Partial Results of NTP Chronic Carcinogenicity Studies of Cell Phone Radiofrequency Radiation in Rats

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Background

- U.S. Food and Drug Administration (FDA) nominated cell phone radiofrequency radiation (RFR) emissions for toxicology and carcinogenicity testing
  - Human exposure is widespread, little known about potential health effects of long-term exposure
  - Current exposure guidelines are based on protection from acute injury from thermal effects
- Epidemiology studies demonstrate a potential increase in glial cell tumors in the brain and vestibular schwannomas (acoustic neuromas) may be associated with cell phone usage
  - Inconsistent results, confounding factors, biases, and long latency periods
- Studies in laboratory animals have not associated exposure to RFR with an increase in tumors at any site
  - Study inadequacies and limitations; physical and logistical challenges
- IARC 2B classification – *Possibly carcinogenic to humans*

What US Government Agencies Are Concerned With RF?

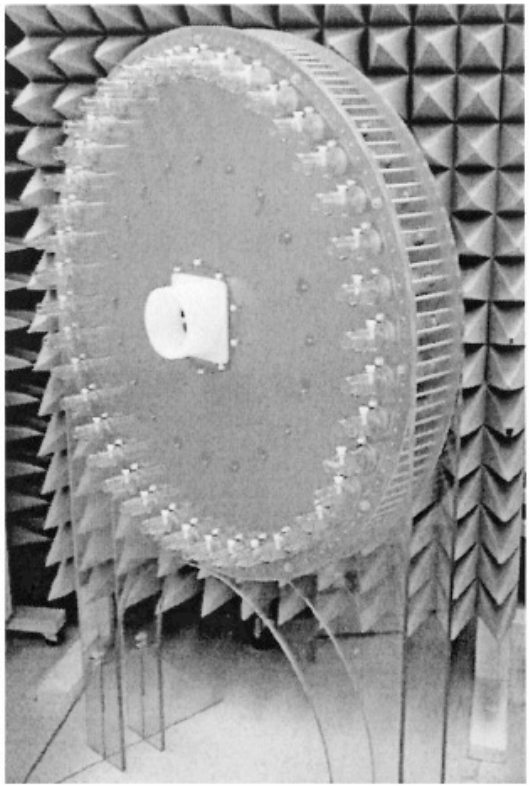
- **Federal Communications Commission (FCC)**
  - Cell phone devices are required to meet exposure guidelines set by the FCC
  - Based on acute effects from higher levels of exposure, and may not be protective against chronic, lower levels of exposures
- **Food and Drug Administration (FDA)**
  - FDA jurisdiction for any health-related issues under the 1968 Radiation Control for Health and Safety Act
  - Cannot mandate the cell phone industry to provide data on health effect
- **Other agencies have interest**
  - National Cancer Institute (NCI), Environmental Protection Agency (EPA), National Institute for Occupational Safety and Health (NIOSH)

RFR exposure system evaluation and design

- Most animal studies at the time used a Ferris-wheel exposure system
  - Maintained uniform field exposures, but short duration of exposure in restrained animals

- Established collaboration with the **National Institute of Standards and Technology (NIST)** to develop an exposure system that would address the limitation in existing exposure systems

- Established collaboration with **IT'IS Foundation** (Switzerland) to conduct complex computational models of RF dosimetry to provided estimates of whole-body and organ-specific internal field strengths and specific absorption rates (SAR) at 900 and 1900 MHz



Faraone *et al.* (2006) *Radiation Research* **165**, 105–112

The NTP RFR exposure facility

- **IT'IS Foundation** built and tested a prototype chamber based on the technical parameters obtained and optimized in the NIST studies
- Constructed 21 reverberation chambers in Switzerland
  - Separate chamber for each power level (SAR) for each modulation
  - 2 signal modulations: Code Division Multiple Access (CDMA) and Global System for Mobile Communications (GSM)
    - **GSM: low, med, high**; **CDMA: low, med, high; control chamber*** without any RFR signals
    - 7 chambers for mouse studies at 1900MHz
    - 14 chambers for rat studies at 900MHz (7 for males and 7 for females)
- Installed chambers at **IIT Research Institute** (IITRI) in Chicago, IL

