

NTP Toxicology and Carcinogenicity Studies of Cell Phone Radiofrequency Radiation

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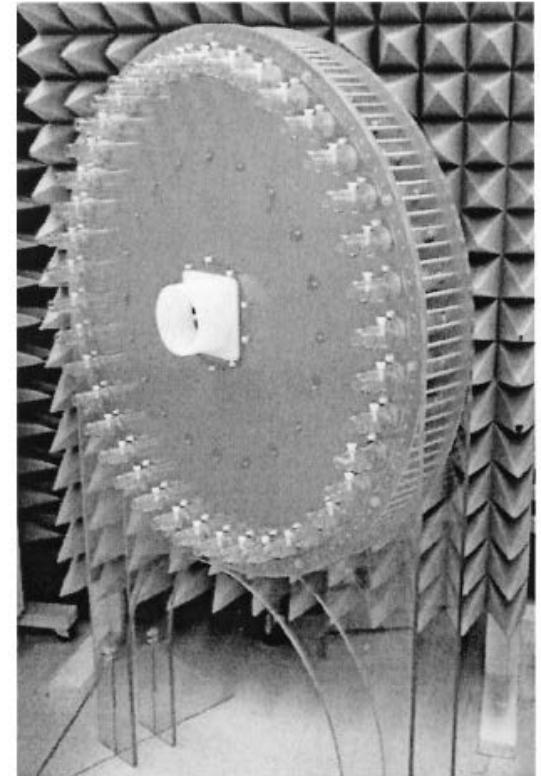


- U.S. Food and Drug Administration (FDA) nominated cell phone radiofrequency radiation (RFR) emissions for toxicology and carcinogenicity testing
- Specific concern raised for cell phone RFR exposure to the head
- Epidemiology studies demonstrate a potential increase in glial cell tumors in the brain 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 inherent in testing RFR
- IARC 2B classification – *Possibly carcinogenic to humans*



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
 - Unrestrained, individually housed animals
 - Exposure to RFR for a minimum of 6 hr/day
 - Exposure to a uniform field
 - Exposure to maximum power levels whereby animals are capable of thermoregulation (non-thermal range)





Simulation modeling for RF dosimetry

- Established collaboration with **IT'IS Foundation** (Switzerland)
- Created complex computational models of RF dosimetry that provided estimates of whole-body and organ-specific internal field strengths and specific absorption rates (SAR)
- Goals for computational models:
 - Evaluate SAR distribution within animals to determine penetration and exposure of internal organs to RFR
 - Determine if SAR distribution indicates overexposure of RFR to certain organs or body parts (i.e., the tail)
 - 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



Building 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
 - Architectural modifications to the building were required to accommodate installation of chambers

*Each sex/species had a common control chamber for both GSM and CDMA modulations 5



