Comments about the NTP Cell Phone Radiation Studies

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A brief history of the NTP cell phone radiation research is provided to provide some context for my comments about the NTP partial report and draft technical reports. My comments are followed by a discussion of the implications of the NTP studies and other recently published animal and human studies for re-classification of the carcinogenicity of radio frequency radiation.

Brief History of the NTP Cell Phone Radiation Studies

In 1999, the Food and Drug Administration sent a letter to the National Toxicology Program (NTP) that called on the NTP to conduct “high priority” research on the effects of “radio frequency radiation emissions from wireless devices” (FDA, 1999).

In 2004, the NTP issued a $10 million request for proposals to conduct a series of animal studies on cell phone radiation, but no research groups responded to the request. NIEHS then negotiated a sole-source contract with IIT Research Institute in Chicago.

At a U.S. Senate hearing in 2009, John Bucher, PhD, the NTP associate director at the time, made the following statement:

> "The pilot studies are nearly complete. Subchronic studies will begin early next year and the chronic toxicology and carcinogenicity studies will start in late 2010, finish in 2012, with peer review and reporting in the 2013-2014 time frame."

In May, 2016, the NTP published partial findings from the long-awaited, $25 million study of tumor risk from long-term exposure to cell phone radiation in rats and mice (NTP, 2016). The partial report summarized the cancer data on heart schwannoma and glioma risk in rats:

> “These studies found low incidences of malignant gliomas in the brain and schwannomas in the heart of male rats exposed to RFR of the two types [Code Division Multiple Access (CDMA) and Global System for Mobile Communications (GSM)] currently used in U.S. wireless networks. Potentially preneoplastic lesions were also observed in the brain and heart of male rats exposed to RFR.” (NTP, 2016)

> “Given the widespread global usage of mobile communications among users of all ages, even a very small increase in the incidence of disease resulting from exposure to RFR [radiofrequency radiation] could have broad implications for public health.”

In June, at the annual BioEM meeting, Michael Wyde, PhD, director of the NTP cell phone radiation studies, provided four reasons why the NTP decided to release partial study results (Wyde, 2016):

- given widespread cell phone use, even a small increase in disease incidence could have major public health implications;
- high level of public and media interest in the study;
- the tumor types observed in these studies are similar to those found in human studies of cell phone use; and
- the results support the IARC classification of radiofrequency radiation as potentially cancer-causing in humans.

Dr. Wyde presented evidence from the NTP studies for DNA damage in mice as well as in rats (Wyde, 2016). Statistically significant evidence of DNA damage was observed in the following organs from long-term exposure to cell phone radiation:

- male rats: frontal cortex, hippocampus, liver, blood
- female rats: frontal cortex
- male mice: frontal cortex
- female mice: liver, blood

Later that month, Christopher Portier, PhD, who previously served as director of the NIEHS environmental toxicology program, associate director of the NTP, and director of the CDC National Center for Environmental Health, wrote the following about the NTP two-year study (Portier and Leonard, 2016):

> "This study found that cellphone exposure increases the incidence of malignant gliomas of the brain, i.e., brain cancer, and schwannomas (also called neuromas) of the heart in the male rats.
>
> The increases were small (3-4 percent over controls), but since these are rare tumors, the findings are still significant. What make these studies even more significant are the findings of similar tumors in humans."
>
> "In our opinion, the exposure to RF-EMF caused the tumors seen in the male rats in the NTP study. With the positive case-control studies seen in humans and a similar positive finding in a well-conducted laboratory study in rats, the evidence that cell phones can cause cancer has strengthened.
>
> Do we think cellphones cause cancer in humans? Probably. But proximity matters, as does duration, and level of exposure."
>
> "Cellphones probably cause cancer if the exposure is close enough, long enough, and in sufficient magnitude. We don't yet know the risk for a given level of exposure in humans."

In February, 2018, the NTP released two draft technical reports on the cell phone radiation studies--one for rats and one for mice along with supplemental data tables (NTP, 2018a, 2018b). The reports and data tables are available at http://bit.ly/NTPreports.

The strongest finding in the draft technical reports was increased cancer incidence in Schwann cells in the hearts of male rats exposed to cell phone radiation. These rats also exhibited twice as many total schwannomas across all organs of the body compared to control rats, but this difference was not statistically significant (6% vs. 3%).

Other organs in male rats were observed to have low incidences of tumors that exceeded those found in the unexposed controls, including the brain (i.e., glioma), the adrenal, pituitary, and prostate glands, the pancreas, and the liver.

Female rats exposed to cell phone radiation also had elevated tumor incidence in the brain (i.e., glioma) and adrenal glands but these differences were not statistically significant.