*Each sex/species had a common control chamber for both GSM and CDMA modulations

The NTP RFR exposure facility

The NTP RFR reverberation chambers

Empty Chamber

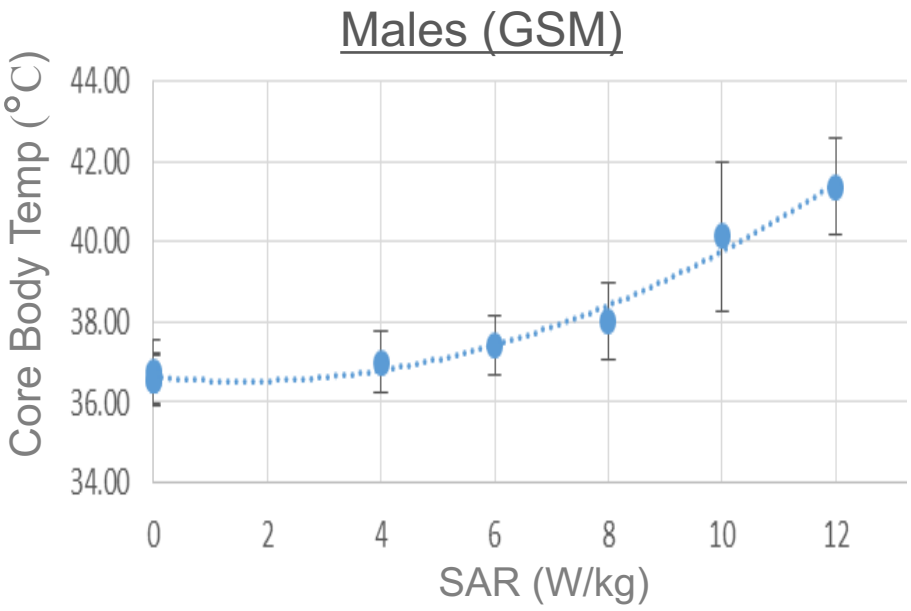
Cage Racks

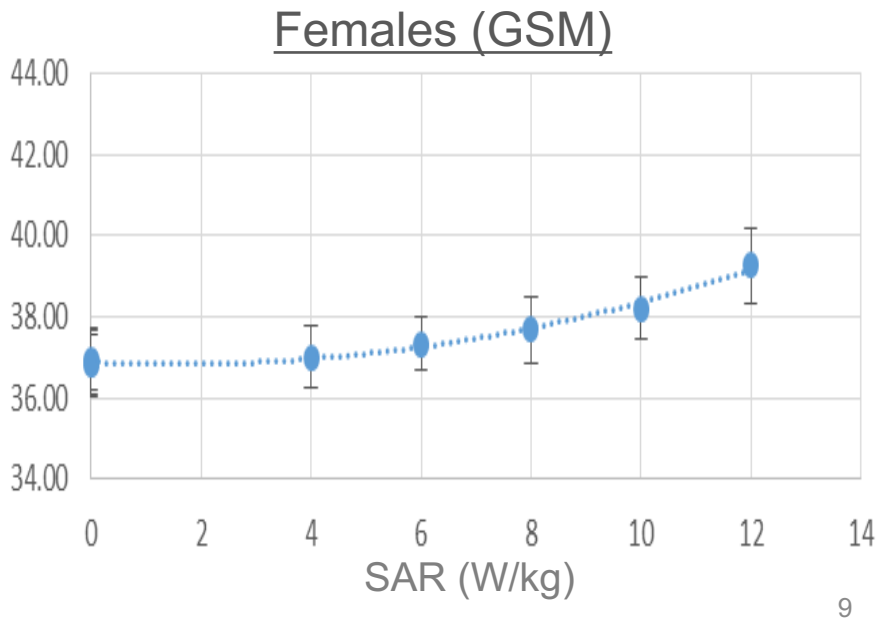
Cell phone RFR research program

- Three-phase toxicology and carcinogenicity studies in Harlan Sprague Dawley rats and B6C3F$_1$ mice
  - **5-day thermal pilot** studies at SARs of 4-12 W/kg in young and aged rats and mice and pregnant rats (10 studies)
  - **28-day prechronic** toxicology studies
  - **2-year** toxicology and carcinogenicity studies
- In all studies, daily exposure to RFR in reverberation chambers for ~9 hours (18 hr 20 min per day in 10 min on/10 min off cycles)
  - Rats exposed to GSM- or CDMA-modulated signals at 900 MHz
  - Mice exposed to GSM- and CDMA-modulated signals at 1900 MHz

5-day thermal pilot studies

- Determined if animal size (young and aged) or pregnancy status affect RFR thermal effects
  - Measured body temperature, body weight, and survival
- Body temperatures collected via implanted microchips at multiple time points over 5 days
  - A body temperature increase of 1°C was considered an upper tolerable, thermal limit





Summary: Results for 5-day pilot study in rats

- Excessive increases in body temperature were observed in pregnant and aged male and female rats at >8 W/kg
- Effects on body temperature observed for GSM and CDMA
- Effects more robust in males than females
- These results suggest upper limit of exposures of 6 W/kg GSM and CDMA in the chronic studies

