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Commentary on the utility of the National Toxicology Program study on cell phone radiofrequency radiation data for assessing human health risks despite unfounded criticisms aimed at minimizing the findings of adverse health effects

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ABSTRACT

The National Toxicology Program (NTP) conducted two-year studies of cell phone radiation in rats and mice exposed to CDMA- or GSM-modulated radiofrequency radiation (RFR) at exposure intensities in the brain of rats that were similar to or only slightly higher than potential, localized human exposures from cell phones held next to the head. This study was designed to test the (null) hypothesis that cell phone radiation at non-thermal exposure intensities could not cause adverse health effects, and to provide dose-response data for any detected toxic or carcinogenic effects. Partial findings released from that study showed 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. These results, as well as the findings of significantly increased DNA damage (strand breaks) in the brains of exposed rats and mice, reduced pup birth weights when pregnant dams were exposed to GSM- or CDMA-modulated RFR, and the induction of cardiomyopathy of the right ventricle in male and female rats clearly demonstrate that the null hypothesis has been disproved. The NTP findings are most important because the International Agency for Research on Cancer (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 strengthens the animal-to-human association. This commentary addresses several unfounded criticisms about the design and results of the NTP study that have been promoted to minimize the utility of the experimental data on RFR for assessing human health risks. In contrast to those criticisms, an expert peer-review panel recently concluded that the NTP studies were well designed, and that the results demonstrated that both GSM- and CDMA-modulated RFR were carcinogenic to the heart (schwannomas) and brain (gliomas) of male rats.

1. Introduction

The US Food and Drug Administration's (FDA) Center for Devices and Radiological Health nominated cell phone radiofrequency radiation (RFR) to the NTP for evaluation of potential toxicity and carcinogenicity. This nomination was made because of the rapidly growing use of cell phones in the 1990s, because exposure guidelines were based on protection from acute injury from thermal effects, and because little was known about possible health effects of long-term exposure to 'non-thermal' levels of RFR. Because of the widespread use of cell phones among the general public, even a small increase in cancer risk would have a serious health impact. The FDA nomination noted that "a significant research effort, involving large well-planned animal experiments is needed to provide the basis to assess the risk to human health of wireless communications devices" (FDA, 1999).

Radiofrequency (RF) fields are part of the electromagnetic (EM) spectrum; however, unlike ionizing radiation, electromagnetic waves at frequencies used in mobile phones do not have sufficient energy to break chemical bonds or ionize molecules (Moulder et al., 1999). Tissue heating at high exposure intensities is the most firmly established mechanism for effects of RFR in biological systems. Consequently, it has been hypothesized that there is little theoretical basis for anticipating that nonionizing RFR at power levels used by mobile phones would have a significant effect on biological processes, such as causing direct DNA damage or inducing tumor formation by non-thermal mechanisms (Adair, 2003; Moulder et al., 2005).

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In the United States, the Federal Communications Commission (FCC) limits for maximum permissible exposure to RF fields are designed to protect against adverse effects that might occur due to increases in tissue or body temperature of 1 °C resulting from acute exposures. FCC exposure limits for controlled occupational exposure to cell phone RFR are 0.4 W/kg SAR averaged over the whole body and spatial peaks not to exceed 8 W/kg averaged over any 1 g of tissue; for the uncontrolled general population, exposure limits are 0.08 W/kg SAR averaged over the whole body and spatial SARs not to exceed 1.6 W/kg averaged over any 1 g of tissue (FCC, 1997). The SAR, or specific absorption rate, is a measure of the rate of RF energy absorbed per unit mass, and is expressed as W/kg or mW/g.

This commentary describes the general design and partial results of the NTP study on cell phone RFR and addresses several unfounded criticisms that have been promoted to minimize the findings of adverse health effects of cell phone RFR and the utility of the experimental data for assessing human health risks.

