Health Matters

Clear Evidence of Cell-Phone RF Radiation Cancer Risk

■ **James C. Lin**

During 26–28 March 2018, the National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program (NTP), a part of the U.S. National Institutes of Health, convened a three-day technical reports peer-review panel meeting in Research Triangle Park, North Carolina, to review the NTP's draft reports on its carcinogenesis studies of cell-phone RF radiation in mice and rats [1].

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The invited 14-member peer-review panel included three electrical engineering professors, ten pathologists and toxicologists (three from academia and seven from industry), and one biostatistician. None of the participants were from the cell-phone industry.

This project is the largest NTP animal cancer study. It was initiated by the U.S. Food and Drug Administration (FDA) in 1999. The planned five-year project was sole-sourced in 2004 to an industrial research firm, which served as the principal investigator. The work began in 2005. However, the project was protracted for more than 12 years with huge budget overruns and an estimated eventual price tag of US$25 million [2], [3], [13].

From the outset, NIEHS/NTP was tight-lipped about the study and did not release any progress reports or information. In contrast to the scientific norm, project investigators had not openly discussed any of its aspects or presented its progress or interim findings at scientific meetings. The first report from the investigators was issued in May 2016, when the NTP announced the occurrence of two types of rare cancers in exposed rats: 1) malignant schwannomas of the heart and 2) gliomas in the brain [4]. However, that announcement spoke only to partial findings from their two-year (or lifelong) exposure study of rats subjected to 900- and 1,900-MHz RF radiation involving code division multiple access (CDMA) and Global System for Mobile Communications (GSM) wireless cellular telephone operations.

Histopathological Findings

On 28 March 2018, following a thorough review of the draft NTP reports, pathologists and toxicologists on the peer-review panel concluded that, among other observations, there was 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 the Harlan-Sprague-Dawley strain). Further, there

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

In addition, based on statistical significance, the panel concluded 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 when compared with concurrent controls.

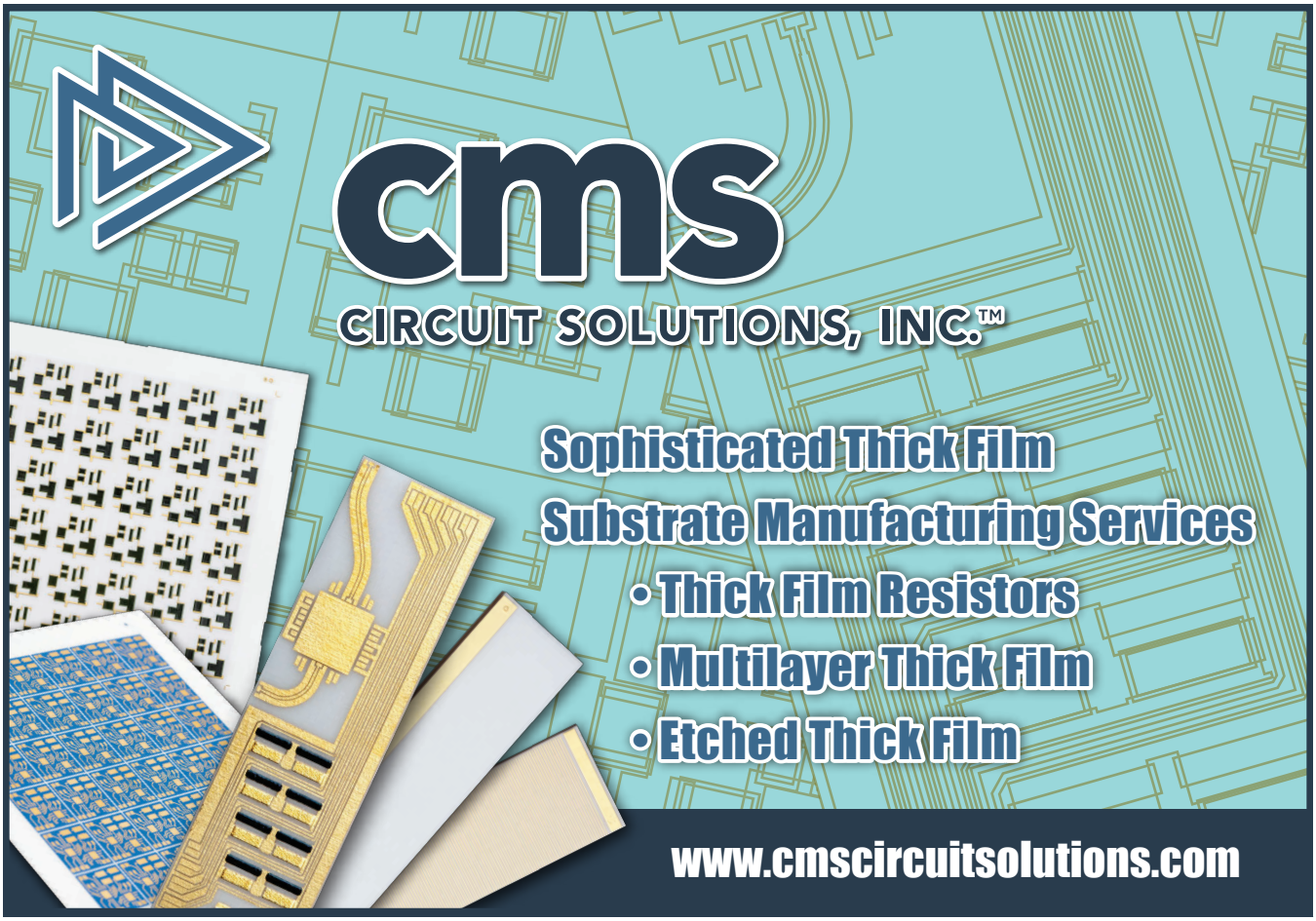
The NTP uses five categories of evidence for carcinogenic activity to classify the strength of evidence observed in their reports: "clear evidence" and "some evidence" for positive findings; "equivocal evidence" for uncertain results; "no evidence" for no observable effects; and "inadequate study" for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