NTP classified the increased malignant schwannoma in male rats as "some evidence of carcinogenic activity." Other elevated incidences of tumors were considered "equivocal evidence of carcinogenic activity" because they failed to display a classic dose-response relationship.

NIEHS will conduct a peer-review of the NTP draft technical reports from March 26-28, 2018.

Comments on the NTP Partial Report

The researchers stated that the greater incidence of heart schwannoma observed in the male rats was likely caused by their exposure to cell phone radiation because this was an experimental study.

That they labeled the increased cancer risk in the exposed rats "low incidence" seems arguable when one examines the overall risk of developing either heart or brain cancer.

Using the data in the report, I analyzed the overall tumor risk, that is, the risk of an animal developing either type of cancer due to cell phone radiation exposure. Overall, 5.5%, or 30 of 540 male rats, exposed to cell phone radiation developed heart or brain cancer as compared to 0% of 90 unexposed male rats ($p = .027$). (2-tailed Fisher exact probability test).

Moreover, 16 pre-cancerous hyperplasias were diagnosed among the exposed male rats. Thus, overall 8.5%, or 46 of 540 male rats exposed to cell phone radiation developed either heart or brain cancer or pre-cancerous cells as compared to 0% of 90 unexposed male rats ($p = .002$).

In the group exposed to the lowest intensity cell phone radiation (1.5 watts/kilogram or W/kg), 6.7%, or 12 of 180 male rats, developed heart or brain cancer or pre-cancerous cells. Whereas, in the highest exposure group (6 W/kg), fully 13.3%, or 24 of 180 male rats, developed cancer or pre-cancerous cells as compared to 0% in the 90 unexposed male rats.

The overall risk of cancer appears to increase with the intensity of the cell phone radiation as no cancer or pre-cancerous cells were found in the controls—rats kept in the same apparatus but without exposure to cell phone radiation.

In contrast to the male rats, the incidence of cancer in female rats exposed to cell phone radiation was elevated, but not statistically significant. Overall, 3.0%, or 16 of 540 female rats exposed to cell phone radiation, developed heart or brain cancer or pre-cancerous lesions as compared to 0% of the 90 unexposed females ($p = .146$).

The researchers controlled the temperature of the animals to prevent heating effects so the cancers were caused by a non-thermal mechanism. This is important because despite many hundreds of studies to the contrary, some scientists still deny there can be non-thermal effects from microwave radiation exposure.

Although this is one of the largest animal studies to examine tumor risk caused by cell phone radiation, both the NTP and the FDA are downplaying the announced study results (February, 2018). Yet, in May, 2016, the NTP was sufficiently concerned about the increased risk of schwannoma and glioma in male rats to release a partial report with these results.

NTP should conduct a formal analysis of the overall tumor risk, that is, the risk of an animal developing any type of tumor due to cell phone radiation exposure. There are several strong justifications for conducting this analysis.

First, a 5-year, $5 million Air Force study found low incidences of many types of tumors in male rats exposed to microwave radiation (Chou et al, 1992). In that study, the exposed rats were three times more likely to get cancer than the control rats. The study employed much lower intensity microwave radiation than the NTP studies.

Second, early toxicology research on the effects of tobacco found low incidences of many types of tumors among animals exposed to tobacco smoke. Scientists dismissed this evidence because they assumed an agent could not cause cancer in different types of tissue. History later proved them wrong.

Finally, my analysis of the overall tumor risk using summary data from the appendices to the NTP report (NTP, 2018a), found that **male rats exposed to cell phone radiation were significantly more likely to develop cancer than control rats (38% vs. 25.5%; p = .021), and more likely to develop a nonmalignant tumor (70% vs. 54%; p = .003).**

Male rats in the lowest cell phone radiation exposure group (1.5 W/kg), were also more likely to develop a nonmalignant tumor than control rats (74% vs. 54%; $p < .001$). Although cancer incidence for this low exposure group was greater than for the control group, this difference did not reach statistical significance (34% vs. 25.5%; p = .163).

Schwann cells and glial cells both produce myelin

The new NTP report points out that Schwann cells are similar to glial cells. Thus, the mechanism that caused schwannoma in this study may be similar to what caused glioma:

> "Schwann cells are similar to glial cells in the brain in that they are specialized supportive cells whose functions include maintaining homeostasis, forming myelin, and providing support and protection for neurons of the peripheral nervous system (PNS). In the PNS, Schwann cells produce myelin and are analogous to oligodendrocytes [a type of glial cells] of the central nervous system" (NTP 2018a, page 162).

