NTP
National Toxicology Program

NTP Toxicology and Carcinogenicity Studies of Cell Phone Radiofrequency Radiation

Michael Wyde, PhD, DABT
Toxicology Branch

National Institute of Environmental Health Sciences

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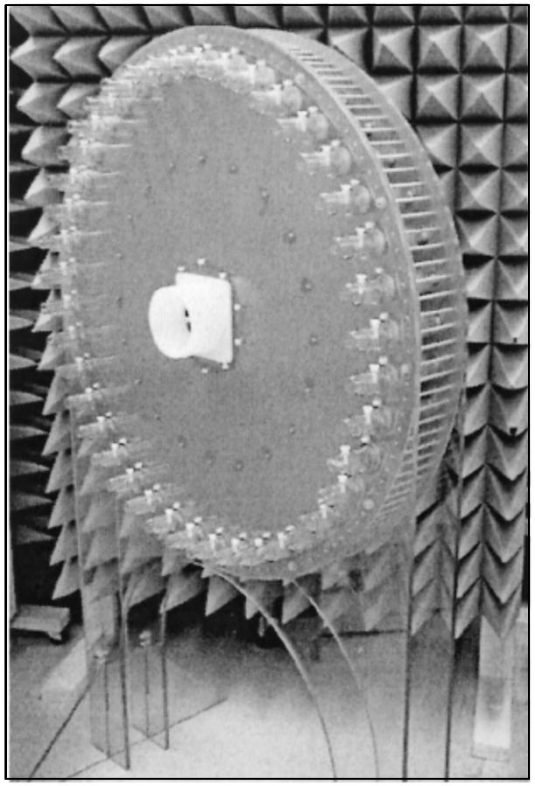
Nomination and background

- 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 demonstrated 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*

RFR exposure system evaluation and design

- Most animal studies at time used a Ferris-wheel exposure system
  - Maintained uniform field exposures, but short duration in restrained animals
- Established collaboration with the National Institute of Standards and Technology (NIST) to develop new exposure system



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

- Reverberation chamber exposure system
  - Shielded room with RFR antenna and a vertical and horizontal paddle to create a homogeneous electromagnetic environment
  - Field exposure is from all directions and all polarizations

Simulation modeling for RF dosimetry

- IT'IS Foundation (Switzerland) created complex computational models of RF dosimetry to provide estimates of whole-body and organ-specific internal field strengths and specific absorption rates (SAR)
  - Evaluate SAR distribution within animals to determine penetration and exposure of internal organs to RFR
  - Evaluate the impact of frequency on SAR in rats and mice
- RF dosimetry modeling demonstrated optimal exposure frequencies of 900 MHz for rats and 1900 MHz for mice

Cell phone RFR research program

- Constructed, tested, and validated RFR exposure facility at IIT Research Institute (IITRI) in Chicago, IL
- Three-phase toxicology and carcinogenicity studies in Harlan Sprague Dawley rats and B6C3F$_1$ mice
  - **5-day 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
- 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 beginning *in utero*
  - Mice exposed to GSM- and CDMA-modulated signals at 1900 MHz beginning at 5 weeks of age

