Clear Evidence of Cell Phone RF Radiation Cancer Risk

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On March 26 to 28, 2018, the National Institute of Environmental Health Sciences' (NIEHS) National Toxicology Program (NTP), a part of the U.S. National Institutes of Health (NIH), convened a 3-day Technical Reports Peer Review Panel meeting in Research Triangle Park, NC to review NTP's draft reports on their carcinogenesis studies of cell phone radiofrequency (RF) radiation in mice and rats [1].

The invited 14-member peer review panel included 3 electrical engineering professors, 10 pathologists and toxicologists (3 from academia and 7 from industry), and one biostatistician; none were from the cell phone industry.

This project is the largest NTP animal cancer study ever. It was nominated by the Food and Drug Administration (FDA) in 1999. The supposedly 5-year project was sole-sourced in 2004 to an industrial research firm as the project's principal investigator. The work began in 2005. However, the project had been protracted for more than a dozen years with huge budget overruns, and an estimated eventual price tag of $25 million [2], [3].

From the outset, NIEHS/NTP had decided to be tight-lipped about it and did not release any progress reports or any information. In contrast to scientific norm, project investigators had not openly discussed any of its aspects or made any presentations of its progress or interim findings at scientific meetings. The first report from the project was in May 2016, when NTP came out and announced occurrences of two types of rare cancers in exposed rats: malignant schwannomas of the heart and gliomas in the brain [4]. However, that announcement spoke only to partial findings from their 2-year (or lifelong) exposure study of rats subjected to 900/1900 MHz RF radiation involving CDMA and GSM wireless cellular telephone operations.

Histopathological Findings

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On March 28, 2018, following a thorough review of the draft NTP reports, pathologists and toxicologists on the peer review panel concluded, among other observations, there is statistically significant and "clear evidence" that both GSM and CDMA-modulated RF radiation had led to the development of malignant schwannoma, a rare form of tumor in the heart of male rats (of Harlan-Sprague-Dawley strain), and there was "equivocal evidence" for the same schwannoma risk among female rats. The panel also noted that there were unusual patterns of cardiomyopathy, or damage to

heart tissue, both in RF-exposed male and female rats compared with concurrent control animals.

In addition, the panel concluded, based on statistical significance, that the pathology findings showed indications of “some evidence” for RF-dependent carcinogenic activity in the brain of male rats, specifically glioma. However, the findings for female rats were deemed as providing only “equivocal evidence” for malignant gliomas compared with concurrent controls.

The NTP uses five categories of evidence of carcinogenic activity to classify the strength of evidence observed in their reports: “clear evidence” and “some evidence” for positive findings; “equivocal evidence” for uncertain results; “no evidence” for no observable effects; and “inadequate study” for results that cannot be evaluated because of major experimental flaws.

RF Exposure in Large RCs

So-called reverberation chamber (RC) method and technology were employed for RF exposure. The exposure regime included 10-min-on and 10-min-off for 19 h per day for 2 years. Rats were exposed for a total of 9 h each day to cell phone RF radiation. Whole-body-average RF absorption rates (SAR) of 0, 1.5, 3, or 6 W/kg did not raise body temperature of exposed animals to more than 1ºC. The study was successful in its aim to provide maximum uniformity of exposure. In particular, the reported local SARs in the brains and hearts of rats were only 1.05 and 2.27 times the whole-body-average SARs, respectively. Indeed, most tissues and organs inside the rats’ bodies had experienced similar SARs from RF exposure.

It is well-known that the NTP cell phone RF exposure study is, by far, the largest study of its kind [5]. It was rather expensive and took a long time to get to this point. There may even be better ways to do the study. Nevertheless, the study points up the fact that prolonged exposures to RF radiation at levels that are similar to, or a little above, the currently existing RF exposure regulations could lead to tumor development.

Note that the current RF exposure guidelines of 1.6 or 2.0 W/kg are promulgated with a reduction factor of 50, as a safety margin for the general public, to provide protection against presumed hazardous biological effects in humans [5],[6]. The finding that RF exposure could lead to dose-dependent cancer development at levels that are the same or at 3 times above current exposure guidelines is significant.

This implies that the safety margin may be no more than a factor of 3. In fact, one recommendation (IEEE C95.1-2005) has a set of guidelines under controlled environments that would allow local SARs of the brain and heart to be as much as 10 W/kg [7]. An SAR of 10 W/kg is considerably higher than the 1.5, 3.0, and 6.0 W/kg used in the NTP study.