This raises a question for future research--are myelinated nerve cells particularly sensitive to microwave radiation?

Implications of Recent Cell Phone Radiation Research Including NTP Study for Re-Classification of Carcinogenicity of Radio Frequency Radiation

The International Agency for Research on Cancer (IARC) in May, 2011, classified radio frequency radiation as "possibly carcinogenic to humans" (Group 2B) based upon the consensus of a working group of 31 international experts. In Monograph #102 which documents the research, IARC concluded that there is "limited evidence" in both humans and experimental laboratory animals for the carcinogenicity of radiofrequency radiation, especially from cell phones (IARC, 2013).

Regarding the human research, IARC noted in the monograph that, "Positive associations have been observed between exposure to radiofrequency radiation from wireless phones and glioma, and acoustic neuroma" (IARC, 2013, p. 421). IARC noted that children may be at greater risk because their brains grow faster and are exposed to higher levels of cell phone radiation:

> "Due to the closer proximity of the phone to the brain of children compared with adults, the average exposure from use of the same mobile phone is higher by a factor of 2 in a child's brain and higher by a factor of 10 in the bone marrow of the skull." (IARC, 2013, p. 408)

In addition to the NTP studies of cell phone radiation (NTP, 2016; NTP 2018a; NTP 2018b), three studies have reported increased cancer risk in animal models from long-term exposure to lower intensity microwave radiation than employed in the NTP studies (see references below for study abstracts: Chou et al., 1992; Repacholi et al., 1997; Falcioni et al., 2018).

Newly-published results by the **Ramazzini Institute** from the largest study on the health effects of cell phone radiation in rats **replicate the brain and heart tumor results from the NTP rat study** (Falcioni et al., 2018). Yet, the Institute used a different GSM carrier frequency (1800 MHz vs. 900 MHz) and much lower intensity microwave radiation exposures than the NTP study. The Specific Absorption Rates ranged from 0.001 - 0.1 W/kg SAR in this study as compared to 1.5 - 6.0 W/kg in the NTP study. These results suggest that the cancer effects observed in the male rats of the NTP study are robust.

The NTP and the other animal studies are the missing links. These studies prove that long-term exposure to low intensity, non-thermal levels of microwave radiation can cause DNA damage and cancer in an animal model. To date, many hundreds of studies have found increased oxidative stress (including stress proteins, free radicals and DNA damage) from exposure to low intensity microwave radiation.

Since the 2011 IARC review, additional human studies have been published which find an association between long-term, heavy cell phone use and risk of glioma (Coureau et al., 2014; Grell et al., 2016; Hardell et al., 2013a, 2013b; Momoli et al., 2017; Turner et al, 2016) or vestibular schwannoma (also known as acoustic neuroma) (Benson et al., 2013; Hardell et al., 2013c; Moon et al, 2014).

Due to the new animal and human evidence of carcinogenicity since 2011, many EMF scientists are now calling for re-classification of radio frequency radiation either to "probably carcinogenic to humans" (Group 2A) or "carcinogenic to humans" (Group 1) (e.g., Morgan et al., 2015; Carlberg and Hardell, 2017).

References

Benson et al (2013). Mobile phone use and risk of brain neoplasms and other cancers: prospective study.Int J Epidemiol. 42(3):792-802. *https://www.ncbi.nlm.nih.gov/pubmed/23657200*

Carlberg and Hardell (2017) Evaluation of mobile phone and cordless phone use and glioma risk using the Bradford Hill viewpoints from 1965 on association or causation. Biomed Res Int. 2017: 9218486. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5376454/*

Chou et al (1992). Long-term, low-level microwave irradiation of rats. Bioelectromagnetics. 13(6):469-96. *http://bit.ly/AirForceFCC*

Abstract

Our goal was to investigate effects of long-term exposure to pulsed microwave radiation. The major emphasis was to expose a large sample of experimental animals throughout their lifetimes and to monitor them for effects on general health and longevity.

An exposure facility was developed that enabled 200 rats to be maintained under specific-pathogen-free (SPF) conditions while housed individually in circularly-polarized waveguides. The exposure facility consisted of two rooms, each containing 50 active waveguides and 50 waveguides for sham (control) exposures. The experimental rats were exposed to 2,450-MHz pulsed microwaves at 800 pps with a 10-microseconds pulse width. The pulsed microwaves were square-wave modulated at 8-Hz. Whole body calorimetry, thermographic analysis, and power-meter analysis indicated that microwaves delivered at 0.144 W to each exposure waveguide resulted in an average specific absorption rate (SAR) that ranged from 0.4 W/kg for a 200-g rat to 0.15 W/kg for an 800-g rat. Two hundred male, Sprague-Dawley rats were assigned in equal numbers to radiation-exposure and sham-exposure conditions. Exposure began at 8 weeks of age and continued daily, 21.5 h/day, for 25 months. Animals were bled at regular intervals and blood samples were analyzed for serum chemistries, hematological values, protein electrophoretic patterns, thyroxine, and plasma corticosterone levels. In addition to daily measures of body mass, food and water consumption by all animals, O2 consumption and CO2 production were periodically measured in a sub-sample (N = 18) of each group. Activity was assessed in an open-field apparatus at regular intervals throughout the study.

