"Clear Evidence" of Cell Phone Cancer Risk, Say Leading Pathologists

Why Peer Review Panel and NTP Interpreted the Same Animal Data Differently

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"You had it right the first time." That was the implicit message to the National Toxicology Program (NTP) from an expert panel after a point-by-point review of NTP's draft reports on its $25 million study of cancer risks of cell phone radiation in mice and rats.

Two years ago, with the results in hand, the NTP rushed to warn the public about the dangers of cell phones. It issued an interim report pointing to higher rates of tumors in the hearts and brains of male rats exposed to two different kinds of phone radiation. Then early this February with the release of the formal draft reports, the NTP made a U-turn, saying that using a cell phone "is not a high-risk situation."

Now a peer review panel —11 pathologists and toxicologists from academia and industry and one statistician— has concluded that there is "clear evidence of carcinogenic activity" in those male rats. The panel, which met* March 26-28 in Research Triangle Park, NC, determined that both GSM and CDMA signals had led to the development of a rare tumor in the hearts of rats, malignant schwannoma. The NTP, on the other hand, had concluded there was only "some evidence" for this association.

The panel saw some evidence of that same schwannoma risk among female rats, where the NTP had found only equivocal evidence.

The NTP uses five categories to classify evidence of carcinogenicity. The strongest is "clear evidence." In decreasing order of severity, the others are: "some," "equivocal," "no" and "inadequate" evidence. For more details, go here.

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Beyond the schwannomas in the heart, the panel members saw more evidence of a cancer risk than the NTP for tumors in two other organs of the male rats: the brain and in the adrenal gland. In both cases, the panel again raised the finding a notch, from equivocal to some evidence.

All in all, the panel upgraded *seven* different NTP findings, an unprecedented number. “It is highly unusual for a peer review panel to recommend so many upgrades to NTP’s conclusions,” Ron Melnick told us after the meeting. “As far as I recall, no panel has ever recommended so many, in fact, I don’t remember any at all.” Melnick led the team that designed the animal study. He retired in early 2009 after close to 30 years as a staff scientist at NTP.

In February, after NTP’s about-face, we speculated about the political forces that might have led NTP to change its outlook. The NTP presentations at the peer review meeting followed by the comments of the panelists shed light on how the two groups could look at the same tumor data and reach very different conclusions.

The panelists unanimously praised the design and execution of the NTP project. But when it came to interpreting the results, they diverged. Two factors that kept coming up over the course of the three-day meeting help explain the dynamics of their disagreement: (1) The role of the unexposed comparison animals, known as the “controls,” and (2) How RF radiation interacts with living systems. In the end, the peer reviewers were willing to accept the idea that RF radiation does not necessarily behave in the same way as the toxic chemicals that the NTP has been testing for decades.

Concurrent vs. Historical Controls

In a standard cancer bioassay, animals are exposed to the agent under study while a second set of similar animals, the controls, is treated exactly the same way without receiving the agent. At the end of the experiment, the tumor counts in the two groups are compared and inferences drawn.

To understand how the controls became an issue, we must first describe the NTP’s RF–exposure system. From the outset, Melnick was convinced that the animals should not be restrained and be able to run free while being exposed to the radiation. Restraint could put the animals under stress and would likely confound the experiment. A set of six animal studies in the 1990s used restrained animals. Even though RF exposures were limited to only a few hours a day (NTP’s were over nine hours a day), the animals showed signs of stress. The entire $10 million project was a washout.

The NTP commissioned 21 large, sealed rooms —called reverberation chambers— to house the exposed and control animals. There were 14 for the rats and 7 for the mice to allow for three levels of exposure (1.5, 3 & 6 W/Kg) to the two different signals (GSM & CDMA) under study. (Rats are larger than mice and required twice as many chambers). Every aspect of what went on in those closed spaces was controlled and monitored. The

chambers were expensive: they cost on the order of $100,000 each.



NTP reverberation chambers in Chicago. They were built by the IT'IS Foundation in Zurich. Details here.

Photo: Myles Capstick and Niels Kuster

To save money and space, NTP used the same control animals for both GSM and CDMA exposure groups. This meant that NTP did not need to build and install three additional reverberation chambers (two for rats and one for mice). While this seemed to be a good idea at the time, it would later blunt the power of the statistical analyses. It became more difficult to show that an outcome was statistically significant, a key measure for judging the reliability of an experimental finding. "If we could do this over, we would have had a second control group," said John Bucher, who led the NTP RF study team and helped preside over the meeting.

A common workaround is to compare the exposed animals to historical controls —data from control groups used in past studies. But this option was limited in this case because of the small number of available historical controls. About ten years ago, the NTP began using a new breed of rats (Sprague-Dawley) in its chronic studies and, since then, has completed only a few two-year bioassays.

