the animals (age/size, species and strain) and the parameters of the RF signal. Afterwards, results of the 28 day studies were used to evaluate the short term toxicity of RFR and to select the appropriate exposure levels for the 2 year studies. A maximum SAR of 6W/kg for rats and of 10W/kg for mice were chosen to ensure that the mean body temperature increase remained below 1°C. The lowest selected exposure level was 1.5 W/kg (close to the RFR guidelines in the United States – 1.6 W/kg) in rats and 2.5 W/kg in mice.

Comments on the reports

The NTP studies are probably the most extensive studies on RFR that have ever been carried out on animals and the quality of the studies is high. However, the interpretation and evaluation of results should be done with caution, for the following reasons:

- An important concern relates to the lower survival rate of control animals compared to exposed animals. Gliomas and schwannomas are tumors that develop later in life, and consequently, the slightly increased incidence of tumors in the exposed groups may have nothing to do with a carcinogenic effect of the RFR, but simply with aging;
- The low number of tumors in the animals (even in the male rats with the highest exposure) also raises questions: tumor incidences are almost entirely within the historical control range. Random effects cannot be excluded, further complicating a straightforward interpretation of the results;
- Importantly, effects only occurred in male rats and not in female rats nor in mice. At present, there is no explanation for this observation, which further complicates the interpretation of the results;
- While complete histopathology was performed on a large number of tissues, schwannomas were observed only in the heart. However, Schwann cells are part of the peripheral nervous system, and consequently, you would also expect schwannomas to occur in other tissues;
- The highest exposure level was chosen in such a way that the increase in body temperature remained below 1°C. Consequently, the mean body temperature could still have been higher in the rats of the 6 W/kg group than in the controls and may also have played a role in the development of tumors.

Generalization of results to humans?

NTP experts concluded that high exposure to RFRs generated by cell phones was associated with clear evidence of tumors in the hearts of male rats. But can these results be extrapolated to humans?

In 2011, IARC classified RFR as possibly carcinogenic to humans (Group 2B), based on an increased risk for glioma, a malignant type of brain cancer, associated with cell phone use. Limited evidence was also retained for an increased risk for acoustic neuroma, a benign tumor, among users of cell phones. It is

noteworthy that the tumors observed in the heart of rats occurred on the same cell type (Schwann cells[2]).

However, in addition to the comments summarized above, several other elements prevent generalization of the NTP results to humans. First, exposure conditions in the NTP study are clearly different from human exposure. Rats in the NTP study were exposed for almost their complete lifespan to intensities that are much higher than those allowed in humans. Second, animals were exposed over their whole body whereas humans are only exposed locally when using a cell phone. Finally, the rats in the NTP study have been exposed over a long time period to relatively high intensities, and consequently, tumor development could have been caused by the higher body temperature and not directly by RFR.

The NTP studies are important but more research is needed to ensure the reliability of the results and to provide explanations for the discrepancies observed between males/females and mice/rats. Moreover, the results of the NTP study are only one piece of information and all other available scientific studies should be considered as well when evaluating the potential adverse human health effects of RFR.

References

Capstick M, Kuster N, Kuehn S, Berdinas-Torres V, Gong Y, Wilson P, Ladbury J, Koepke G, McCormick DL, Gauger J, Melnick RL. A Radio Frequency Radiation Exposure System for Rodents based on Reverberation Chambers. IEEE Trans Electromagn Compat. 2017 Aug;59(4):1041-1052. doi: 10.1109/TEMC.2017.2649885. Epub 2017 Mar 17. PubMed PMID: 29217848; PubMed Central PMCID: PMC5714549.

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[2] Schwann cells are the cells that surround the nerves and participate in nerve conduction.

Appendix 1 – Characteristics of the exposure system and the protocol

	Rats		Mice	
Study length	28 days	2 years[3]	28 days	2 years[4]
Number of animals	Groups of 10 males and 10 females offspring selected at weaning (postnatal day, PND, 21): across 10 litters	Groups of 105 males and 105 females offspring selected at weaning (PND 21): 3 males and 3 females per litter from 35 litters, at random	Groups of 10 male and 10 female mice	Groups of 105 male and 105 female mice
Beginning of exposure	From gestation day (GD) 6 – Groups of 20 females	From GD 5 - Groups of 56 females	At 5 to 6 weeks old	At 5 to 6 weeks old
Beginning of the study period	Weaning occurred on the day the last litter reached postnatal day (PND) 21, marking the beginning of the 28-day study	Weaning occurred on the day the last litter reached PND 21, marking the beginning of the 2-year studies.		
Characteristics of the signals and exposed groups[5]	Gestational female rats and offspring		Mice housed	
	900 MHz GSM and CDMA 0 (sham control), 3, 6, or 9 W/kg	900 MHz GSM and CDMA 0 (sham control), 1.5, 3, or 6 W/kg	1900 MHz GSM and CDMA 0 (sham control), 5, 10, or 15 W/kg	1900 MHz GSM and CDMA 0 (sham control), 2.5, 5, or 10 W/kg
Duration of exposures	18 hours and 20 minutes per day 10 minutes on and 10 minutes off			
	5 to 7 days per week for 28 days	7 days per week for 106 (males) or 107 (females) weeks	5 or 7 (last week of study) days per week for at least 28 days	7 days per week for 106 (males) or 108 (females) weeks

[3] Note: *After 14 weeks of exposure, 10 rats per group were randomly selected for interim histopathologic evaluation and five were designated for genetic toxicity evaluation.* (p 10)

[4] Note: *Fifteen mice per group were randomly selected from the core group after 10 weeks of study; 10 of those 15 mice per group were used for interim evaluation at 14 weeks, and five mice per group were used for genetic toxicity testing at 14 weeks. The remaining 90 animals per group were exposed up to 2 years. (p 7)*

[5] Seven exposure groups per sex, including a shared sham control

Note: See further information on the characteristics for the exposure system in Capstick et al. (2017) and on tissue-specific RFR exposure modelling in Gong et al. (2017)