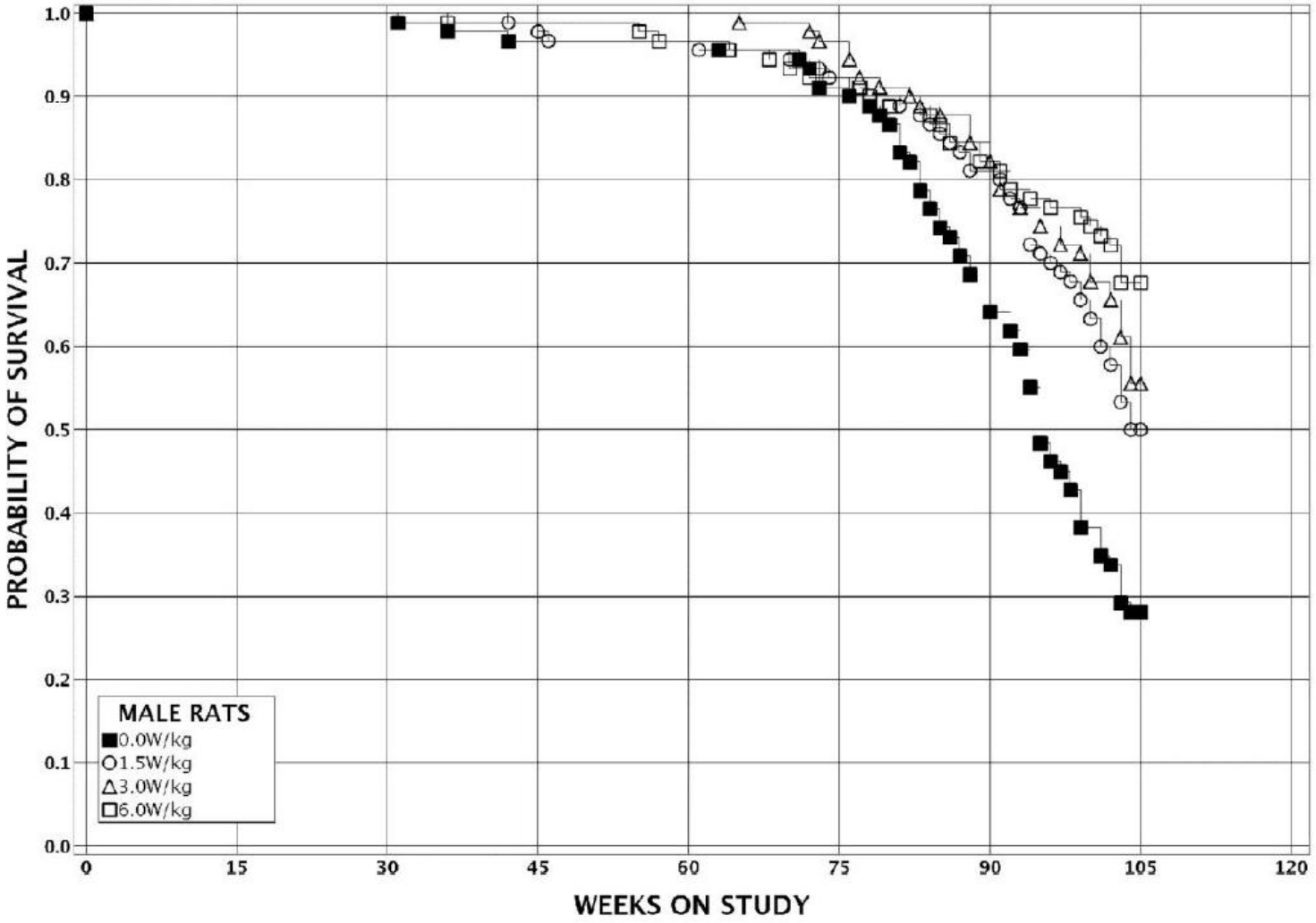
Chronic toxicology/carcinogenicity study design – Rats

- Time-mated, pregnant, female Harlan Sprague Dawley rats (n=56 per group) randomly assigned to SAR groups of 0, 1.5, 3, and 6 W/kg GSM or CDMA RFR
  - ~9 hrs exposure/day (10 min on/off cycling), 7 days/week started *in utero* on GD 5 and through gestation and lactation
  - Dams removed at weaning on PND 21; pups housed individually on PND 35
- On PND 21, weanlings randomly selected for chronic exposure
- Interim evaluation after 13 weeks (n=15/sex/exposure group)
- Study termination after 107 weeks (n=90/sex/exposure group)