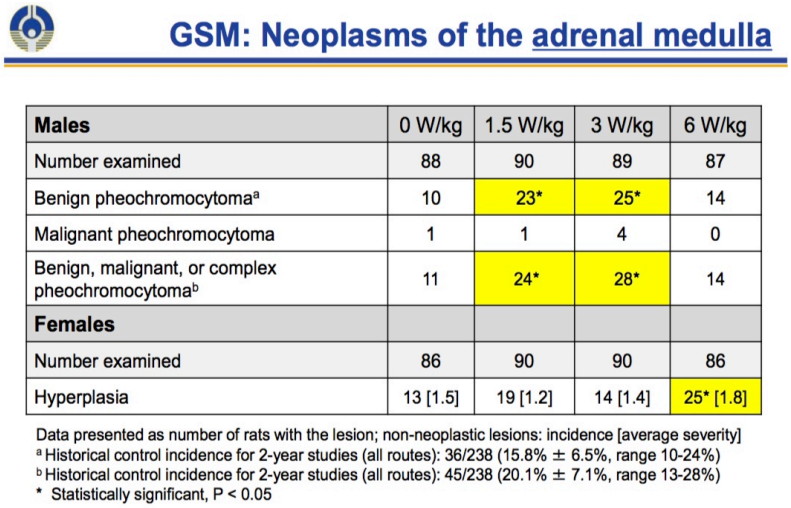
Another important difference between the RF control animals and the historical controls has to do with the nature of the reverberation chambers. In the RF study, the rats and mice lived in completely shielded rooms with air and white noise piped in —a more artificial environment than the open cages that housed the controls in NTP studies on toxic chemicals. The reverberation chambers also featured incandescent lighting instead of the fluorescent bulbs that were used in the past.

For all these reasons, the control animals from past studies may not be a suitable comparison group for those in the RF study. "The historical controls are an important issue," said David Eaton, the

dean of the graduate school at the University of Washington, Seattle, who served as the non-voting chairman of the peer review panel.

The NTP presentations often referred to the historical controls to question the reliability of some of the findings. The panel tended to rely on the concurrent controls.

One example of their different approaches was the evaluation of the pheochromocytomas ("pheos" for short), tumors of the adrenal gland. Here is NTP's table of tumor incidences and related data for rats exposed to GSM radiation:



GSM: Neoplasms of the adrenal medulla

Males	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	88	90	89	87
Benign pheochromocytoma[a]	10	23*	25*	14
Malignant pheochromocytoma	1	1	4	0
Benign, malignant, or complex pheochromocytoma[b]	11	24*	28*	14
Females				
Number examined	86	90	90	86
Hyperplasia	13 [1.5]	19 [1.2]	14 [1.4]	25* [1.8]

Data presented as number of rats with the lesion; non-neoplastic lesions: incidence [average severity]
[a] Historical control incidence for 2-year studies (all routes): 36/238 (15.8% ± 6.5%, range 10-24%)
[b] Historical control incidence for 2-year studies (all routes): 45/238 (20.1% ± 7.1%, range 13-28%)
* Statistically significant, P < 0.05

Source: Michael Wyde, Presentation at March 28, 2018, NTP Peer Review Meeting

The number of pheos was statistically significantly higher at 1.5 W/Kg and 3 W/Kg, relative to the concurrent controls. Importantly, the number of control animals with tumors (12.5%) was well below the average (20.1%) of the historical controls. In addition, the range (16-31%) in the three exposure groups was within or just above that seen in the historical controls (13-28%).

The NTP decided that the pheos were an equivocal finding. The peer review panel disagreed and voted to upgrade it to some evidence of carcinogenic activity. "If you have [concurrent] controls, you have to believe the controls," commented Mark Cline, a pathology professor at Wake Forest School of Medicine and the member of the panel who made the motion to raise the classification. It passed by a vote of six-to-four, with one abstention.

Linear vs Nonlinear Responses

Another one of the critera used by the NTP to determine whether an agent is carcinogenic is whether more animals develop a tumor as the dose is increased. This is called a linear dose-response relationship. Without it, there is often a lingering suspicion that the tumors were random events rather than causal.

Take, for instance, the results for glioma (brain tumors) and glial cell hyperplasia (abnormal growth, seen as an early indicator of a developing tumor) among male rats exposed to GSM radiation in the NTP table below.

GSM: Brain lesions

Males	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90
Malignant glioma[a]	0	3	3	2
Glial cell hyperplasia	0	2 [2.0]	3 [3.0]	1 [4.0]

Data presented as number of rats with the lesion; non-neoplastic lesions: incidence [average severity]
[a] Historical control incidence for 2-year studies (all routes): 2/190 (1.3% ± 2.3%, range 0-4%)

Source: Michael Wyde, Presentation at March 28, 2018, NTP Peer Review Meeting

There were tumors in all the RF–exposed groups and none in the controls. But there were more tumors at the two lower doses than at the highest dose. This is a "nonlinear" response. The same mixed trend was seen for glial hyperplasia. (As well as in the pheos example above.)