Cell phone RFR research program

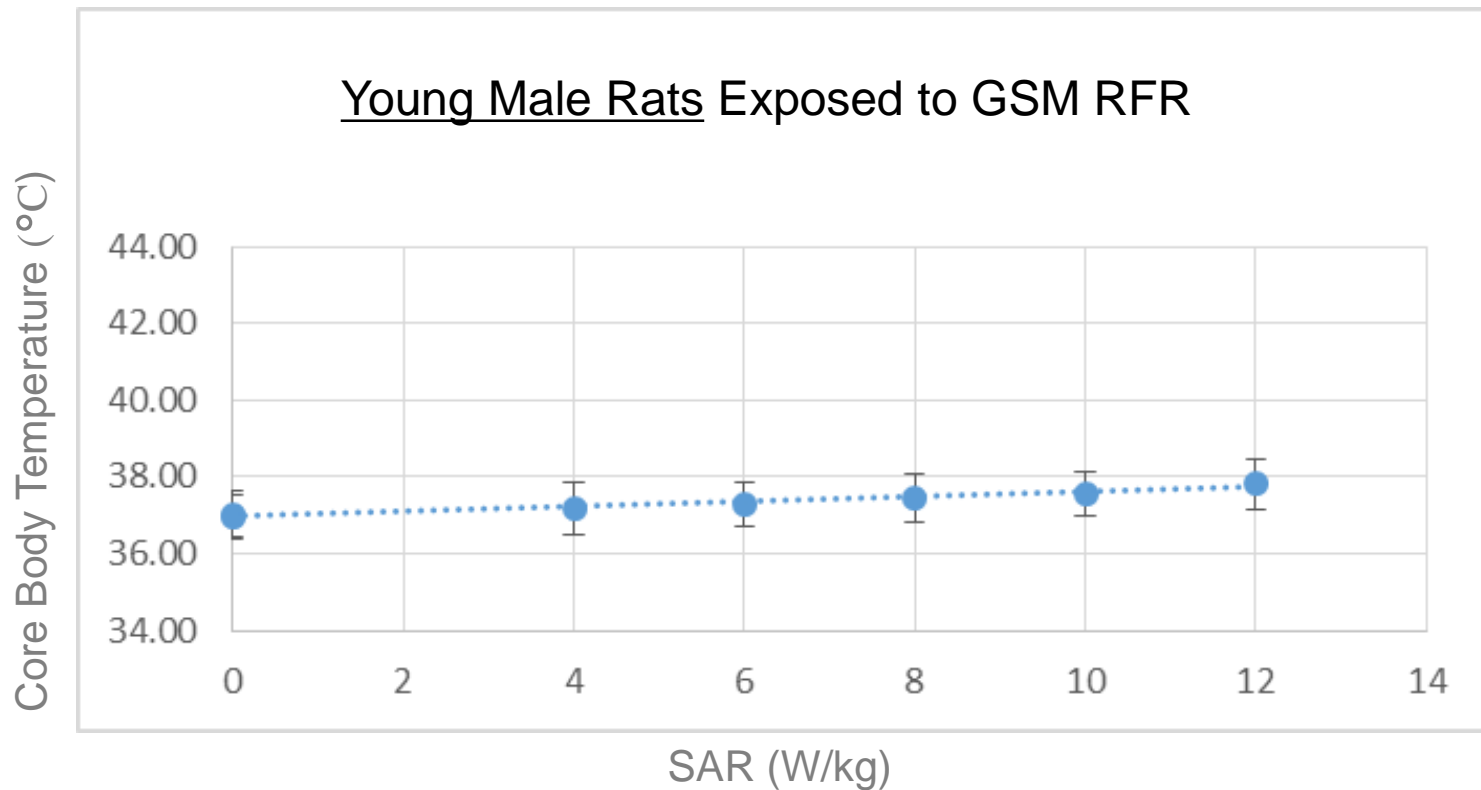
- Three-phase toxicology and carcinogenicity studies in Harlan Sprague Dawley rats and B6C3F₁ mice
 - **5-day pilot** studies at SARs of 4-12 W/kg in young and aged rats and mice and pregnant rats (10 studies)
 - **28-day prechronic** toxicology studies
 - **2-year** toxicology and carcinogenicity studies
- 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 either 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



- Determined if animal size and pregnancy status affect RFR thermal effects
 - Measured body temperature, body weight, and survival
- Conducted series of 10 studies in young (5 weeks), aged (>20 weeks), and pregnant rats, and in young (5 weeks) and aged (82 weeks) mice
- Exposed to either GSM- or CDMA-modulated RFR at 0, 4, 6, 8, 10, 12 W/kg for 5 days
 - Pregnant rats exposed during gestation days (GD) 10-15
- Collected body temperatures via implanted microchips at multiple time points over 5 days
 - A body temperature increase of 1°C was considered an upper, tolerable, thermal limit



