Japan EMF Information Center
Rapid Response Group**

Professor Michael H. Repacholi*

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Report: 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). Draft 5-19-2016

Authors: US National Toxicology Program report. bioRxiv preprint first posted online May. 26, 2016; doi: http://dx.doi.org/10.1101/055699.

Introduction: The US National Toxicology Program (NTP) has carried out extensive rodent toxicology and carcinogenesis studies of radiofrequency radiation (RF) at frequencies and modulations used in the US telecommunications industry. Their report presents partial results, prompted by the widespread global use of mobile communications among users of all ages and the fact that, even a small increase in the incidence of disease from RF exposure, could have a public health impact.

Further, the Report notes that International Agency for Research on Cancer (IARC) classified RF as a *possible human carcinogen* based on "limited evidence" of an association between exposure to RF from heavy wireless phone use and glioma and acoustic neuroma (vestibular schwannoma) in human epidemiology studies, and "limited evidence" for the carcinogenicity of RF in experimental animals. (IARC, 2013).

The NTP study was designed to evaluate potential, long-term health effects of whole-body RF exposures. Studies were carried out at the IIT Research Institute (IITRI) in Chicago on rats and mice using a reverberation chamber exposure system with two signal modulations [Code Division Multiple Access (CDMA) and Global System for Mobile Communications (GSM)] at two frequencies (900 MHz for rats and 1900 MHz for mice). The groups were controls (no RF exposure) and groups with calculated whole body SARs of 1.5 W/kg, 3 W/kg or 6 W/kg.

Not all the results obtained in the study have been reported. However, it can be assumed that the most important results in rats, that relate to cell phone use, have been released. Nevertheless, a full analysis of the study awaits all publications on the study.

Exposure conditions: Exposures to RF were initiated *in utero* beginning with the exposure of pregnant dams (approximately 11-14 weeks of age) on Gestation Day (GD) 5 and continuing throughout gestation. After birth, dams and pups were exposed in the same cage through weaning on postnatal day (PND) 21, at which point the dams were removed and exposure of 90 pups per sex per group was continued for up to 106 weeks. Pups remained group-housed from PND 21 until they were individually housed on PND 35. Control and treatment groups were populated with more than 3 pups per sex per litter. All RF exposures were conducted over a period of approximately 18 hours using a continuous cycle of 10 minutes on (exposed) and 10 minutes off (not exposed), for a total daily exposure time of approximately 9 hours a day, 7 days/week. Only a single, common group of unexposed

animals of each sex served as controls for both CDMA and GSM modulations. Control rats were housed in identical reverberation chambers with no RF signal generation. Each chamber was maintained on a 12-hour light/dark cycle, within a temperature range of 72 ± 3°F (23 ± 2°C), a humidity range of 50 ± 15%, and with at least 10 air changes per hour.

Results: The results for male rats is shown in Table 1.

Table 1. Incidence of brain lesions in male Hsd:Sprague Dawley® SD® (Harlan) rats exposed to GSM-or CDMA-modulated RF[§]

	Control	GSM			CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
# examined	90	90	90	90	90	90	90
Mal. glioma†‡	0*	3 (3.3%)	3 (3.3%)	2 (2.2%)	0	0	3 (3.3%)
Glial hyperplasia	0	2 (2.2%)	3 (3.3%)	1 (1.1%)	2 (2.2%)	0	2 (2.2%)

[§]Data presented as number of animals per group with lesions (percentage of animals per group with lesions).
*Significant SAR-dependent trend for CDMA exposure by poly-6 ($p < 0.05$). See appendix B
†Poly-6 survival adjusted rates for malignant gliomas: 0/53.48 in controls; GSM: 3/67.96 (4.4%), 3/72.10 (4.2%), and 2/72.65 (2.8%) in the 1.5, 3, and 6 W/kg groups, respectively;
CDMA: 0/65.94, 0/73.08, and 3/57.49 (5.2%) for the 1.5, 3, and 6 W/kg groups, respectively.
‡Historical control incidence in NTP studies: 11/550 (2.0%), range 0-8%

As can be seen from Table 1, a low incidence of malignant gliomas and glial cell hyperplasia was found in all groups of male rats exposed to GSM-modulated RF. Glial cell hyperplasia is a pre-neoplastic lesion that may progress to malignant glioma. In males exposed to CDMA-modulated RF, a low incidence of malignant gliomas occurred only in rats exposed to 6 W/kg. Glial cell hyperplasia was also observed in the 1.5 W/kg and 6 W/kg CDMA-modulated exposure groups. No malignant gliomas or glial cell hyperplasia were observed in controls even though the historical incidence of gliomas in male rats was 2% and within the range from 0-8%. There was no statistically significant difference between the incidences of lesions in exposed male rats compared to control males for any of the GSM- or CDMA-modulated RF groups. However, there was a statistically significant positive trend in the incidence of malignant glioma only for CDMA-modulated RF exposures, but not for GSM exposures. This was based on no gliomas in the controls, 1.5 W/kg, or 3 W/kg groups, but 3 gliomas in the 6W/kg group.