RF Exposure in Large Reverberation Chambers

The 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/day for two years. Rats were exposed to cell-phone RF radiation for a total of 9 h each day. Whole-body average-RF specific absorption rates (SARs) of 0, 1.5, 3, or 6 W/kg did not raise the body temperature of the exposed animals more than 1 °C. The study was successful in providing maximum uniformity of exposure. In particular, the reported local SARs in the brains and hearts of the rats were only 1.05 and 2.27 times the whole-body average SARs, respectively. Indeed, most tissue and organs inside the rats' bodies had experienced similar SARs from RF exposure.

The NTP cell-phone RF exposure study is, by far, the largest study of its kind [5]. It was expensive and time consuming, and there may even have been better ways to perform the study. Nevertheless, it highlights that prolonged exposure to RF radiation at, or a little above, currently existing RF exposure regulation levels could lead to tumor development.

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 and 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



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or three times above current exposure guidelines is significant.

This implies that the safety margin may be no more than a factor of three. In fact, one recommendation (IEEE C95.1-2005) has a set of guidelines under controlled environments that allows 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 initiating and the NIEHS/NTP praised for having sponsored the research and conducted the cell-phone RF radiation studies. It's important for the U.S. government to step in and conduct such research programs and not leave the matter entirely to the cell-phone industry. The wireless industry has had nearly free reign to develop and distribute 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 continue to be exposed to more RF radiation every day [8], [9].

A question arose during the panel meeting concerning the unusually small number of concurrent control animals.

Moreover, a systematic review of 59 published studies on 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%), and mixed sources (including industry) funded 14 (24%); in 22 studies (37%), the source of funding was not reported. Research funded exclusively by industry reported the largest number of outcomes but was 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, the RC method and technology were employed for exposure of rats and mice to cell-phone RF radiation. The report's descriptions of what was implemented are fairly clear, and measurement techniques are accurate. However, there are limitations.

The RC method was selected a priori for the project. It is not clear whether RC is the optimal technology for such a project or if other competing technologies, e.g., circular waveguides or small rectangular multimodal chambers, were seriously considered for exposure of free-moving animals inside a holding cage.

The large number of RCs specifically constructed for this project represents the most expensive one-time or single-use equipment or facilities for RF biological-effect research. These would likely not be used for another project; thus, the RCs would be wasted, if they have not been scrapped already. The NIEHS/NTP has moved on to other types of exposure chambers to continue its biological-effect research regarding RF exposure.