Effect of RFR on body temperature – Rats

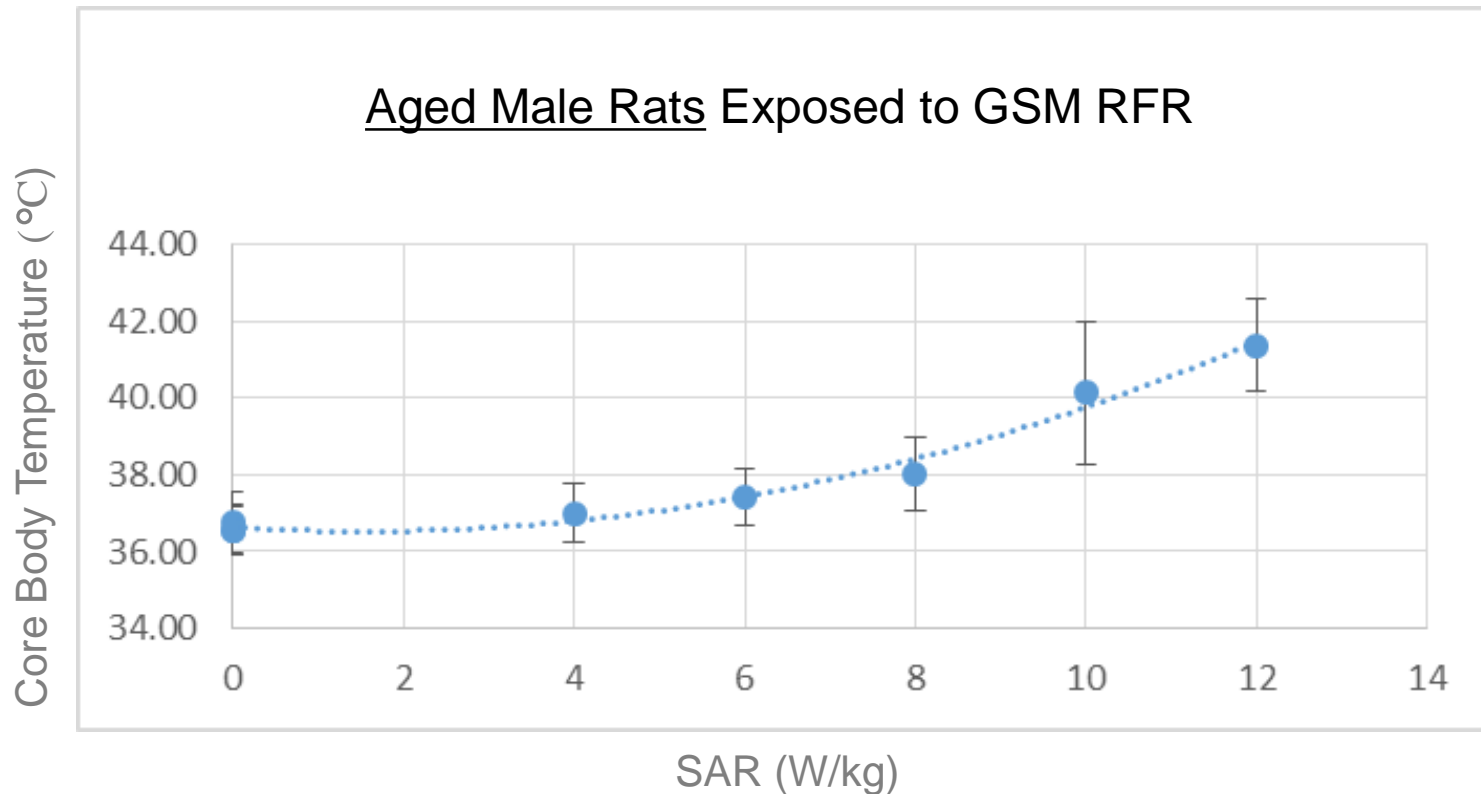


Note: Data points represent mean body temperature for all time points combined

- Similar results observed in young female rats



Effect of RFR on body temperature – Rats

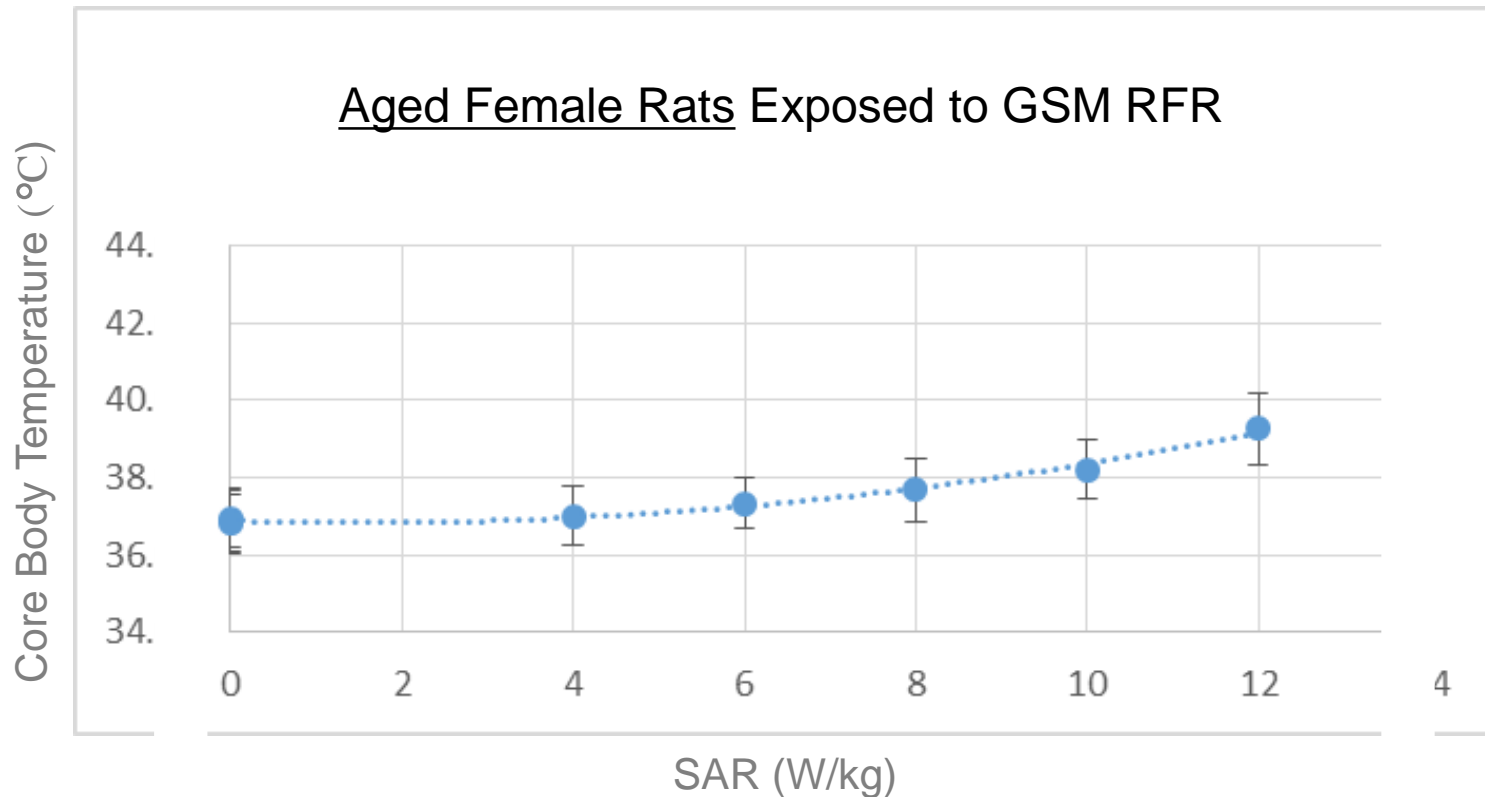


Note: Data points represent mean body temperature for all time points combined

- SAR-dependent increase in core body temperature following RFR exposure in both modulations (CDMA and GSM)



Effect of RFR on body temperature – Rats



Note: Data points represent mean body temperature for all time points combined

- SAR-dependent increase in core body temperature following RFR exposure in both modulations (GSM and CDMA)
- Less pronounced effect in females



Results for 5-day pilot study in rats

- 10 and 12 W/kg GSM and CDMA
 - Excessive increases in body temperature in pregnant and aged male and female rats with increased mortality in aged males
 - Increase in early resorptions at 12 W/kg GSM in pregnant rats
- 8 W/kg GSM and CDMA
 - Several instances of increased body temperature considered excessive in pregnant and aged male and female rats
- 6 W/kg GSM and CDMA
 - Some increases in body temperature in aged male and female rats only



28-day prechronic study designs

- Based on pilot study results, NTP selected SAR exposures of 0, 3, 6, 9 W/kg in rats and 0, 5, 10, and 15 W/kg in mice