28-day prechronic study in rats

- Perinatal exposure in HSD rats to 0, 3, 6, 9 W/kg GSM- or CDMA-modulated RFR at 900 MHz
- Significant effects observed at 9 W/kg
  - Increased pup loss during the lactation phase (CDMA only)
  - Decreased body weight in dams and pups during the lactation phase (GSM and CDMA)
  - Excessive increases in body temperature observed in dams at several time points during gestation and lactation (GSM and CDMA)

Chronic Studies

- NTP released partial report on May 26, 2016
  - http://biorxiv.org/content/early/2016/05/26/055699
- **Why not wait and release all study data together?**
- High level of public and media interest
- Two tumor types observed in this study are similar type to those observed in some epidemiology studies of cell phone users
- Support IARC conclusions of potential carcinogenic potential of RFR
- Given widespread global usage, even a small increase in incidence of disease resulting from RFR exposure could have broad implications for public health

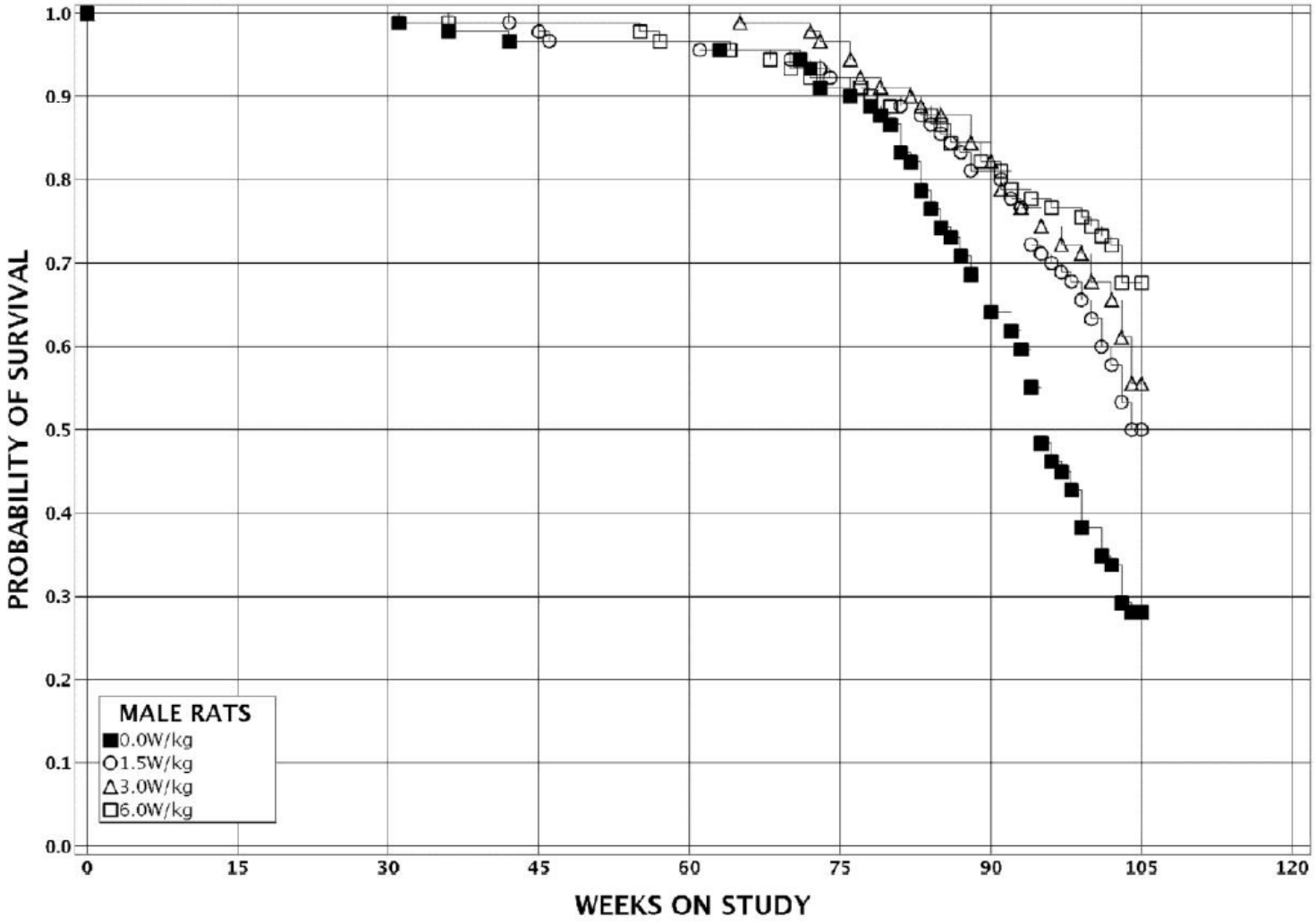
Chronic toxicology/carcinogenicity study design – Rats