2. Design of the NTP study on cell phone radiofrequency radiation

Because little was known about possible health effects of long-term exposure to non-thermal or minimally thermal levels of cell phone RFR, and because guidelines for cell phone RFR are based largely on protection from acute injury due to thermal effects, the NTP study was designed to test the (null) hypothesis that cell phone radiation at non-thermal exposure intensities could not cause adverse health effects, and to provide dose-response data for any detected toxic or carcinogenic effects for health risk assessments.

In order to expose unrestrained animals to cell phone RFR in individual cages and for durations well beyond 2 h/day, the feasibility of using reverberation chambers for the exposure system was demonstrated in collaboration with Perry Wilson and other scientists from the RF fields group at the National Institute of Standards and Technology (NIST) in Boulder, Colorado. A reverberation chamber is a shielded room (shielded from penetrating electromagnetic fields, EMFs) with excitation antennae and ventilation panels. Field exposures emanate from all directions, while rotating paddles distribute the fields to create a statistically homogeneous electromagnetic environment. The feasibility study conducted at NIST showed that a uniform electromagnetic environment could be created in a reverberation chamber with cell phone RFR at two frequencies that are at the centers of the primary cellular bands used in the US (900 and 1900 MHz), and that the emitted power from the antenna was efficiently transmitted into biological simulation fluids located in different regions of the reverberation chamber.

Studies were then conducted for the NTP at IT'IS (Niels Kuster, principal investigator) in Zurich, Switzerland to (a) evaluate the actual absorbed dose and tissue uniformity in anatomical models in relation to animal orientation, animal number, and cage location in reverberation chambers, (b) to determine the influence of plastic animal racks, cages, bedding, and water bottles on animal dosimetry, and (c) to estimate the whole-body and organ-specific dosimetry of RFR in rats and mice exposed over lifetime in reverberation chambers. To eliminate absorption of RF power by the water bottles, a shielded automatic watering system was developed with a choke to prevent RF burns to animals while drinking water during exposures. Descriptions of the RFR reverberation chamber exposure system (Capstick et al., 2017) and the lifetime dosimetry assessment for rats and mice (Gong et al., 2017) have been published. The studies of RFR in anatomical models of rats and mice showed that the organ-specific SAR values compared to whole-body SARs was more uniform in rats exposed to 900 MHz RFR and in mice exposed to 1900 MHz RFR. Thus, for example, the SAR in the brain was nearly the same as the whole-body SAR in rats exposed to 900 MHz and in mice exposed to 1900 MHz RFR. In tissues with lower conductivity, e.g., fat, the SAR is much lower than the whole-body SAR. Therefore, 900 and 1900 MHz were the frequencies selected for the subsequent NTP toxicity/carcinogenicity studies in rats and mice, respectively. To simulate actual cell phone use, animals were exposed to GSM (global system for mobile communication) or CDMA (code division multiple access) modulated signals at each frequency.

The NTP study, which was conducted at the IIT Research Institute (IITRI) in Chicago (David McCormick, principal investigator), comprised 4 phases:

Phase 1. Procurement of equipment and materials needed to construct the exposure and RFR monitoring systems, and validation that the systems function appropriately and meet NTP specifications (e.g., ventilation, temperature and humidity control, lighting, noise, EMF shielding, field uniformity, etc.). The NTP chronic studies required a total of 21 reverberation chambers: 3 power levels for mice exposed to 1900 MHz GSM modulated signals, 3 power levels for mice exposed to 1900 MHz CDMA modulated signals, 1 mouse sham chamber, 3 power levels for male and 3 power levels for female rats exposed separately to 900 MHz GSM modulated signals, 3 power levels for male and 3 power levels for female rats exposed separately to 900 MHz CDMA modulated signals, and 1 male and 1 female rat sham chamber. Rat chambers hold 100 rats and mouse chambers hold 200 mice.

Phase 2. Thermal pilot study: to determine the effects of modulated cell phone RFR exposures (whole body SARs ranging from 4 to 12 W/kg) on body temperature, body weight, and survival of rats and mice of varying ages. Body temperature was measured with subcutaneously implanted programmable temperature microchips.