Perinatal effects of RFR exposure

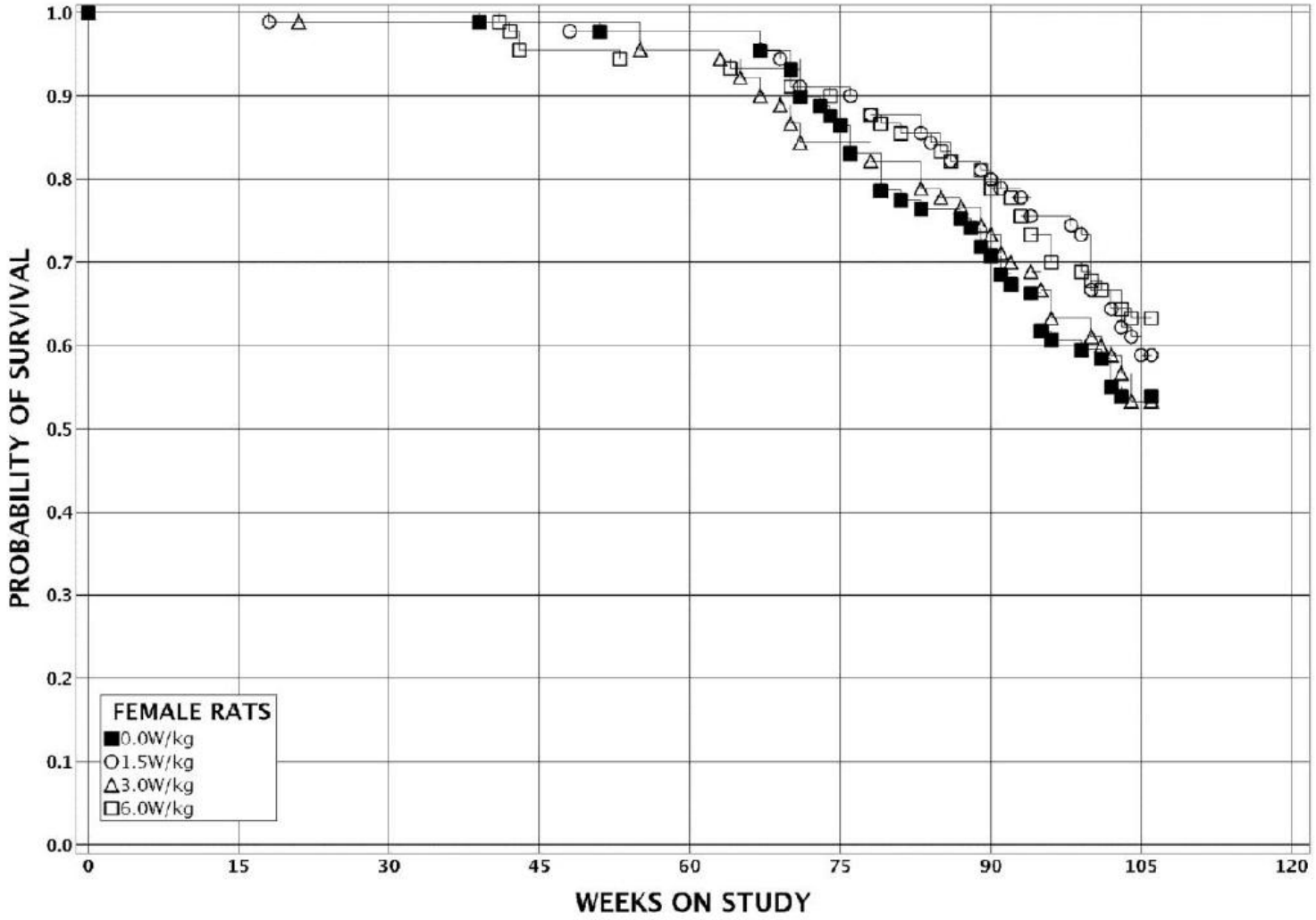
- No exposure-related effects on percentage of dams delivering, frequency of implantations or resorptions, number of litters, litter size, or sex distribution of pups (GSM and CDMA)
- Litter weights on PND 1
  - SAR-dependent decrease (5-8%) in mean litter weights of pups (males and females) from dams exposed to GSM RFR
  - Deceased (9%) mean litter weights of female pups from dams exposed to CDMA RFR
- Body weights during lactation
  - Decreased body weight in male (6-8%) and female (5-8%) pups at 3 and 6 W/kg GSM RFR
  - Decreased body weight in male (10-14%) and female (9-15%) pups at 6 W/kg CDMA RFR
- Decreased (7-9%) dam weights at 6 W/kg on PND 14-21 (GSM and CDMA)