- Harlan Sprague Dawley rats were exposed to SARs of 0, 1.5, 3, and 6 W/kg GSM- or CDMA-modulated RFR starting *in utero* on GD 5
- Interim evaluation after 13 weeks (n=15/sex/exposure group)
- Study termination after 104 weeks (n=90/sex/exposure group)

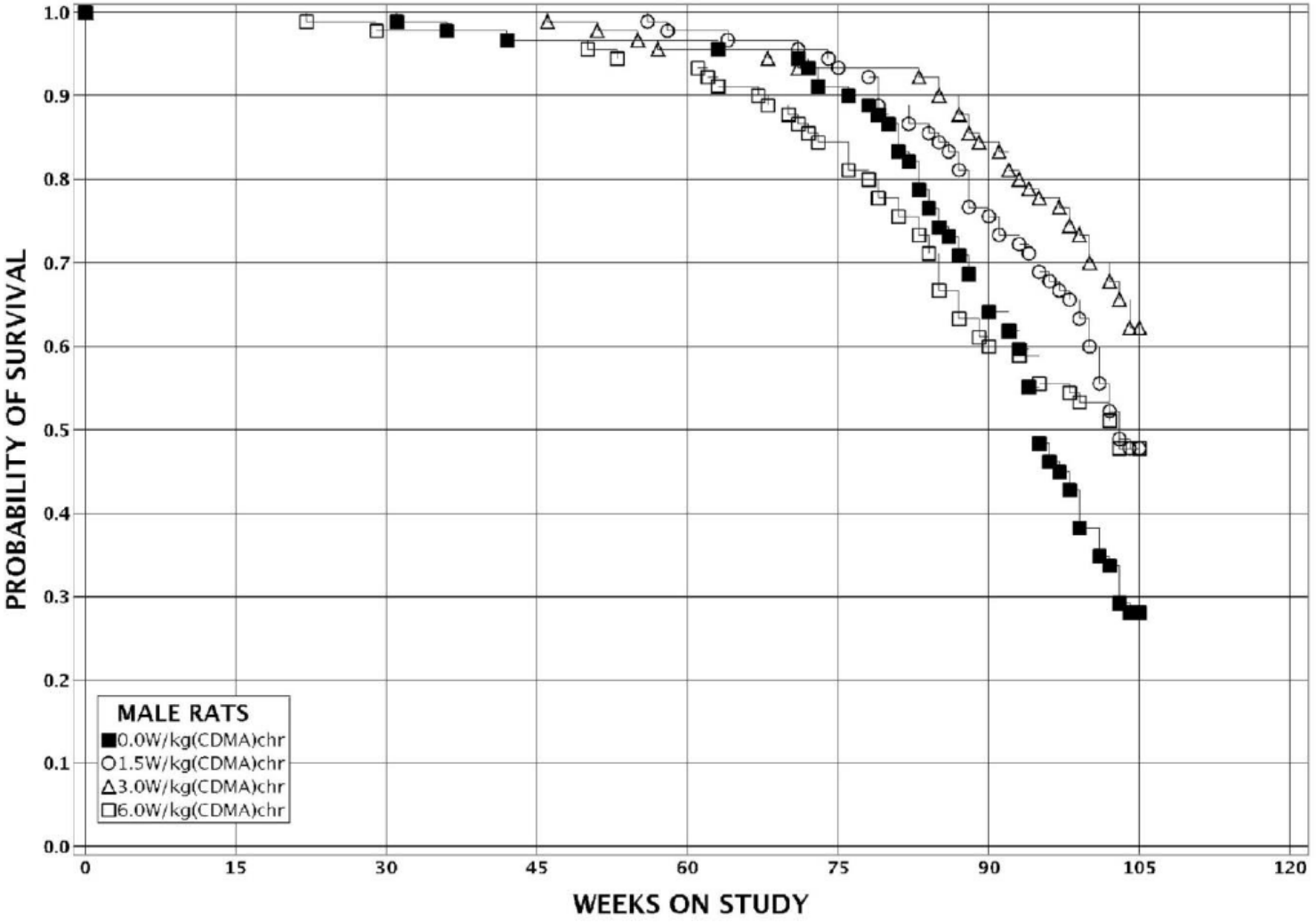
Perinatal effects of RFR exposure

- No exposure-related effects on pregnancy or littering
  - Percentage of dams delivering, frequency of implantations or resorptions, number of litters, litter size, or sex distribution of pups (GSM and CDMA)
- On PND1, decreases (5-9%) were observed on litter weights of male (GSM) and female (GSM and CDMA) pups
- During lactation, decreased body weights in dams and in males and female pups (GSM and CDMA)
  - Decreases more robust in CDMA pups (10-15%) compared to GSM exposed pups (6-8%)