Phase 3. Perinatal/prechronic toxicity study: to determine possible toxic effects of cell phone RFR and to determine appropriate power levels for each species and sex to be used in the chronic toxicity/carcinogenicity study. The study involved exposing pregnant animals beginning on gestation day 6 and continuing exposure of offspring until 7 weeks of age.

Phase 4. Chronic study: to determine chronic effects including carcinogenicity of modulated cell phone RFR in rats exposed *in utero* until 106 weeks of age and in mice exposed for 2 years beginning at 6 weeks of age. During the prechronic and chronic studies, animals were exposed 18 h per day on a continuous cycle of 10 min on and 10 min off. Thus, total daily exposures were 9 h; animal hygiene and collection of clinical signs, body weight and survival data were conducted during the 6-h period when the RFR exposures were shut off. The number of animals per group in the chronic study was 90; this is somewhat larger than typical NTP chronic studies (N = 50) in order to increase the statistical power of the study. Also, blood and brain tissue were collected (N = 10) at 19 weeks of age for micronuclei determinations and analyses of possible DNA strand breaks.

The experimental design was presented to scientists from the Radiofrequency Interagency Work Group (includes FDA, EPA, FCC, NIOSH, and OSHA), to the Toxicology Forum (2003), and at the 25th annual meeting of the Bioelectromagnetics Society (2003). The consensus opinion of participants at these presentations was that the NTP study would trump all studies that have examined the carcinogenic potential of RFR in experimental animals.

3. Partial results from the NTP studies on cell phone radiation

In the design of the NTP studies, the original expectation was that the maximum exposure intensity would be limited to a whole-body SAR of 4 W/kg to avoid increasing body temperature by approximately 1 °C. After all, the FCC limit for maximum permissible exposure to RFR was 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 °C from acute exposures (FCC, 1997). However, results from the NTP thermal pilot and prechronic studies indicated that rats could tolerate daily exposures up to 6 W/kg without significant effects on body temperature, body weights, or induction of tissue damage, while mice could also tolerate 10 W/kg and possibly even higher RFR intensities (Wyde et al., 2018); increases in core body temperature of

rats were less than 1 °C at exposures up to 6 W/kg. The results from these studies provided the basis for the selection of the RFR exposure intensities used in the subsequent chronic studies in rats: SAR = 0 (sham), 1.5, 3.0, and 6.0 W/kg. The maintenance of core body temperature (increases < 1 °C) and the lack of an effect of whole-body RFR exposures at 6 W/kg on rat body weights indicate that these exposure conditions did not create thermal effects that might have impacted the overall physiology of the animal leading to increased tumor incidences in the brain, heart, or other organs of exposed animals.

The histopathology findings from the chronic study in rats underwent rigorous peer review before the diagnoses were finalized. Complete necropsies and histopathology evaluations were conducted on every animal by a veterinary pathologist. The subsequent pathology peer review of the heart and central nervous system was first performed by two quality assessment pathologists, and then by Pathology Working Groups involving 30 pathologists from NTP and external to the program.

In May of 2016, NTP released partial findings from the chronic study of RFR in rats (NTP, 2016). The findings in that report were reviewed by 8 expert peer reviewers selected by the NTP and the NIH. The report focused on two organs in which the incidences of tumors were increased in exposed rats compared to controls; the diagnosed tumors were malignant gliomas in the brain and schwannomas of the heart. In addition, focal hyperplasias in these organs, which are considered to be preneoplastic lesions (i.e., part of a continuum of pathological changes leading to malignant glioma or schwannoma), were also observed in exposed rats. Table 1 shows the incidences of tumors and hyperplasias in the brain and heart of male rats.

Based on significant increases in incidence and trend for hyperplastic lesions and tumors of the brain and heart in RFR-exposed male rats, the NTP concluded “Under the conditions of these 2-year studies, the hyperplastic lesions and glial cell neoplasms of the heart and brain observed in male rats are considered likely the result of whole-body exposures to GSM- or CDMA-modulated RFR.” Six of the expert peer reviewers agreed that tumor responses were the result of exposure to modulated RFR, one felt that study limitations complicate interpretations of risk, and one disagreed with the NTP conclusion.