Survival in male rats exposed to GSM RFR



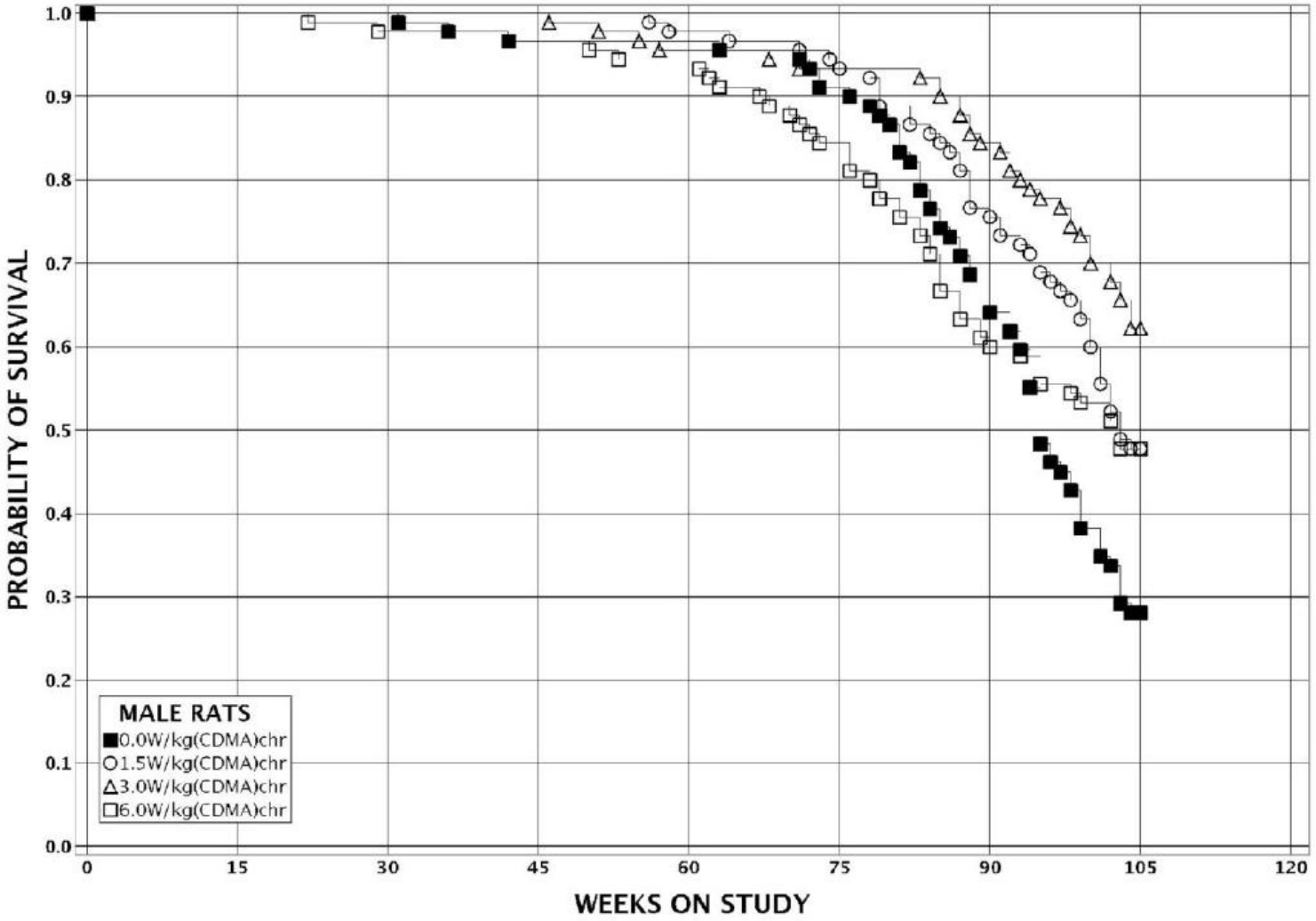
- Greater survival in all groups of exposed males compared to controls