In females exposed to GSM-modulated RF, a malignant glioma was observed in a single rat exposed to 6 W/kg, and glial cell hyperplasia was observed in a single rat exposed to 3 W/kg. In females exposed to CDMA-modulated RF, malignant gliomas were observed in two rats exposed to 1.5 W/kg. Glial cell hyperplasia was observed in one female in each of the CDMA-modulation exposure groups (1.5, 3, and 6 W/kg). There was no glial cell hyperplasia or malignant glioma observed in any of the control females, even though the historical incidence rates were 0.18% and within the range 0-2%.

Cardiac schwannomas were observed in male rats in all exposed groups of both GSM- and CDMA-modulated RF, while none were observed in controls. For both modulations (GSM and CDMA), there was a significant positive trend in the incidence of schwannomas of the heart with respect to increasing SAR exposure. Additionally, the incidence of schwannomas in the 6 W/kg males was significantly higher in CDMA-modulated RF-exposed males compared to controls. The incidence of schwannomas in the 6 W/kg GSM-modulated RF-exposed males was higher,

but not statistically significant compared to controls. Schwann cell hyperplasia of the heart was also observed in three males exposed to 6 W/kg CDMA-modulated RF. In the GSM-modulation exposure groups, a single incidence of Schwann cell hyperplasia was observed in a 1.5 W/kg male.

In female rats, there was no statistically significant or apparent exposure-related effect on the incidence of schwannomas in the heart or the combined incidence in the heart or other sites

From the BioElectromagnetics Society meeting in Ghent, Belgium, at which an NTP staff member, Dr Michael Wyde (NTP Study Scientist), gave an update on the study. He stated that there was no significant increase in cancers in any of the mouse exposure groups.

Discussion: This is the first but only partial report from a long-awaited $25 million NTP study investigating the effects of RF whole-body exposure from two commonly-used cell (mobile) phone signals on the development of health effects, including cancer, in rats and mice. However, whole-body exposures occur from devices such as cell phone base stations which are not the same as the localised cell phone exposure against the head.

The NTP study used the highest possible RF exposures that could be tolerated and thermo-regulated by rodents, so that no significant body temperature increase would occur. However, exposures to rodents used in this study are much higher than would occur to humans from base stations or cell phones.

It is known that rodents thermo-regulate differently, depending on their size. At the highest RF exposures (6 W/kg) male rats would not thermo-regulate as well as smaller female rats, and even smaller mice would handle this heating well. Therefore, one cannot rule out the possibility that any effects found were due to lifetime thermoregulation-induced stress and not from any specific actions of the RF field.

If the study was only interested in cell phone exposures, a much larger number of rodents would be needed to investigate any increases in the rare cancers suggested by some of the cell phone epidemiology studies, and local exposure to the head should have been used.

The RF exposures used in the study were large and would lead to the triggering of an intense thermoregulatory response in rats, which raises another potential concern. While the control group was kept under the same climatic and environment conditions as the RF exposed groups, if the results are due to thermoregulation-induced stress, then the controls are RF controls but not heating controls, therefore potentially biasing the study.

Despite being the most expensive ever conducted by NTP, and one the best conducted animal experiments investigating the long-term health effects from RF exposures, the results are far from conclusive, and there are serious limitations in the results presented, not least because many pertinent details about the study are missing from the report. Further, the results are considered preliminary because the report only gives results for two types of cancer, which are considered most important to cell phone users.