The FDA should be applauded for nominating, and NIEHS/NTP should be lauded for having sponsored the research and conducted the Cell Phone Radio Frequency Radiation (RFR) Studies. It's important for the U.S. government to step in to conduct such a research program, and not leave the matter entirely to the cell phone industry. The wireless industry has had nearly free reign to develop and roll out cellular mobile phones and related RF devices as they see fit. The completion of this NTP study should not signify the end of the U.S. government's role in supporting RF biological effects research, because we all are being exposed to increasingly more and more RF radiation every day [8],[9].

Moreover, a systematic review of 59 published studies of controlled exposure to RF radiation with health-related outcomes [10] showed that public agencies or charities funded 11 (19%), the wireless communications industry funded 12 (20%), mixed sources (including industry) funded 14 (24%), and in 22 (37%) the source of funding was not reported. Research funded exclusively by industry reported the largest number of outcomes, but were least likely to report a statistically significant result compared with studies funded by public agencies or charities. This finding was not altered when analysis was adjusted for the number of outcomes reported, study quality, or other factors.

As for the NTP study, RC method and technology were employed for exposure of rats and mice to cell phone RF radiation. Descriptions in the report of what was implemented are fairly clear, and measurement techniques are accurate to the extent they were applied. However, there are limitations.

It appears that RC was selected *a priori* for the project. It is not clear whether RC is the optimal technology for the project or whether other competing technologies such as circular waveguides or small rectangular multimodal chambers were seriously considered for exposure of freely moving animals inside the holding cage.

The large number of RCs specifically constructed for this project are the most expensive one-time use or single-purpose equipment or facility for RF biological effect research. They likely would not be used for another project; thus the RCs would end up as "white elephants" by default, if they have not been scrapped already. (It appears that NIEHS/NTP has moved on to other types of exposure chambers to continue its biological effects research regarding RF exposure.)

The study could have been better designed. There were obvious flaws concerning the experimental design involving RCs for RF exposure. A question arose during the panel meeting concerning the unusually small number of concurrent control animals. The NTP study used the same concurrent control animals for both GSM and CDMA exposure groups. The "designer" and the same person who had "sole-sourced" this $25-million NTP study to an industry contractor responded to the query with a not-enough space answer--the contractor only had space for 21 RCs. Thus, only one RC was available for sham or concurrent control. It begs the question of what the rationale was for choosing to sole-source the contractor as principal investigator for the project.

The availability of facilities and space to conduct the study should be top priorities in any list of criteria for awarding such a contract! Any allusion to saving money for a couple more RCs in a $25-million project, like the use of round plastic bottles instead of rat-shaped experimental phantoms, sounds like a rather feeble excuse. The NTP project easily could have saved a lot more money, if the 21 large RCs were not produced and transported from Zurich, Switzerland over land, ocean, and river to Chicago for reassembly.

Concurrent and Historical Control Animals

The small number of concurrent control rats renders it more challenging to reliably show that experimental findings are statistically significant, especially when multiple comparisons are involved. Was the small number of concurrent controls an integral part of the design for this large animal cancer study to start with?

This experimental design question brings up the matter of control animals for a closer examination. In bioassay research involving animals, there are normally two types of controls: cage controls and sham controls. In cage controls, animals are housed in the vendor's open-stack vivarium, subjected only to routine house-keeping and handling protocols. They are not subjected to any of the proposed experimental treatments or manipulations. In principal, they could include data from control animals used in prior NTP studies.

In sham controls, referred to as concurrent control, animals are subjected to the same protocols, RF apparatus, and environment, except without being subjected to treatment by the experimental agent, in this case, RF exposure.

It appears that the NTP study design had planned to use "historical controls" for statistical comparisons. Historical controls may come from the animal breeder or supplier for the strain of rats used—Harlan-Sprague-Dawley. Or in this case, it was derived from NTP's in-house control data with this strain of rats, which were not subjected to treatment by any exogenous test agent. However, NTP's experience with this strain of rats was not long or extensive: a few 2-year studies over 5 to 10 years. More importantly, the life history of these historical control rats was quite different from the concurrent controls involved in the RF study.

Instead of NTP facilities in Research Triangle Park, NC, the RF study took place in Chicago, where both sham-control and exposed animals were housed in custom designed and constructed RCs. The RC environment is totally different from the NTP animal facilities. Aside from one-of-a-kind sealed, shielded, steel chambers with piped-in ambient sonic noise and air through specially designed inlets and outlets, animal access to food and water were delivered using ingenious and unique systems.