After 13 months, 10 rats from each group were euthanatized to test for immunological competence and to permit whole-body analysis, as well as gross and histopathological examinations. At the end of 25 months, the survivors (11 sham-exposed and 12 radiation-exposed rats) were euthanatized for similar analyses. The other 157 animals were examined histopathologically when they died spontaneously or were terminated in extremis.

Statistical analyses by parametric and non-parametric tests of 155 parameters were negative overall for effects on general health, longevity, cause of death, or lesions associated with aging and benign neoplasia. Positive findings of effects on corticosterone level and immune system at 13 months exposure were not confirmed in a follow-up study of 20 exposed and 20 control rats. Differences in 0, consumption and C0, production were found in young rats. A statistically significant increase of primary

malignancies in exposed rats vs. incidence in controls is a provocative finding, but the biological significance of this effect in the absence of truncated longevity is conjectural. The positive findings need independent experimental evaluation. Overall, the results indicate that there were no definitive biological effects in rats chronically exposed to RF radiation at 2,450 MHz.

Coureau et al (2014). Mobile phone use and brain tumours in the CERENAT case-control study. Occup Environ Med. 71(7):514-22. *https://www.ncbi.nlm.nih.gov/pubmed/24816517*

Falcioni et al (2018). Report of final results regarding brain and heart tumors in Sprague-Dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8 GHz GSM base station environmental emission. Environmental Research. Article in press. *Accessed from ScienceDirect on March 9, 2018.* *https://doi.org/10.1016/j.envres.2018.01.037*

Abstract

Background: In 2011, IARC classified radiofrequency radiation (RFR) as possible human carcinogen (Group 2B). According to IARC, animals studies, as well as epidemiological ones, showed limited evidence of carcinogenicity. In 2016, the NTP published the first results of its long-term bioassays on near field RFR, reporting increased incidence of malignant glial tumors of the brain and heart Schwannoma in rats exposed to GSM – and CDMA –modulated cell phone RFR. The tumors observed in the NTP study are of the type similar to the ones observed in some epidemiological studies of cell phone users.

Objectives: The Ramazzini Institute (RI) performed a life-span carcinogenic study on Sprague-Dawley rats to evaluate the carcinogenic effects of RFR in the situation of far field, reproducing the environmental exposure to RFR generated by 1.8 GHz GSM antenna of the radio base stations of mobile phone. This is the largest long-term study ever performed in rats on the health effects of RFR, including 2448 animals. In this article, we reported the final results regarding brain and heart tumors.

Methods: Male and female Sprague-Dawley rats were exposed from prenatal life until natural death to a 1.8 GHz GSM far field of 0, 5, 25, 50 V/m with a whole-body exposure for 19 h/day.

Results: A statistically significant increase in the incidence of heart Schwannomas was observed in treated male rats at the highest dose (50 V/m). Furthermore, an increase in the incidence of heart Schwann cells hyperplasia was observed in treated male and female rats at the highest dose (50 V/m), although this was not statistically significant. An increase in the incidence of malignant glial tumors was observed in treated female rats at the highest dose (50 V/m), although not statistically significant.

Conclusions: The RI findings on far field exposure to RFR are consistent with and reinforce the results of the NTP study on near field exposure, as both reported an increase in the incidence of tumors of the brain and heart in RFR-exposed Sprague-Dawley rats. These tumors are of the same histotype of those observed in some epidemiological studies on cell phone users. These experimental studies provide

sufficient evidence to call for the reevaluation of IARC conclusions regarding the carcinogenic potential of RFR in humans.