- Perinatal exposure in Sprague Dawley rats (900 MHz)
 - 10 pregnant rats exposed per power level (SAR), per modulation (GSM or CDMA) beginning on GD 6
 - Exposure continued through lactation and for an additional 28-day period [postnatal day (PND) 21-49]
- 28-day study in B6C3F1 mice (1900 MHz)
 - 10 male and female mice per power level (SAR), per modulation
 - 5 weeks old at study initiation



28-day prechronic study results – Rats

- CDMA-exposed rats: Increased pup loss during the lactation phase (PND 4-PND 14) at 9 W/kg
- GSM- and CDMA-exposed rats: Decreased body weight in dams and pups during the lactation phase
 - Decreased body weight in dams at 9 W/kg
 - SAR-dependent decrease in body weight of male and female pups at 6 and 9 W/kg throughout lactation
 - Body weight gains in pups exposed to 9 W/kg were similar to controls, but body weights remained lower (up to 17%) than controls
- Increased body temperature in GSM- and CDMA-exposed rats
 - 6 and 9 W/kg GSM dams during gestation and lactation
 - 9 W/kg CDMA dams during late gestation and throughout lactation
- At several time points during gestation and lactation, body temperatures observed at 9 W/kg exceeded controls by $>1^{\circ}\text{C}$



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
 - Exposures initiated *in utero* on GD 5
 - Exposure continued throughout 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)