Survival in male rats exposed to GSM RFR



Survival in male rats exposed to CDMA RFR



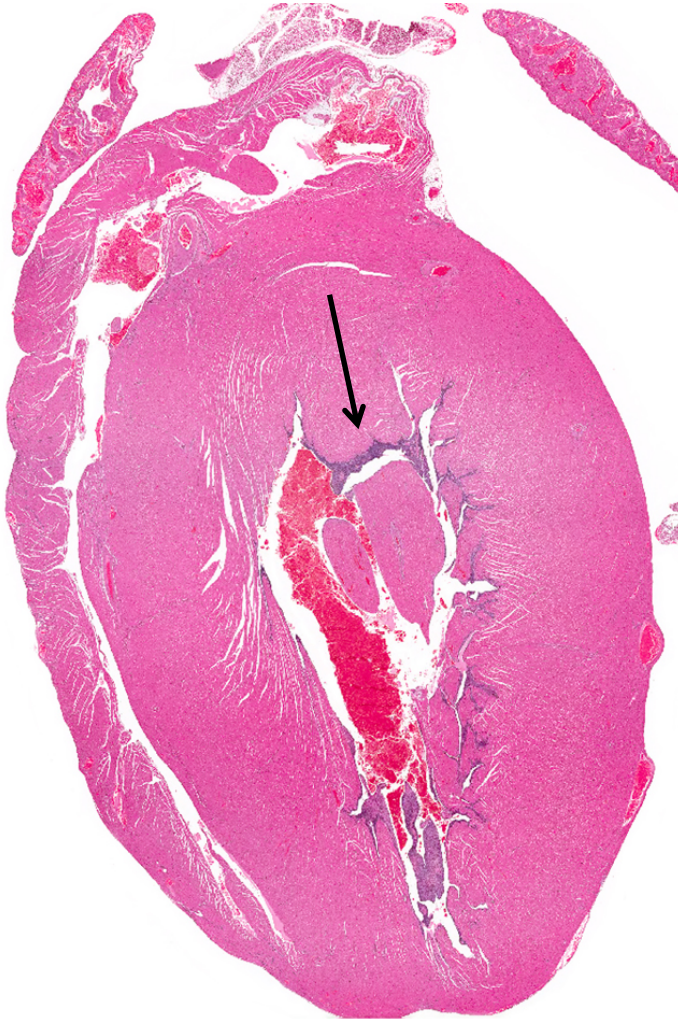
Survival in rats exposed to RFR

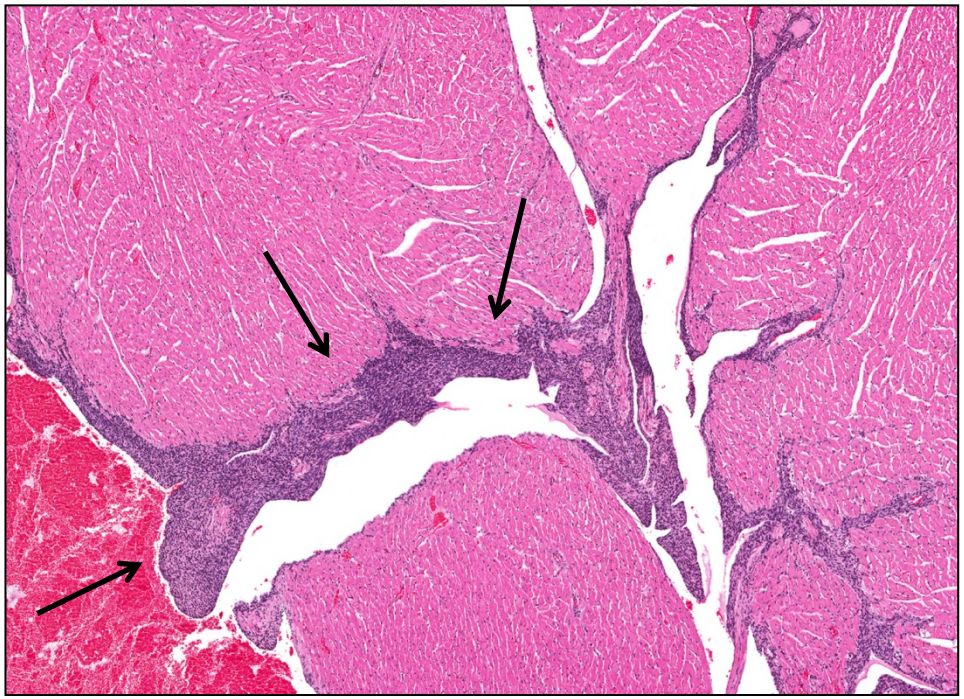
- Greater survival in all groups of exposed males compared to controls (GSM and CDMA)
- Less pronounced effect in survival in females (GSM and CDMA)