Furthermore, the RCs used incandescent light bulbs instead of the fluorescent lamps that were commonly used in the past. Fluorescent and incandescent lighting have different color and temperature properties. Fluorescent lamps do not produce the

continuous spectrum of light that is characteristic of incandescent bulbs. It should be noted that RF radiations (100+/- 50 kHz) are emitted by fluorescent lamps when in operation because of the starter electrodes and electronic switching ballast in them.

Clearly given the above-mentioned issues, the historical controls from past NTP studies are not appropriate for statistical comparison in this RF exposure study. The review panel opted to base their evaluation and conclusion on the concurrent control data. Nevertheless for reference purposes, historical control data for the Harlan Sprague-Dawley strain and from NTP are an important source of information as background material.

Back to Tumor Findings in the NTP Study

In addition to malignant schwannomas in heart tissue and to some degree gliomas in the brain of male rats, the review panel concluded that there was "some evidence" for carcinogenicity in the adrenal gland. The number of pheochromocytomas, a tumor of the adrenal gland, was significantly higher ($p < 0.05$) in male rats at 1.5 W/kg and 3 W/kg, compared with the concurrent controls. Also, the increase in malignant tumor-like hyperplasia in the adrenal gland of female rats was significantly higher at 6.0 W/kg, relative to the concurrent controls ($p < 0.05$).

There were also findings of "equivocal evidence" for carcinogenicity in other tissues or organs, such as adenoma of pars digitalis in the pituitary gland and adenomas and carcinomas in the liver of both RF-exposed male and female rats.

The key exposure metric chosen was the whole-body-average SAR. Reports from the NTP study indicated that an RF field uniformity within 10% was achieved throughout the RC volume [1], [11]. This level of field uniformity enabled similar SAR values throughout the rats' bodies. Specifically, the local SAR in the brains and hearts of rats were a mere 1.05 and 2.27 times the whole-body-average SAR, respectively. This means that tissues and organs inside the rat's body had experienced similar SARs from GSM and CDMA RF exposures.

Since all tissues and organs were similarly exposed and had similar SARs, it is important for the NTP team to perform a statistical comparison of total primary malignancies in all tissues and organs observed in RF-exposed and concurrent control rats before issuing its final report. Given that hyperplasia often leads to neoplasm, the statistical analysis should also include findings of hyperplasia. (Hyperplasia is the enlargement of tissues or organs caused by increased rate of growth of its cells in the initial stage of cancer development.)

The World Health Organization's International Agency for Research on Cancer (IARC) had classified exposure to RF radiation including those used for cell phones as possibly carcinogenic to humans [12]. IARC had assessed available scientific papers and concluded that while evidence was incomplete and limited, especially with regard to results from animal experiments, epidemiological studies reporting increased risks for

malignant gliomas and acoustic neuromas among heavy or long-term users of cell phones are sufficiently strong to support a classification of RF exposure possibly causing cancer in humans. Note that acoustic neuromas are also known as acoustic schwannomas, a non-malignant tumor of Schwann-cells-sheathed auditory nerves on the side of the brain.

It is remarkable to note the complete absence of histopathological results from the inner ear or auditory nerve tissue in the NTP RF study. This is totally unacceptable and may speak volumes to the inadequacies and flaws of the study as it was designed.

The significance and necessity for histopathological examinations of tissue specimens surrounding the auditory nerve should have been a clear priority because of the role acoustic schwannomas played in IARC's possible carcinogenic classification of cell phone RF radiation. In any case, it is hoped that NTP has preserved or has access to pertinent histological materials to allow them to go back and examine them with regard to acoustic schwannomas.

What is even more startling to note is that malignant schwannoma in rat hearts were the most salient findings from the NTP RF bioassay. While acoustic schwannomas in human brains and malignant schwannomas in rat hearts were independently observed from two different body tissues in humans and rats, there actually could be a link in that Schwann cells wrap around both nerve tissues in the heart and along the auditory nervous system.

Questions to Ponder

Now that the NTP review panel has concluded that there is clear evidence of carcinogenicity from long-term RF exposure in rats, is it conceivable that IARC would upgrade its epidemiology-based classification of RF exposure to the next higher levels of carcinogenicity to humans?

It is noteworthy that the existing RF exposure guidelines of 1.6 or 2.0 W/kg are promulgated with a reduction factor of 50, as a safety margin for the general public. The finding that long-term RF exposure could lead to cancer development in rats at levels that are the same or no more than a factor of 3 above these exposure guidelines is significant.

While complacencies abound for the short-term exposure guidelines in providing safety protection, an outstanding question persists on the adequacy of these guidelines for safe long-term exposure to RF radiation at or below 1.6 or 2.0 W/kg. Perhaps, the time has come to judiciously reassessed, revised, and updated these guidelines.

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