Aside from the concerns about rodent thermoregulation and use of RF exposures well in excess of those normally encountered by people, the following summarizes other concerns related to this study:

1. Historical incidence rates of malignant gliomas among this strain of rat found in previous NTP studies is, on average, about 2%, so the study should normally have seen 1-2 rats with these lesions in the 90 rats in the controls and in each exposure group. One reviewer of the Report (Lee, Report pages 51-52), who commented on the text prior to publication, conducted a test of significance of the glioma results by assuming one glioma in the controls (below the historical average number expected). When this was done, none of the glioma results (incidence or trend) was significant. This shows how unstable the results are when a lower number of rats were used than could provide the statistical power to detect any significant increase in the normally very low incidence of gliomas. If one rat glioma in the controls could change the results from positive to negative the results are not very convincing. In effect, the number of gliomas in each group seems to be due to historical incident rate variability, and not due to any real consequence of RF exposure.
2. NTP reports a trend to higher incidence of gliomas in the CDMA but not the GSM exposed rats. However, this is not a convincing trend when the number of lesions, shown in brackets were; controls (0), 1.5 W/kg (0), 3 W/kg (0), and 6 W/kg (3), especially when historical incidence rates suggest there can be between 0-7 gliomas in each group of 90 rats.
3. Referring to Appendix D (Report page 26) the control incidence rates of astrocytoma, glioma, oligodendroglioma (grouped as gliomas) in 3 separate NTP studies conducted within a 5 month period (in 2011) varied between 0-8%. The genetic makeup of the rats was the same in each study and the same as in this RF study. Since only 50 rats were used in each of previous study groups it shows the high variability in glioma incidence with low numbers in each group. Hence, with the low numbers in each group (90), variability is high and so any results showing less than about 8% difference is only due to variability of the background incidence rates. In effect, the study was severely underpowered (i.e. the number of rats in each group is far too small to produce meaningful results). NTP admitted that the number of animals in each group was a compromise between the cost and being able to detect any health effects, not only cancers. The number of gliomas found in each group of this study are all within the historical incidence levels of controls and so the results are unconvincing. Given the high variability in the historical incidence of gliomas in this rat model one can conclude that it was not an appropriate model if using only 90 rats in each group. This concern is compounded by having only one control group.
4. When one control with schwannoma was added to the schwannoma results, the results still remained marginally significant. Again, the number of rats in each group is still too low to produce meaningful results. Why would there be an increased schwannoma incidence in the heart and not for schwannoma cells in the head? It's unlikely that schwannoma cells in the head are less sensitive than the heart, or received less RF exposure since at 900 MHz the absorption within the rat body would have been similar throughout.
5. Another concern is the lower survival rate in the controls than the RF exposed groups. The Report notes that malignant gliomas are a late-developing tumour, so the absence of these tumours in the control group may be due to their shorter survival rates compared to exposed rats. This is supported by the fact that the Report states that most of the gliomas were observed in animals that died late in the study. The reason for the shorter survival in the controls is also a concern with this study and calls into question whether something untoward happened to the controls. While the NTP responds by saying that they have no explanation for this low survival, they say it is not uncommon.
6. One would not expect any difference in DNA damage between GSM and CDMA signals that could lead to an increase in cancers from CDMA and not GSM. Further, reliable *in*

vitro studies using CDMA or GSM exposures have not found any DNA damage that would suggest an RF modulation effect (see AGNIR, 2012).

7. All these coincidences; low control survival and no gliomas in the control group when historically there should have been between 1-2 gliomas, suggests the possibility of a false-positive result. While it is true that low numbers of rats in each group would normally lead to a false negative result, this is not always the case. The concern here is that there was only one control group for the whole study, so that non-historic incidence rates found in this group would affect the results and limit conclusions that could be drawn.

Conclusions: Given the significant concerns described above, while the results are important, the available data do not alter the balance of evidence in relation to human exposure to RF fields from wireless communications technology. This means that the current international standards limiting RF exposure to workers and the public are considered to be safe and do not need to be lowered because of the results of the NTP study. As one of the reviewers of the Report states “I am unable to accept the authors’ conclusions” (Lauer, reviewer in Report page 37).

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* Professor Michael H. Repacholi
・ Department of Information Engineering, Electronics and Telecommunications,
"La Sapienza" University of Rome, Italy.
・ Former Team Leader of the Radiation and Environmental Health Unit, World Health Organization (WHO) .

** Rapid Response Group (RRG): The RRG provides a rapid response on the analysis of newly published scientific studies that JEIC considers important and in need of expert scientific review to provide information for all stakeholders. The RRG is composed of a coordinator and experts in all areas of science appropriate for reviewing and assessing scientific studies. Prof. M. H. Repacholi has served as the coordinator from the time of launch of RRG in 2010.