Partial pathology results in rats

- Currently only reporting partial findings
- Target organs:
  - Heart (schwannomas)
  - Brain (gliomas)

Heart (endocardium) - Schwannoma

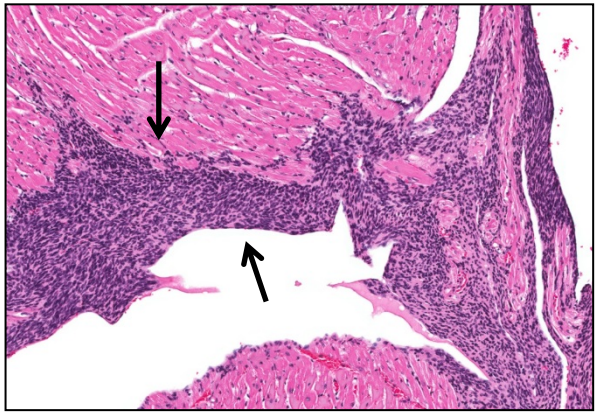




Pathology findings – Heart

Hyperplastic Heart Lesions in Male Rats

	Control		GSM Modulation		
	0 W/kg		1.5 W/kg	3.0 W/kg	6.0 W/kg
Number examined	90		90	90	90
Schwannoma‡	0*		2 (2.2%)	1 (1.1%)	5 (5.5%)
Schwann cell hyperplasia	0		1 (1.1%)	0	0



* Significant SAR-dependent trend for GSM and CDMA exposures by poly-3 ($p < 0.05$)

Pathology findings – Heart

Hyperplastic Heart Lesions in Male Rats

	Control		GSM Modulation			CDMA Modulation		
	0 W/kg		1.5 W/kg	3.0 W/kg	6.0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Number examined	90		90	90	90	90	90	90
Schwannoma‡	0*		2 (2.2%)	1 (1.1%)	5 (5.5%)	2 (2.2%)	3 (3.3%)	6** (6.6%)
Schwann cell hyperplasia	0		1 (1.1%)	0	0	0	0	3 (3.3%)

* Significant SAR-dependent trend for GSM and CDMA exposures by poly-3 ($p < 0.05$)