In addition, to the tumor data described above, DNA damage (strand breaks detected with the comet assay) was significantly increased in the brains of rats and mice exposed to GSM- and CDMA-modulated RFR (Wyde, 2016).

The tumor and genotoxicity data (DNA strand breaks), as well as the findings of reduced pup birth weights when pregnant dams were exposed to GSM- or CDMA-modulated RFR and the induction of cardiomyopathy of the right ventricle in male and female rats from the NTP study clearly show that the null hypothesis (i.e., low-level cell phone radiation at thermally insignificant exposures cannot cause adverse health effects) has been disproved. The NTP findings are most important because, in 2011, IARC classified radio frequency radiation 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 (IARC, 2013).

Table 1
Incidence of gliomas and glial cell hyperplasias of the brain, and schwannomas and Schwann cell hyperplasias of the heart in male rats exposed to GSM- or CDMA-modulated RFR.

Organ: lesion	Sham	GSM (SAR, W/kg)			CDMA (SAR, W/kg)		
	0	1.5	3.0	6.0	1.5	3.0	6.0
Brain: Incidence, %							
Glioma[a]	0	3.3	3.3	2.2	0	0	3.3
Glial cell hyperplasia	0	2.2	3.3	1.1	2.2	0	2.2
Total proliferative	0	5.5*	6.6*	3.3	2.2	0	5.5*
Heart: Incidence, %							
Schwannoma[a,b]	0	2.2	1.1	5.5*	2.2	3.3	6.6*
Schwann cell hyperplasia	0	1.1	0	2.2	0	0	3.3
Total proliferative	0	3.3	1.1	7.7*	2.2	3.3	9.9*

* $p < 0.05$ compared to sham control.
[a] Significant trend CDMA.
[b] Significant trend GSM.

4. Unfounded criticisms and facts concerning the interpretation and utility of the animal data for assessing potential human health risks

After the release of the partial results from the NTP study on cell phone radiation, several unfounded criticisms of that study that were promoted and published in the popular media (e.g., Carroll, 2016; Foster, 2016; Singal, 2016). Most of these criticisms are presented below followed by explanations as to why those comments misrepresent the relevance and utility of the results of the NTP study for assessing potential human health risks.

Criticism 1: This is a rat study and does not represent what might happen in humans.

Fact: Because animals and humans exhibit similarities in biological processes of disease induction, data from studies in experimental animals are used to assess health risks from exposures to environmental or occupational agents. Similarly, the pharmaceutical industry relies on the results of animal studies prior to conducting clinical trials of new drugs in humans. The rationale for conducting carcinogenicity studies in animal models is based on experimental data showing that every agent that is known to cause cancer in humans has been shown to be carcinogenic in animals when adequately tested (IARC, 2006) and that almost one-third of human carcinogens were identified after carcinogenic effects were found in well-conducted animal studies (Huff, 1993). In addition, the careful control of exposure conditions in animal studies can eliminate the potential impact of confounding factors on the interpretation of study results. There is no reason to believe that a physical agent such as RFR would affect animal tissue but not human tissue. The concordance between rats and humans in cell type affected by RFR strengthens the animal-to-human association (US EPA, 2005).

Public health agencies that evaluate human cancer risks, rely on animal carcinogenicity data when there is insufficient or inadequate cancer data from studies in humans. The IARC monographs preamble notes: “it is biologically plausible that agents for which there is sufficient evidence of carcinogenicity in experimental animals also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans;” the US EPA Guidelines for Cancer Risk Assessment (US EPA, 2005) note “the default option is that positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans. Thus, if no adequate human or mode of action data are present, positive effects in animal cancer studies are a basis for assessing the carcinogenic hazard to humans.” Because of the long latency for many cancers (clinical manifestation may take as much as 30 years from time of first exposure), animal studies can eliminate the need to wait for sufficient human cancer data before implementing public health protective strategies.

Criticism 2: RFR exposure levels in the NTP study were much higher (19–75 times) than human exposure limits.

Fact: 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. 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.