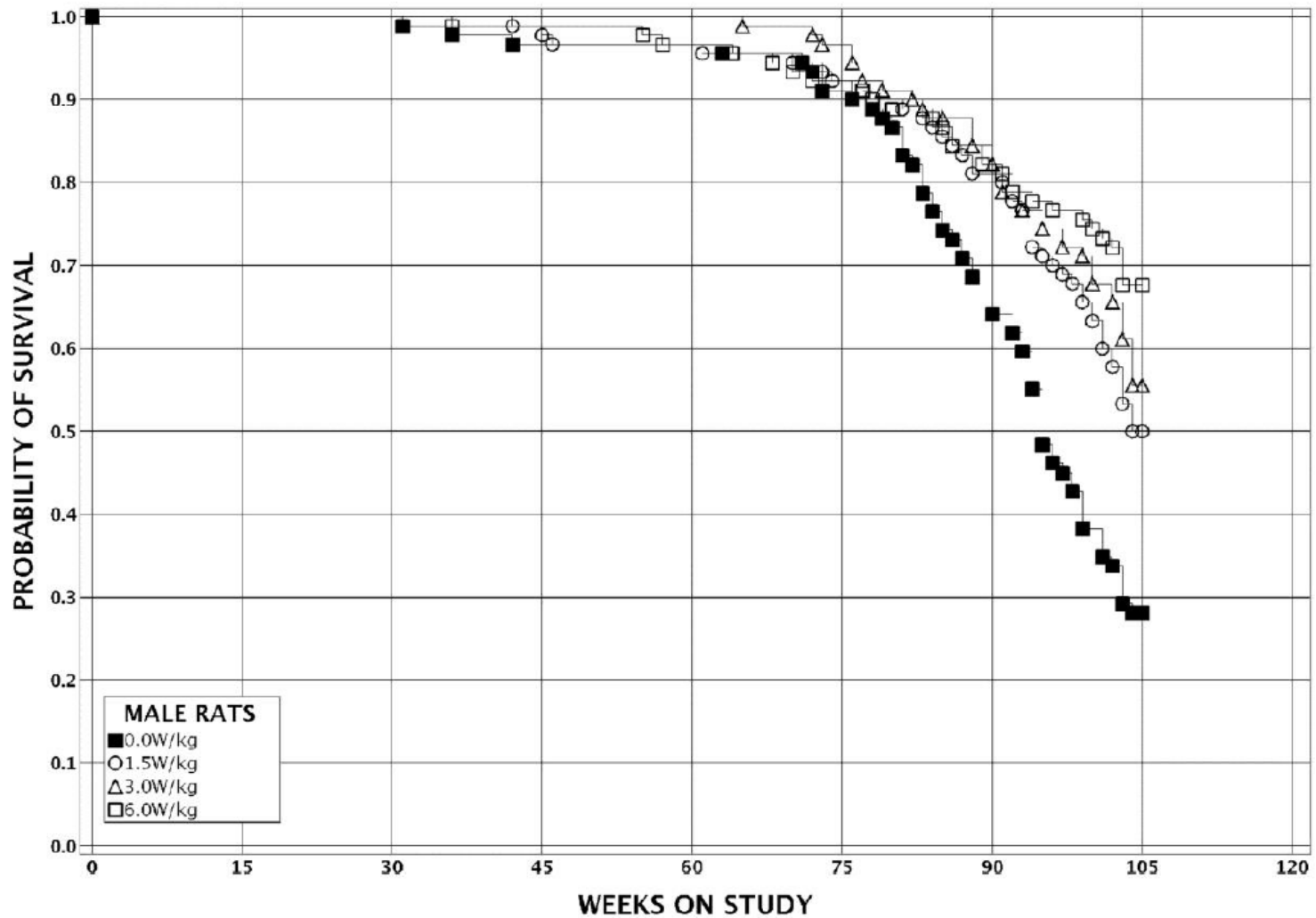


Perinatal effects of RFR exposure

- 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
 - Decreased (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)