** Significant different than controls poly-3 ($p < 0.05$)

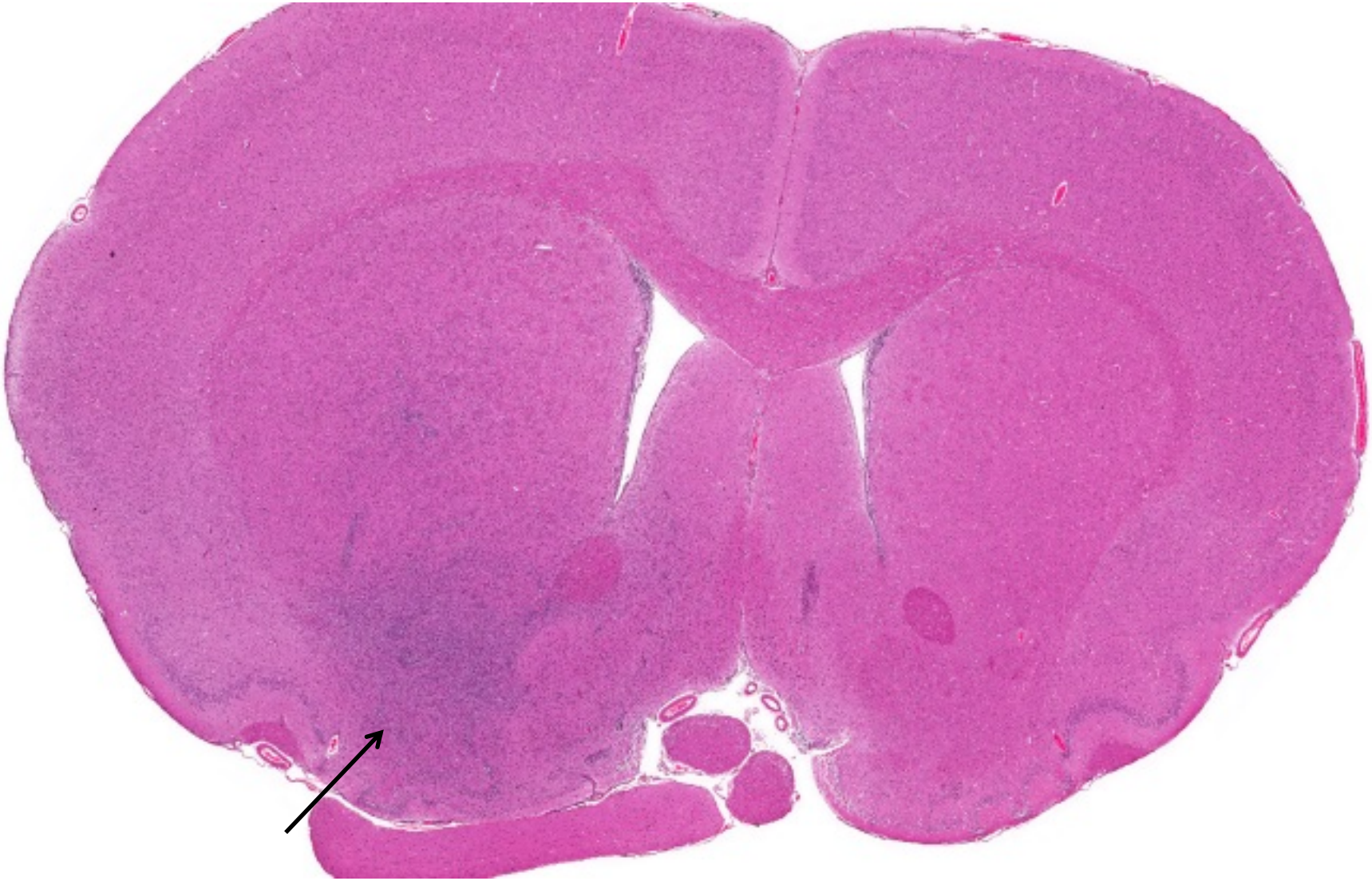
Pathology findings – Heart

Hyperplastic Heart Lesions in Female Rats

	Control		GSM Modulation			CDMA Modulation		
	0 W/kg		1.5 W/kg	3.0 W/kg	6.0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Number examined	90		90	90	90	90	90	90
Schwannoma‡	0		0	2 (2.2%)	0	2 (2.2%)	0	2 (2.2%)
Schwann cell hyperplasia	0		0	0	0	1 (1.1%)	1 (1.1%)	1 (1.1%)

- Incidences of heart lesions were not significantly different in female rats

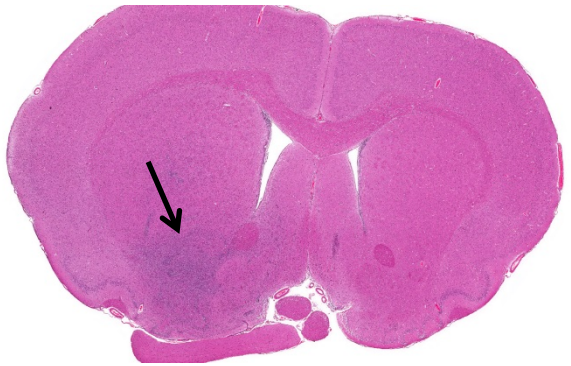
Brain – malignant glioma



Pathology findings – Brain

Hyperplastic Brain Lesions in Male Rats

	Control		GSM Modulation		
	0 W/kg		1.5 W/kg	3.0 W/kg	6.0 W/kg
Number examined	90		90	90	90
Malignant glioma‡	0		3 (3.3%)	3 (3.3%)	2 (2.2%)
Glial cell hyperplasia	0		2 (2.2%)	3 (3.3%)	1 (1.1%)



Pathology findings – Brain

Hyperplastic Brain Lesions in Male Rats

	Control		GSM Modulation			CDMA Modulation		
	0 W/kg		1.5 W/kg	3.0 W/kg	6.0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Number examined	90		90	90	90	90	90	90
Malignant glioma‡	0*		3 (3.3%)	3 (3.3%)	2 (2.2%)	0	0	3 (3.3%)
Glial cell hyperplasia	0		2 (2.2%)	3 (3.3%)	1 (1.1%)	2 (2.2%)	0	2 (2.2%)

* Significant SAR-dependent trend for CDMA exposures by poly-6 ($p < 0.05$)

Pathology findings – Brain

Hyperplastic Brain Lesions in Female Rats

	Control		GSM Modulation			CDMA Modulation		
	0 W/kg		1.5 W/kg	3.0 W/kg	6.0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Number examined	90		90	90	90	90	90	90
Malignant glioma‡	0		0	0	1 (1.1%)	2 (2.2%)	0	0
Glial cell hyperplasia	0		0	1 (1.1%)	0	1 (1.1%)	1 (1.1%)	1 (1.1%)