Criticism 3: Daily exposures in rats were longer than typical human exposures to RFR.

Fact: Experimental carcinogenicity studies are generally conducted in small groups of rodents (e.g., 50 per exposure or control group), and incidence values of adverse effects are used to assess health risks to potentially millions of exposed people. With this relatively small group size, tumor incidence in an exposed group needs to be increased by ~10% compared to controls in order to achieve statistical significance. While an increased incidence of 1–5% in an experimental study would not be statistically significant, a 1–5% increased risk of brain cancers due to RFR exposures among the hundreds of millions of cell phone users in the US would be of epidemic proportions. Thus, to identify a hazardous agent, exposure levels in small groups of experimental animals are often much higher than human exposures, while lower doses are included for analyses of dose-response relationships. Exposure intensities in the NTP study in rats were limited to an SAR of 6 W/kg due to possible thermal effects at higher exposures that might affect the outcome of the study. To increase the statistical power of the chronic NTP study to detect an effect if one truly existed, group size was increased to 90 animals, and daily exposures were increased to 9 h/day. While the exposure pattern in the NTP study may not be typical for most or all cell phone users (though exposures to RFR are occurring from multiple emitting devices), health risk estimates would be based on the response rate (i.e., tumor incidence and/or other adverse effects) as a function of tissue dosimetry (absorbed power × hours per day of exposure) over the comparable fraction of an exposed lifespan. From these data, cancer risk estimates can be made for any pattern of cell phone use, while actual risks would be related to a number of factors including cell phone emission values, side of head use of the phone, distance from the body that the phone is held, exposure to other RF emitting devices, etc.

Criticism 4: The tumor findings may have been affected by the longer survival of exposed rats compared to controls.

Fact: 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.

Criticism 5: It is odd that increased incidences of gliomas and heart schwannomas were seen only in male rats and not in female rats.

Fact: Actually, there were gliomas and heart schwannomas in female rats exposed to RFR but none in female controls; however, the incidences of these tumors in exposed female rats did not reach statistical significance. Gender differences in tumor incidence occur frequently in experimental toxicity and carcinogenicity studies (https://ntp.niehs.nih.gov/results/index.html), and gender differences in cancer rates also exist in humans (https://seer.cancer.gov/faststats/selections.php?series=cancer). For example, brain cancer mortality rates are approximately 50% higher in men than in women, and for many human cancers (e.g., colorectal, liver, soft tissue including heart, kidney, non-Hodgkin lymphoma, etc.) the incidence and mortality rates are much higher in men than in women. Thus, the different response rates between male and female rats in the NTP study of RFR does not diminish the human relevance of the cancer findings.

Criticism 6. Control rats oddly had low rates of tumors, and the incidence of gliomas and of heart schwannomas in controls were below the rates seen in studies in the past.

Fact: Control rats did have tumors (63% of males and 92% of control female rats); however, the tumor responses associated with exposure to RFR (gliomas and schwannomas of the heart) were not detected in controls. 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. 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.

Criticism 7. Because the study had low statistical power, it is likely to have an increased risk of being a false positive.

Fact: Having low statistical power means that there is a greater chance for a false negative rather than a false positive result (the chance of a false positive result is 5%). That is, with low statistical power there is a high probability of accepting the no-effect hypothesis even when a true effect exists.

Criticism 8. The pathology evaluations were not done blinded with respect to controls or exposed animals; exposed groups were analyzed first and then the unexposed group.

Fact: 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.

5. Discussion and conclusions

In 2011, an IARC expert working group of international scientists classified RFR as a possible human carcinogen based on *limited evidence* of carcinogenicity in humans and in experimental animals (IARC, 2013). Although associations had been observed between exposure to RFR from wireless phones and increased risks of glioma and acoustic neuroma (Schwann cell tumors on the acoustic nerve) among long term human users of cell phones, the positive case-control studies were considered to provide limited evidence of carcinogenicity in humans because of possible selection and recall bias. *Limited evidence* of carcinogenicity means that a causal interpretation for observed associations between exposure to the agent and cancer is credible, but that other explanations (e.g., chance, bias, or confounding) could not be fully ruled out. However, a recent re-analysis of the Canadian data that was included in the Interphone study showed that there was no effect on the risk of glioma after adjustments were made for selection and recall