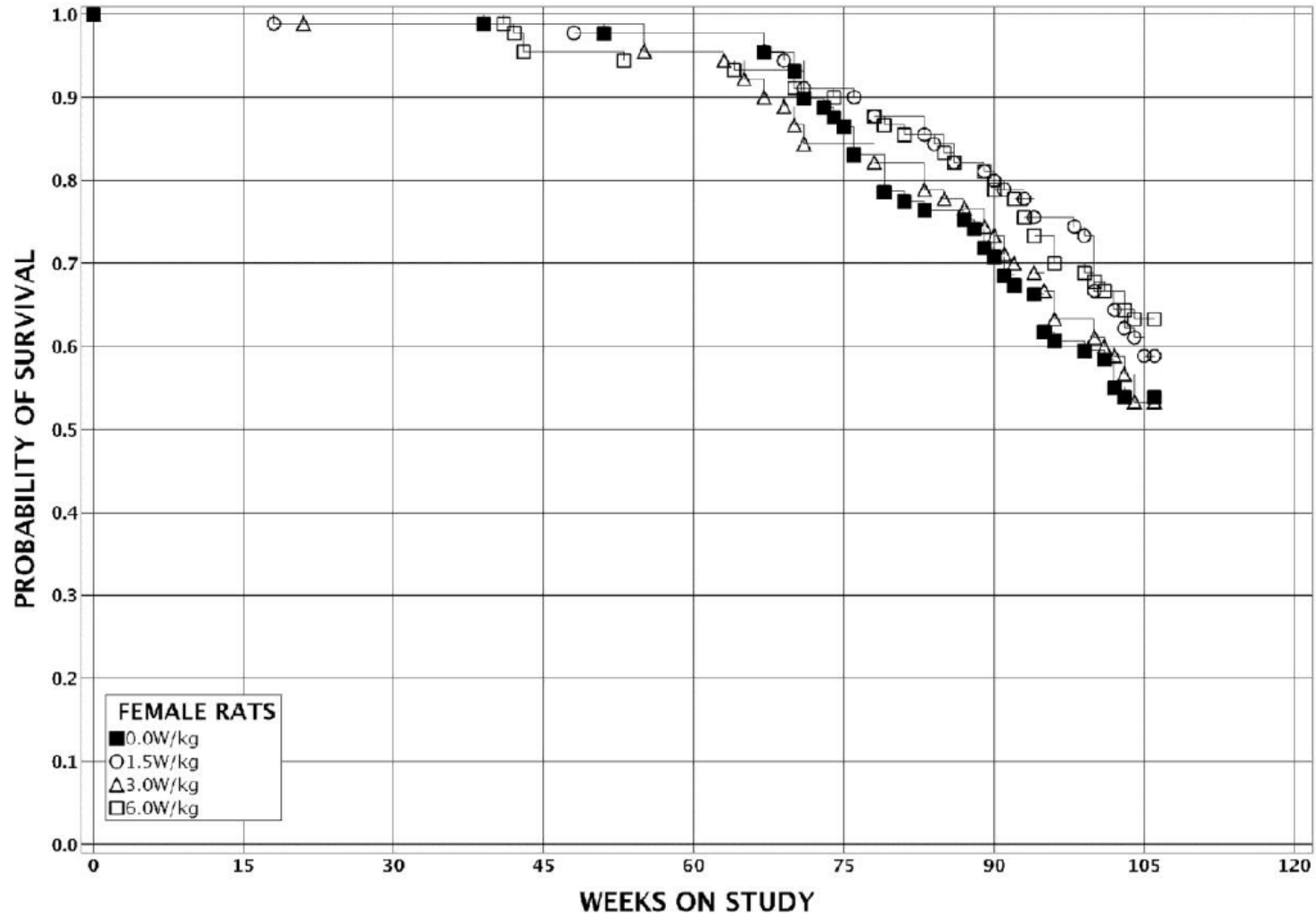
Survival in male rats exposed to GSM RFR