- Incidences of brain lesions were not significantly different in female rats

2-Year study summary

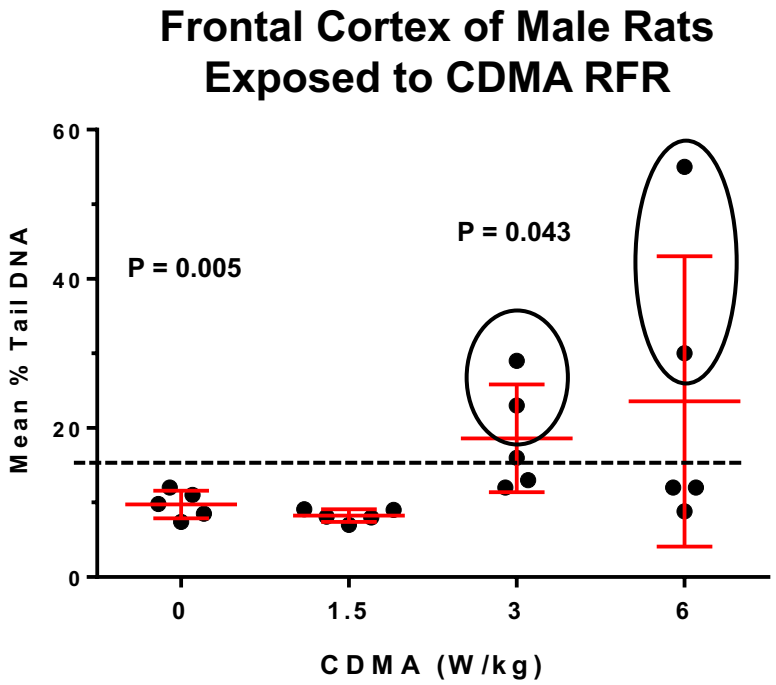
- Body weights at birth and throughout lactation in rat pups exposed *in utero* tended to be lower than controls
- In general, survival was greater in all groups of GSM or CDMA RFR-exposed rats compared to controls
- Increased incidence of schwannoma was observed in the hearts of male rats
  - Significant SAR-dependent positive trend (GSM and CDMA)
  - Significant pair-wise increase at 6 W/kg (CDMA)
- There was a significant SAR-dependent trend for increased gliomas in the brain of rats exposed to CDMA-modulated RFR
- Incidences of heart and brain lesions were not significantly different in female rats

Conclusions

- 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.
  - There is higher confidence in the association between RFR exposure and the neoplastic lesions in the heart than in the brain.
- Exposure of female rats to GSM- or CDMA-modulated RFR resulted in no biologically significant effects in the brain or heart.
- Draft NTP Technical Report is anticipated for peer review at a public meeting in 2017/2018

Genetic toxicology results in rats and mice

- Micronucleus assay
  - No significant increases in micronucleated red blood cells in rats or mice
- Comet assay
  - Mixed results in different tissues and brain regions in rats and mice
  - Responders vs. non-responders



Comet assay summary for rats and mice

		MALE					FEMALE				
RATS	CDMA	Frontal Cortex	Cerebellum	Hippocamp	Liver	Blood	Frontal Cortex	Cerebellum	Hippocamp	Liver	Blood
	GSM	Frontal Cortex	Cerebellum	Hippocamp	Liver	Blood	Frontal Cortex	Cerebellum	Hippocamp	Liver	Blood
MICE	CDMA	Frontal Cortex	Cerebellum	Hippocamp	Liver	Blood	Frontal Cortex	Cerebellum	Hippocamp	Liver	Blood
	GSM	Frontal Cortex	Cerebellum	Hippocamp	Liver	Blood	Frontal Cortex	Cerebellum	Hippocamp	Liver	Blood

Yellow — Statistically significant trend *and* pairwise SAR-dependent increase

Blue — Statistically significant trend *or* a pairwise increase

Green — Not significantly different, but increased in 2 or more treatment groups

What are next steps?

- **Smaller scale exposure facility under development**
  - Chamber design and exposure capabilities similar to original study
  - Verification of exposure characteristics provided by NIST
  - Provides capability to:
    - discover molecular events induced by RFR (e.g. oxidative stress)
    - replicate and expand genetic toxicity findings and assays (DNA repair processes of particular interest)
    - examine early molecular changes in heart
    - explore thermal effects when not induced by RFR (other heat sources)
    - study other frequencies and modulations
    - evaluate newer technologies (4G, LTE, 5G, etc.)

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Thank You!
Questions?

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