biases; the odds ratios (OR) for glioma were significantly increased when comparing the highest quartile of use to those who were not regular users whether or not adjustments were made: OR = 2.0, 95% confidence interval 1.2–2.4 without adjustment; OR = 2.2 95% confidence interval 1.3–4.1 with adjustments (Momoli et al., 2017). Evidently, selection and recall biases do not explain the elevated brain cancer risk associated with use of cell phones.

The IARC working group also concluded that there was *limited evidence* in experimental animals for the carcinogenicity of RFR; chronic studies available at that time provided no evidence for induction of tumors by RFR in conventional animal models, but positive co-carcinogenic effects suggested that RFR may increase the potency of environmental carcinogens to which people are exposed. Mechanistic studies available at that time had minimal impact on the cancer evaluation of RFR; evidence was considered to be weak for RFR causing genotoxic effects, altering gene or protein expression, inducing changes in cell signaling, causing oxidative stress, or altering cell replication. Much of the available mechanistic data showed mixed results or inconsistency in response to RFR exposures.

The results from the NTP carcinogenicity studies clearly demonstrate the induction of proliferative lesions (tumors and hyperplasias in the brain and heart) by RFR in conventional animal models. Recently, Falcioni et al. (2018) from the Ramazzini Institute reported a significant increase in heart schwannomas in male Sprague-Dawley rats exposed to GSM-modulated RFR at a field strength of 50 V/m. The incidence of heart Schwann cell hyperplasia was also increased in that exposure group. The combined incidence of schwannomas and preneoplastic Schwann cell hyperplasias is highly significant ($p = 0.01$). These findings are consistent with the results from the NTP study and demonstrate that the proliferative effect of modulated RFR in heart Schwann cells is a reproducible finding. This consistency is further supported by the fact that Schwann cells are myelin-forming glial cells of the peripheral nervous system and are analogous to oligodendrocytes of the central nervous system (Herbert and Monk, 2017).

The concordance between the tumor types that were increased in the NTP studies and those showing increased risks in human studies strengthens the animal-to-human association for the induction of gliomas and schwannomas from exposure to RFR. Health risk estimates of cell phone RFR should be based on response rates (i.e., incidence of tumors and preneoplastic lesions) as a function of tissue dosimetry (absorbed power times hours per day of exposure) and duration of exposure in animals extrapolated to RFR dosimetry in exposed human. Even a small increase in cancer risk could have a serious health impact due to the widespread use of cell phones (~300 million in the US and 5 billion worldwide). In the meantime, precautionary principles should be promoted by health and regulatory agencies, especially for children and pregnant women.

In addition, previously reported co-carcinogenic effects of modulated RFR radiation in the liver and lung of mice that had been treated with the carcinogen ethylnitrosourea *in utero* (Tillmann et al., 2010) were replicated at exposure levels of 0.04, 0.4, and 2 W/kg SAR (Lerchl et al., 2015). Lerchl et al. concluded that their "findings are a very clear indication that tumor-promoting effects of life-long RF-EMF exposure may occur at levels supposedly too low to cause thermal effects." Thus, the reproducibility of the tumor promoting effects of RFR at non-thermal exposure levels has been demonstrated. Also, Yang et al. (2012) showed that exposure to RFR can induce transformation of normal cells to tumor cells; NIH 3T3 cells that were exposed to 916 MHz RFR for 8–12 weeks formed clones in soft agar and tumors when inoculated onto the backs of immunodeficient mice.