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



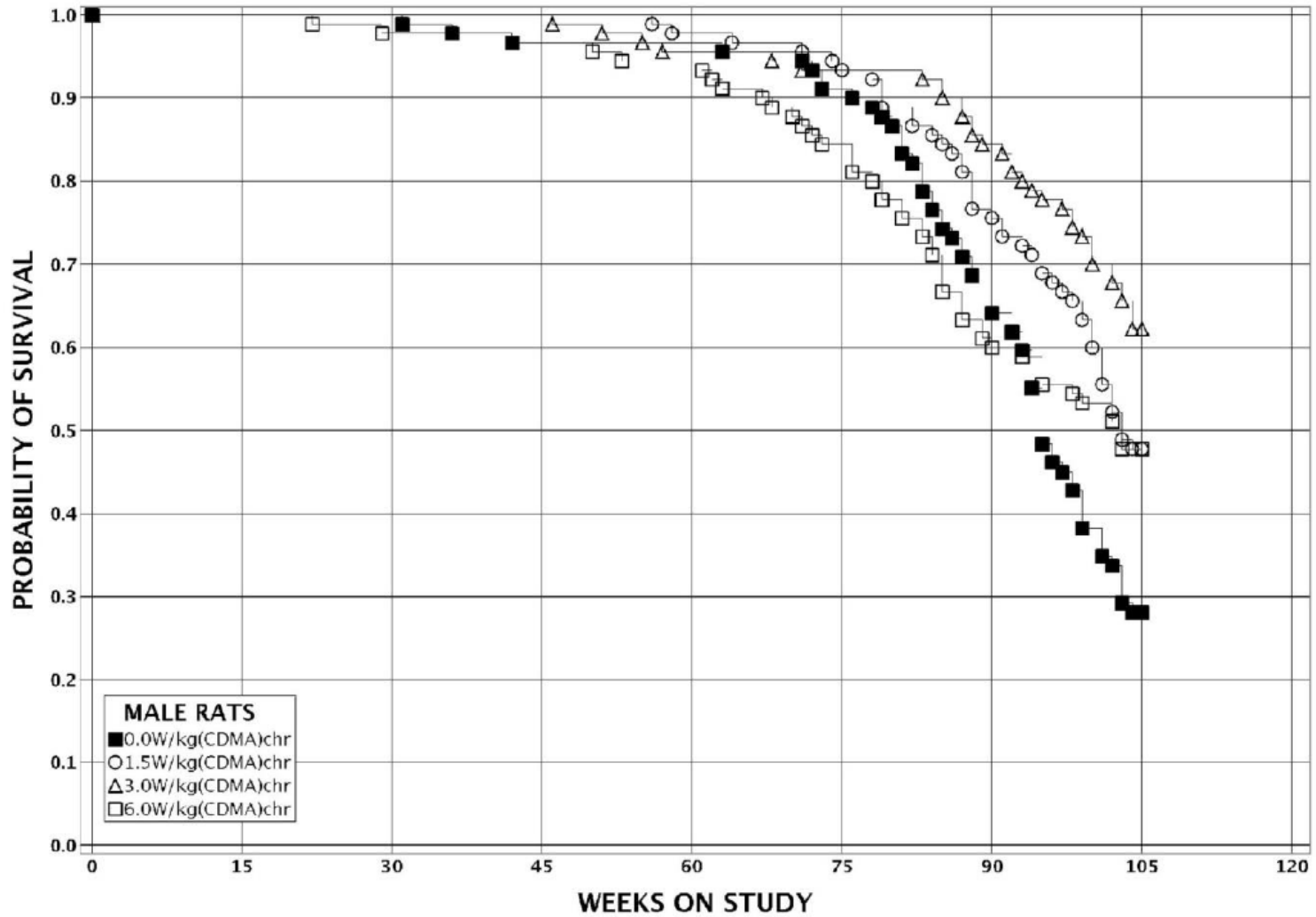
Survival in female rats exposed to GSM RFR