Food and Drug Administration (1999). Letter (dated May 19, 1999) and supporting documentation sent to National Toxicology Program that nominates agents to study. *https://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/wireless051999_508.pdf*

Grell et al (2016). The intracranial distribution of gliomas in relation to exposure from mobile phones: Analyses from the Interphone Study. Ann Epidemiol. 26(12):827-832.e2. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5152665/*

Hardell et al (2013a). Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiology. 20(2):85-110. *https://www.ncbi.nlm.nih.gov/pubmed/23261330*

Hardell et al (2013b). Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use*.* Int J Oncol. 43(6): 1833–1845. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3834325/*

Hardell et al (2013c). Pooled analysis of case-control studies on acoustic neuroma diagnosed 1997-2003 and 2007-2009 and use of mobile and cordless phones. Int J Oncol. 43(4):1036 – 1044. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3829779/*

International Agency for Research on Cancer (IARC) (2013). Non-ionizing radiation, Part II: Radiofrequency electromagnetic fields / IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2011: Lyon, France). (IARC monographs on the evaluation of carcinogenic risks to humans ; v. 102). *http://monographs.iarc.fr/ENG/Monographs/vol102/mono102.pdf*

Momoli et al (2017). Probabilistic multiple-bias modeling applied to the Canadian data from the Interphone Study of mobile phone use and risk of glioma, meningioma, acoustic neuroma, and parotid gland tumors. Am J Epidemiol. 2017 Oct 1;186(7):885-893. *https://www.ncbi.nlm.nih.gov/pubmed/28535174*

Moon et al (2014). Association between vestibular schwannomas and mobile phone use. Tumour Biol. 35(1):581-7. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3907669/*

Morgan et al (2015). Mobile phone radiation causes brain tumors and should be classified as a probable human carcinogen (2A) (review). Int J Oncol. 46(5):1865-71. *https://www.ncbi.nlm.nih.gov/pubmed/25738972*

Myung et al (2009). Mobile phone use and risk of tumors: a meta-analysis. J Clin Oncol. 27(33):5565-72. *http://ascopubs.org/doi/full/10.1200/JCO.2008.21.6366*

National Toxicology Program (2016). 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 2-1-2018. bioRxiv preprint first posted online May. 26, 2016; doi: *http://dx.doi.org/10.1101/055699*

National Toxicology Program (2018a). NTP Technical Report on the Toxicolocy 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. NTP TR 595.
https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2018/march/tr595peerdraft.pdf

National Toxicology Program (2018b). NTP Technical Report on the Toxicolocy and Carcinogenesis Studies in B6C3F1/N Mice Exposed to Whole-Body Radio Frequency Radiation at a Frequency (1800 MHz) and Modulations (GSM and CDMA) Used by Cell Phones. NTP TR 596. *https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2018/march/tr596peerdraft.pdf*

Portier and Leonard (2016). Do Cell Phones Cause Cancer? Probably, but It's Complicated. Guest Blog. Scientific American. June 13, 2016.
https://blogs.scientificamerican.com/guest-blog/do-cell-phones-cause-cancer-probably-but-it-s-complicated/

Repacholi et al (1997). Lymphomas in E mu-Pim1 transgenic mice exposed to pulsed 900 MHZ electromagnetic fields. Radiat Res.147(5):631-40. *https://www.ncbi.nlm.nih.gov/pubmed/9146709*

Abstract

Whether radiofrequency (RF) fields are carcinogenic is controversial; epidemiological data have been inconclusive and animal tests limited. The aim of the present study was to determine whether long-term exposure to pulse-modulated RF fields similar to those used in digital mobile telecommunications would increase the incidence of lymphoma in E mu-Pim1 transgenic mice, which are moderately predisposed to develop lymphoma spontaneously. One hundred female E mu-Pim1 mice were sham-exposed and 101 were exposed for two 30-min periods per day for up to 18 months to plane-wave fields of 900 MHz with a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms. Incident power densities were 2.6-13 W/m2 and specific absorption rates were 0.008-4.2 W/kg, averaging 0.13-1.4 W/kg. Lymphoma risk was found to be significantly higher in the exposed mice than in the controls (OR = 2.4. P = 0.006, 95% CI = 1.3-4.5). Follicular lymphomas were the major contributor to the increased tumor incidence. Thus long-term intermittent exposure to RF fields can enhance the probability that mice carrying a lymphomagenic oncogene will develop lymphomas. We suggest that such genetically cancer-prone mice provide an experimental system for more detailed assessment of dose-response relationships for risk of cancer after RF-field exposure.

Turner et al (2016). Investigation of bias related to differences between case and control interview dates in five INTERPHONE countries. Ann Epidemiol. 2016 Dec;26(12):827-832.e2.
https://www.ncbi.nlm.nih.gov/pubmed/28340909

Wyde (2016). NTP Toxicology & Carcinogenicity Cell Phone Radiofrequency Radiation Studies. Presentation at BioEM 2016 Meeting (Ghent, Belgium). June 8, 2016.
http://ntp.niehs.nih.gov/ntp/research/areas/cellphone/slides_bioem_wyde.pdf