Numerous *in vivo* and *in vitro* mechanistic studies on RFR have been conducted since the IARC review in 2011; many of these used improved exposure systems with more accurate measures of RF dosimetry. The majority of more recently published studies demonstrate consistency for the induction of oxidative stress (Yakymenko et al., 2016), while there were many additional positive genotoxicity studies including the finding of DNA damage induced in brain cells of rats and mice exposed to GSM- or CDMA-modulated RFR in the NTP studies. Oxidative DNA damage can lead to mutations, chromosomal translocations, and genomic instability, which are cellular events that can result in cancer development (Berquist and Wilson, 2012). Induction of oxidative stress, which is a key characteristic of many human carcinogens (Smith et al., 2016), including ionizing radiation and asbestos, may also lead to the genotoxicity and carcinogenicity of nonionizing RFR. Thus, without causing direct DNA damage, RFR may induce oxidative DNA damage and thereby initiate or promote tumor development.

In conclusion, animal studies and mechanistic studies on RFR that have been published since 2011 clearly show that the evidence on the carcinogenicity of RFR is much stronger than it was at the time of the IARC evaluation. If the recent animal and mechanistic findings had been available in 2011, it is likely that RFR would have been classified as a probable human carcinogen.

6. Addendum

After this paper was submitted to *Environmental Research*, the NTP released drafts of the full technical reports on GSM- and CDMA-modulated cell phone RFR in rats and mice. Those reports were peer-reviewed by an external panel of scientists who had expertise in studying biological effects of electromagnetic fields and expertise in interpreting results from experimental carcinogenicity studies (NTP, 2016). The peer-review panel 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 of carcinogenic activity* 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." In addition, the studies in rats showed that the prostate gland was a target organ of proliferative lesions (neoplasms and/or preneoplastic epithelial hyperplasias) induced by GSM- and CDMA-modulated cell phone RFR. The peer review panel also concluded that there was *some evidence of carcinogenic activity* in the adrenal gland of male rats exposed to GSM-modulated RFR. The peer review panel concurred with NTP that there was *equivocal evidence of carcinogenic activity* of RFR in the prostate gland, pituitary gland, liver, meninges of the brain, and pancreas in rats, and for lymphoma and neoplasms in the lung, skin, and liver of mice. The expert peer-review panel clearly recognized the validity and biological significance of the adverse health effects produced in the NTP's studies of cell phone RFR. The overall results from the NTP studies indicate that cell phone RFR is potentially carcinogenic to multiple organs of exposed people.

Declaration of interest

The author has consulted on the design and utility of the NTP study on cell phone radiation.

References

Adair, R.K., 2003. Biophysical limits on athermal effects of RF and microwave radiation. Bioelectromagnetics 24, 39–48.
Berquist, B.R., Wilson III, D.M., 2012. Pathways for repairing and tolerating the spectrum of oxidative DNA lesions. Cancer Lett. 327, 61–72.
Capstick, M., Kuster, N., Kuhn, S., Berdinas-Torres, V., Gong, Y., Wilson, P., Ladbury, J., Koepke, G., McCormick, D., Gauger, J., Melnick, R., 2017. A radio frequency radiation reverberation chamber exposure system for rodents. IEEE Trans. Electromagn. Compat. 59, 1041–1052.
Carroll, A., 2016. Why It's Not Time to Panic about Cell Phones and Cancer. New York Times.

Falcioni, L., Bua, L., Tibaldi, E., Lauriola, M., DeAngelis, L., Gnudi, F., Mandrioli, D., 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 a1.8 GHz base station environmental emission. Environ. Res. 165, 496–503.

Federal Communications Commission (FCC), 1997. Evaluating Compliance with FCC Guidelines for Human Exposure to Radiofrequency Electromagnetic Fields. OET Bulletin 65. Federal Communications Commission Office of Engineering & Technology, Washington, DC.

Food and Drug Administration (FDA), 1999. Nomination Letter to Coordinator of NTP Chemical Nomination and Selection Committee. 〈nomihttps://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/wireless051999_508.pdf〉.

Foster, K., 2016. Cell phone radiation linked to cancer in major rat study. IEEE Spectr. 〈https://spectrum.ieee.org/the-human-os/biomedical/ethics/cellphone-radiation-causes-cancer-in-rats〉.