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



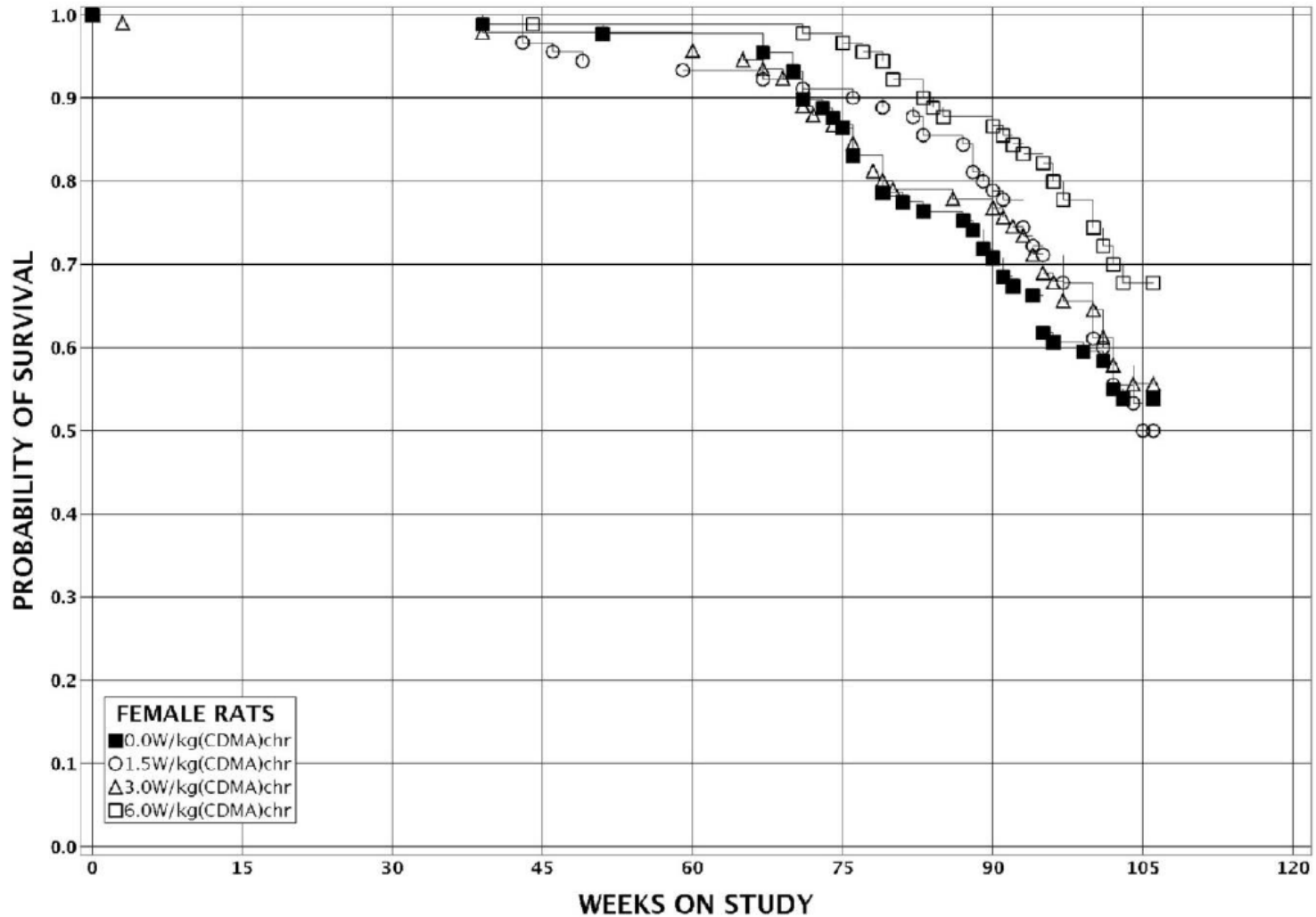
Survival in male rats exposed to CDMA RFR



- 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



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 ($p < 0.05$)



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



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 ($p < 0.05$)



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



- 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



Why not wait and release all study data?

- Given widespread global usage, even a small increase in incidence of disease resulting from RFR exposure could have broad implications for public health
- High level of public and media interest
- Tumor types observed in this study are similar type to those observed in some epidemiology studies of cell phone users
- Supports IARC conclusions of potential carcinogenic potential of RFR

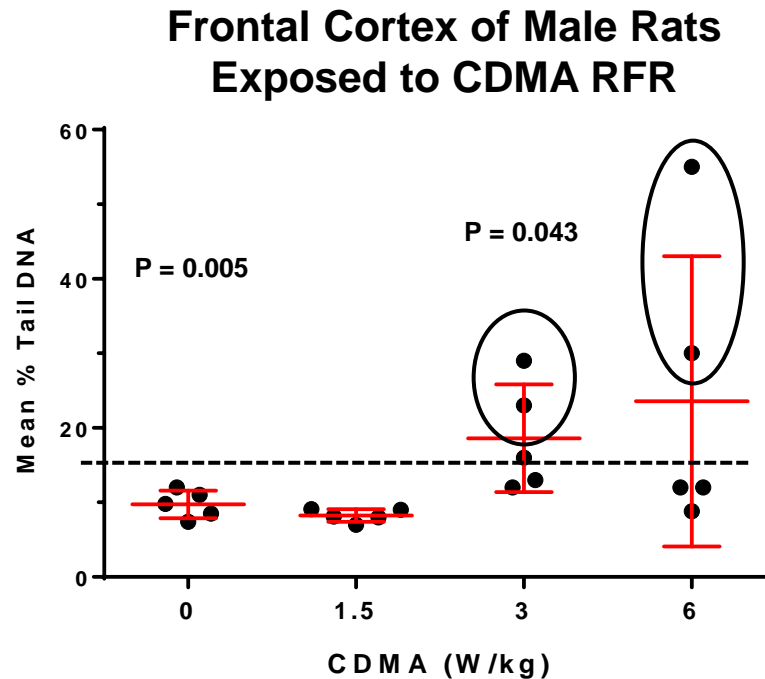


- The hyperplastic lesions and glial cell neoplasms of the heart and brain observed in male rats are considered likely the result of whole-body exposures to GSM- or CDMA-modulated RFR.
 - There is higher confidence in the association between RFR exposure and the neoplastic lesions in the heart than in 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
 - 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



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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