The study could have been designed better. There were obvious flaws concerning the experimental design of 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 who sole-sourced this US$25-million NTP study to an industry contractor responded with a vague answer: the contractor only had space for 21 RCs. Thus, only one RC was available for sham or concurrent control. This begs the question of what the rationale was for sourcing a single contractor as the principal investigator for the project. The availability of facilities and space to conduct the study should be top priorities in listed criteria for awarding such a contract. In a US$25-million project, any mention of saving money by foregoing a couple more RCs or using round plastic bottles instead of rat-shaped experimental phantoms, sounds like a rather feeble excuse. The NTP project could have easily saved more money if the 21 large RCs had not been manufactured in Zürich, Switzerland, and transported for reassembly over land, ocean, and river to Chicago.

Concurrent and Historical Control Animals

The small number of concurrent control rats renders it 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?

In bioassay research involving animals, there are normally two types of controls: cage and sham. In cage controls, animals are housed in the vendor's open-stack vivarium, subjected only to routine housekeeping 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 (or concurrent controls), animals are subjected to the same protocols, RF apparatus, and environment but without being subjected to treatment by the experimental agent: in this case, RF exposure.

It appears that the NTP study designers 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 (here, Harlan-Sprague-Dawley). 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 and included only a few two-year studies lasting five to ten 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 the NTP facilities in Research Triangle Park, North Carolina, the RF study took place in Chicago, Illinois, where both sham control and exposed animals were housed in custom-designed and -constructed

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RCs; this RC environment is completely different from the NTP animal facilities. Aside from their one-of-a-kind sealed and shielded steel chambers with ambient sonic noise and air piped in through specially designed inlets and outlets, the animals' access to food and water was provided using ingenious, unique systems.

Furthermore, the RCs used incandescent light bulbs instead of the fluorescent lamps 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 characteristic of incandescent bulbs. Note that RF radiation (100 ± 50 kHz) is emitted by fluorescent lamps when in operation because of their starter electrodes and electronic switching ballast.

Given these issues, the historical controls from past NTP studies are not appropriate for statistical comparison in this RF exposure study. However, the review panel opted to base its evaluation and conclusion on the concurrent control data. Historical control data for the Harlan-Sprague-Dawley strain and from NTP are important background information for reference purposes.

Tumor Findings in the NTP Study

In addition to the malignant schwannomas in the heart tissue and, to some degree, the 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 and 3 W/kg when 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 tissue 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 through the RC volume [1], [11]. This level of field uniformity enabled similar SAR values throughout rats' bodies. Specifically, the local SAR in the brains and hearts of rats was a mere 1.05 and 2.27 times the whole-body average SAR, respectively. This means that tissue and organs inside the rats' bodies had experienced similar SARs from GSM and CDMA RF exposures.

Research funded exclusively by industry reported the largest number of outcomes but was least likely to report a statistically significant result.

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

The World Health Organization's International Agency for Research on Cancer (IARC) classified exposure to RF radiation, including that which is used for cell phones, as possibly carcinogenic to humans [12]. The IARC 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 were sufficiently strong to support a classification of RF exposure as possibly causing cancer in humans. (Note that acoustic neuromas are also known as acoustic schwannomas, a nonmalignant tumor of Schwann-cell-sheathed auditory nerves on the side of the brain.)

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

The significance of 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 the IARC's classification of cell-phone RF radiation as possibly carcinogenic. It must be hoped that the NTP preserved or has access to pertinent histological materials to allow its researchers to examine them with regard to acoustic schwannomas.

Malignant schwannoma in rat hearts were the most salient findings from the NTP RF bioassay. Acoustic schwannomas in human brains and malignant schwannomas in rat hearts were independently observed from two different body tissues in humans and rats. There could actually be a link between Schwann cells that 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 there is clear evidence of carcinogenicity from long-term RF exposure in rats, is it conceivable that the IARC would upgrade its epidemiology-based classification of RF exposure to the next level of carcinogenicity to humans?

As noted earlier, 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 as or no greater than a factor of three above these exposure guidelines is significant.

While complacencies abound for short-term exposure guidelines in terms of providing safety protection,

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an outstanding question persists concerning 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 reassess, revise, and update these guidelines.

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