Gong, Y., Capstick, M., McCormick, D.L., Gauger, J.R., Horn, T., Wilson, R., Melnick, R.L., Kuster, N., 2017. Life time dosimetric assessment for mice and rats exposed to cell phone radiation. IEEE Trans. Electromagn. Compat. 59, 1798–1808.

Herbert, A.L., Monk, K.R., 2017. Advances in myelinating glial cell development. Curr. Open. Neurobiol. 42, 53–60.

Huff, J.E., 1993. Chemicals and cancer in humans: first evidence in experimental animals. Environ. Health Perspect. 100, 201–210.

IARC (International Agency for Research on Cancer), 2006. Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 〈http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf〉.

International Agency for Research on Cancer (IARC), 2013. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans: Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields. Lyon, France, Volume 102.

Lerchl, A., Klose, M., Grote, K., Wilhelm, A.F., Spathmann, O., Fiedler, T., Streckert, J., Hansen, V., Clemens, M., 2015. Tumor promotion by exposure to radiofrequency electromagnetic fields below exposure limits for humans. Biochem. Biophys. Res. Commun. 459, 585–590.

Maronpot, R.R., Boorman, G.A., 1982. Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10, 71–80.

Momoli, F., Siemiatycki, J., McBride, M.L., Parent, M.E., Richardson, L., Bedard, D., Platt, R., Vrijheid, M., Cardis, E., Krewski, D., 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. 186, 885–893.

Moulder, J.E., Erdreich, L.S., Malyapa, R.S., Merritt, J., Pickard, W.F., Vijayalaxmi, 1999. Cell phones and cancer: what is the evidence for a connection? Radiat. Res. 151, 513–531.

Moulder, J.E., Foster, K.R., Erdreich, L.S., McNamee, J.P., 2005. Mobile phones mobile phone base stations and cancer: a review. Int. J. Radiat. Biol. 81, 189–203.

National Toxicology Program (NTP), 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). 〈http://biorxiv.org/content/biorxiv/early/2016/06/23/055699.full.pdf〉.

Singal, J., 2016. For the love of God, please chill out about that new study about rats and cell phones and cancer. New York Magazine. 〈http://www.newsjs.com/url.php?P=http://nymag.com/scienceofus/2016/05/for-the-love-of-god-chill-out-about-that-new-study-on-cell-phones-and-cancer.html〉.

Smith, M.T., Guyton, K.Z., Gibbons, C.F., Fritz, J.M., Portier, C.J., Rusyn, I., DeMarini, D.M., et al., 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ. Health Perspect. 124, 713–721.

Tillmann, T., Ernst, H., Streckert, J., Zhou, Y., Taugner, F., Hansen, V., Dasenbrock, C., 2010. Indication of cocarcinogenic potential of chronic UMTS-modulated radiofrequency exposure in an ethylnitrosourea mouse model. Int. J. Radiat. Biol. 86, 529–541.

US Environmental Protection Agency (US EPA), 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Washington, DC.

Wyde, M., 2016. NTP toxicology and carcinogenicity studies of cell phone radiofrequency radiation. BioEM2016 Meeting, Ghent, Belgium. 〈https://ntp.niehs.nih.gov/ntp/research/areas/cellphone/slides_bioem_wyde.pdf〉.

Wyde, M.E., Horn, T.L., Capstick, M.H., Ladbury, J.M., Koepke, G., Wilson, P.F., Kissling, G.E., Stout, M.D., Kuster, N., Melnick, R.L., Gauger, J., Bucher, J.R., McCormick, D.L., 2018. Effect of cell phone radiofrequency radiation on body temperature in rodents: Pilot studies of the National Toxicology Program's reverberation chamber exposure system. Bioelectromagnetics 39, 190–199.

Yakymenko, I., Tsybulin, O., Sidorik, E., Henshel, D., Kyrylenko, O., Kyrylenko, S., 2016. Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. Electromagn. Biol. Med. 35, 186–202.

Yang, L., Hao, D., Wang, M., Zeng, Y., Wu, S., Zeng, Y., 2012. Cellular neoplastic transformation induced by 916 MHz microwave radiation. Cell Mol. Neurobiol. 32, 1039–1046.