Survival in female rats exposed to GSM RFR



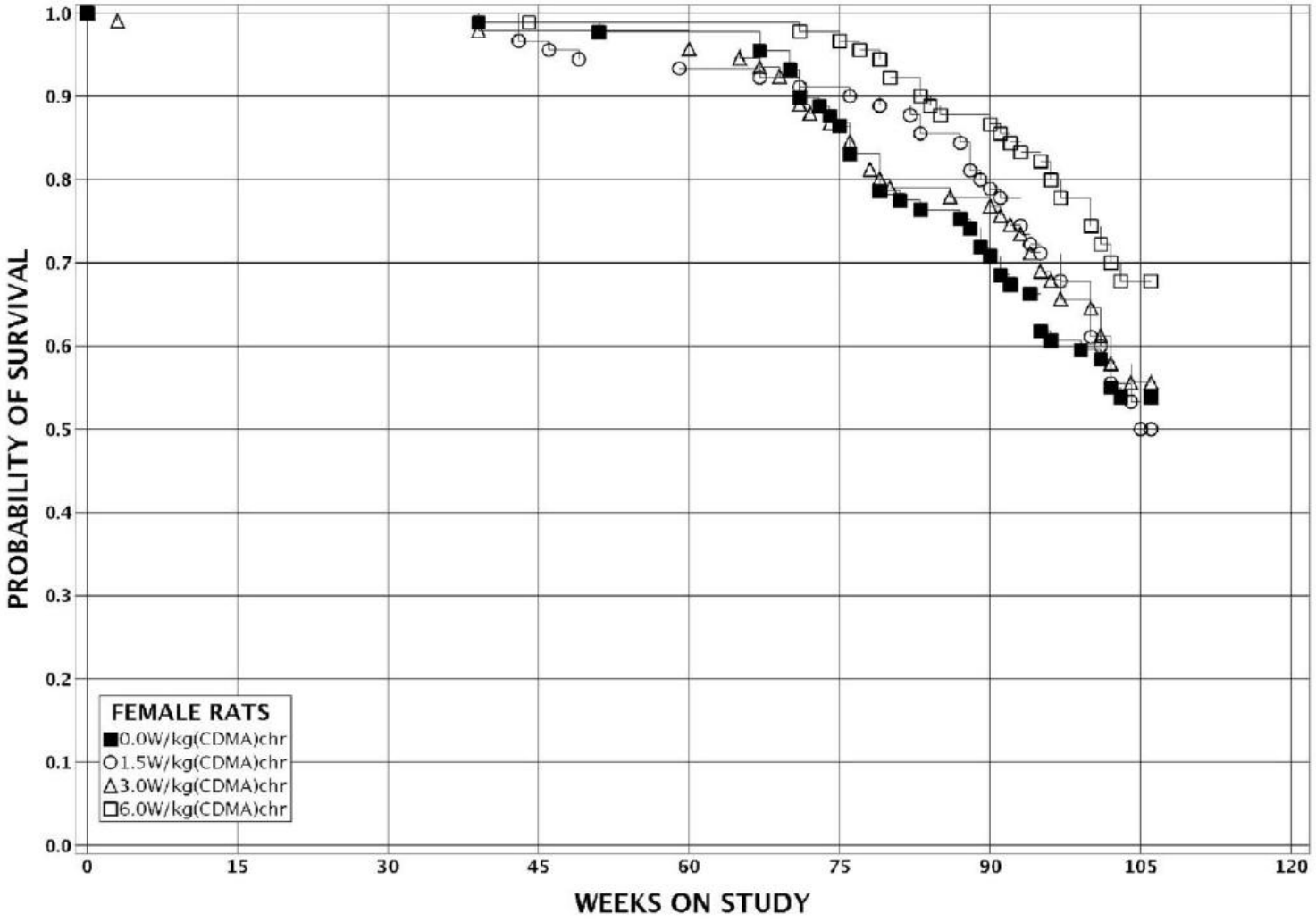
- Greater survival in some groups of exposed females compared to controls