The NTP was ambivalent about this finding and decided that it represented only equivocal evidence of carcinogenicity. This stands in contrast to its view in 2016, when senior managers at the NTP, including Bucher, expressed concern not only about the schwannomas in the heart but also over the gliomas in the brain. (For more on the similarities of these two tumors, see "More Than a Coincidence.")

Here again, the panel upgraded the risk to some evidence, this time by a vote of seven-to-four. A majority of the panel believed that the absence of a linear response did not preclude cause and effect.

Some panel members were likely swayed by a presentation by Melnick during the public comment period. He opened his talk by saying he was there "representing the American people." Melnick showed a slide (below) in which he had combined the incidences of glioma and glial cell hyperplasia and showed that, while the trend was still nonlinear, the increases at the two lower doses were now statistically significant.

Proliferative Lesions (neoplasms and hyperplasias) in the Brain of Male Rats

Male Rats	Sham	GSM (SAR mW/g)			CDMA (SAR mW/g)		
	0	1.5	3.0	6.0	1.5	3.0	6.0
Lesion	Incidence, %						
Glioma[a]	0	3.3	3.3	2.2	0	0	3.3
Glial cell hyperplasia	0	2.2	3.3[b]	1.1[b]	2.2	0	2.2[b]
Total proliferative	0	5.5*	6.6*	3.3	2.2	0	5.5*

* $p<0.05$
[a] Historical control rate (all routes) = 2/190 (1.1%, range 0-4%)
[b] Marked severity of glial cell hyperplasia for one rat in these dose groups; "the hyperplastic lesions are within a continuum leading to malignant glioma"

Source: Ron Melnick, Presentation at March 27, 2018, NTP Peer Review Meeting

"The brain is obviously a target organ and should not be ignored," Melnick advised.

Indeed, Bucher had offered a similar argument at the NTP press briefing in May 2016. The increases in hyperplasias, which are fairly rare," he said on releasing the interim report, "add to our conclusion that, in fact, these tumors are related."

Nonlinear Responses Are To Be Expected

Over the course of the three days of discussions, Frank Barnes, a distinguished professor emeritus of electrical engineering at the University of Colorado in Boulder, noted repeatedly that he has often observed nonlinear effects in RF experiments carried out in his own laboratory. "I would not expect a linear dose-response based on our data," he said. "Nonlinearity is important," he stressed.

Barnes was a member of a second panel that was invited to offer technical advice to the pathologists and toxicologists. The three members of this engineering panel did not have a vote on the cancer classifications.

Some members of the pathology panel were sympathetic. "Nonlinearity is a hot topic today in radiation biology," pointed out George Corcoran, the chairman of the Department of Pharmaceutical Sciences at Wayne State University.

In fact, nonlinear interactions are nothing new in the electromagnetic radiation community. Thirty-five years ago, Ross Adey organized a conference on nonlinear effects of electromagnetic radiation in biological systems. (We covered that meeting.) "There is [now] impressive and growing evidence consistent with nonlinear, nonequilibrium interactions … in widely diverse tissues that include brain, bone, pancreas and leucocytes," Adey said at the time.

Will NTP Revert to Its Earlier Outlook?

In general, members of the peer review panel took a more holistic approach to the NTP results. "I have more questions than answers, but the heart is clearly sending a signal in the rat studies, between the levels of cardiomyopathy [heart disease] and malignant tumors," said Rick Adler, a panel member and the head of pathology for the U.S. arm of GlaxoSmithKline, a large pharmaceutical company.

A week after the NTP meeting, we wrote to Melnick and asked him why he thought the peer reviewers had upgraded so many of NTP's evaluations of the tumor risks. Here's what he told us:

> "NTP relied more heavily on dose-response relationships, historical control data, the magnitude of the responses and p-values for trends and pairwise comparisons. In contrast, the panel did not require linear dose-responses, was not influenced by historical control data and believed that the increased incidences of rare tumors represented true effects."

At the close of the meeting, Bucher said that, "It is very rare for NTP to reject the advice of its advisory panels." If so, the NTP will have come full circle and be back where it was two years ago.

The NTP expects to release the final reports on the project in the fall.

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* The agenda of the meeting is here. Only the rat study is discussed in this article. The mice experiment showed equivocal evidence for a number of different tumors in males, including in the lung and the skin, as well as lymphoma among females.

† The presentations at the peer review meeting are no longer available on the NTP website. They have been archived and are available from the NTP web team. *Microwave News* requested and received pdfs of all the presentations.

NTP, NIEHS, brain cell phones, schwannoma, glioma, John Bucher, Ron Melnick, Mark Cline, Frank Barnes, Rick Adler, pheochromocytoma, nonlinear effects, David Eaton, George Corcoran, cell phones cancer,

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