Survival in male rats exposed to CDMA RFR



- Greater survival in all groups of exposed males compared to controls

Survival in female rats exposed to CDMA RFR



- Greater survival in some groups of exposed females compared to controls

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%)

‡ Historical control incidence in NTP studies: 11/550 (2.0%), range 0-8%

* 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%)

‡ Historical control incidence in NTP studies: 2/340 (0.3%), range 0-2%

- No exposure-related change in the incidence of brain lesions in female rats

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%)

‡ Historical control incidence in NTP studies: 9/699 (1.3%), range 0-6%

* 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%)

‡ Historical control incidence in NTP studies: 4/699 (0.6%), range 0-4%

- No exposure-related change in the incidence of heart lesions in female rats

Pathology findings – Schwannomas

Schwannomas Observed 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
Heart‡	0*		2 (2.2%)	1 (1.1%)	5 (5.5%)	2 (2.2%)	3 (3.3%)	6** (6.6%)
Other sites	3 (3.3%)		1 (1.1%)	4 (4.4%)	2 (2.2%)	2 (2.2%)	1 (1.1%)	2 (2.2%)
All sites (total)	3 (3.3%)		3 (3.3%)	5 (5.5%)	7 (7.7%)	4 (4.4%)	4 (4.4%)	7 (7.7%)

‡ Historical control incidence in NTP studies: 9/699 (1.3%), range 0-6%

* 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 – Schwannomas

Schwannomas Observed 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
Heart‡	0		0	2 (2.2%)	0	2 (2.2%)	0	2 (2.2%)
Other sites	4 (4.4%)		1 (1.1%)	3 (3.3%)	2 (2.2%)	0	2 (2.2%)	2 (2.2%)
All sites (total)	4 (4.4%)		1 (1.1%)	5 (5.5%)	2 (2.2%)	2 (2.2%)	2 (2.2%)	4 (4.4%)

‡ Historical control incidence in NTP studies: 9/699 (1.3%), range 0-6%

- No exposure-related change in the incidence of schwannomas in female rats

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 at 6 W/kg
  - 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
- No exposure-related effects were observed in the brains or hearts of 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.

Genetic toxicology results in rats and mice

- Micronucleus assay – Negative in rats and mice
- Comet assay
  - Mixed results in different tissues and brain regions in 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

Study status and timeline for completion

- NTP pathology peer review is underway for evaluation of all remaining rat tissues
- Pathology materials from the 2-year studies in mice are being transferred from contract lab for initiation of the peer review evaluation
- Resources shifted to accommodate expeditious review of chronic RFR studies
- Completion of pathology review is expected in approximately 18 months
- NTP Technical Report (TR) preparation will be conducted concurrent with the pathology peer-review process
- Draft TR is anticipated for peer review at a public meeting in 2017/2018

Acknowledgements/Collaborations

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