NTP
National Toxicology Program

Peer Review of NTP Technical Reports on Radio Frequency Radiation in Rats and Mice

Chad Blystone, PhD, DABT

Toxicology Branch

National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 20, 2018

NTP Technical Reports

- NTP conducts rodent toxicity and cancer studies on agents of public health concern to identify potential hazards for human health

- NTP technical reports describe the methods, results, and NTP conclusions as “levels of evidence” for carcinogenic activity under the specific conditions of the study

- NTP technical reports undergo external peer review to evaluate the studies and conclusions

Levels of Evidence of Carcinogenic Activity

Clear evidence: Dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy

Some evidence: Test agent related increased incidence of neoplasms in which the strength of the response is less than that required for clear evidence

Equivocal evidence: Marginal increase of neoplasms that may be test agent related

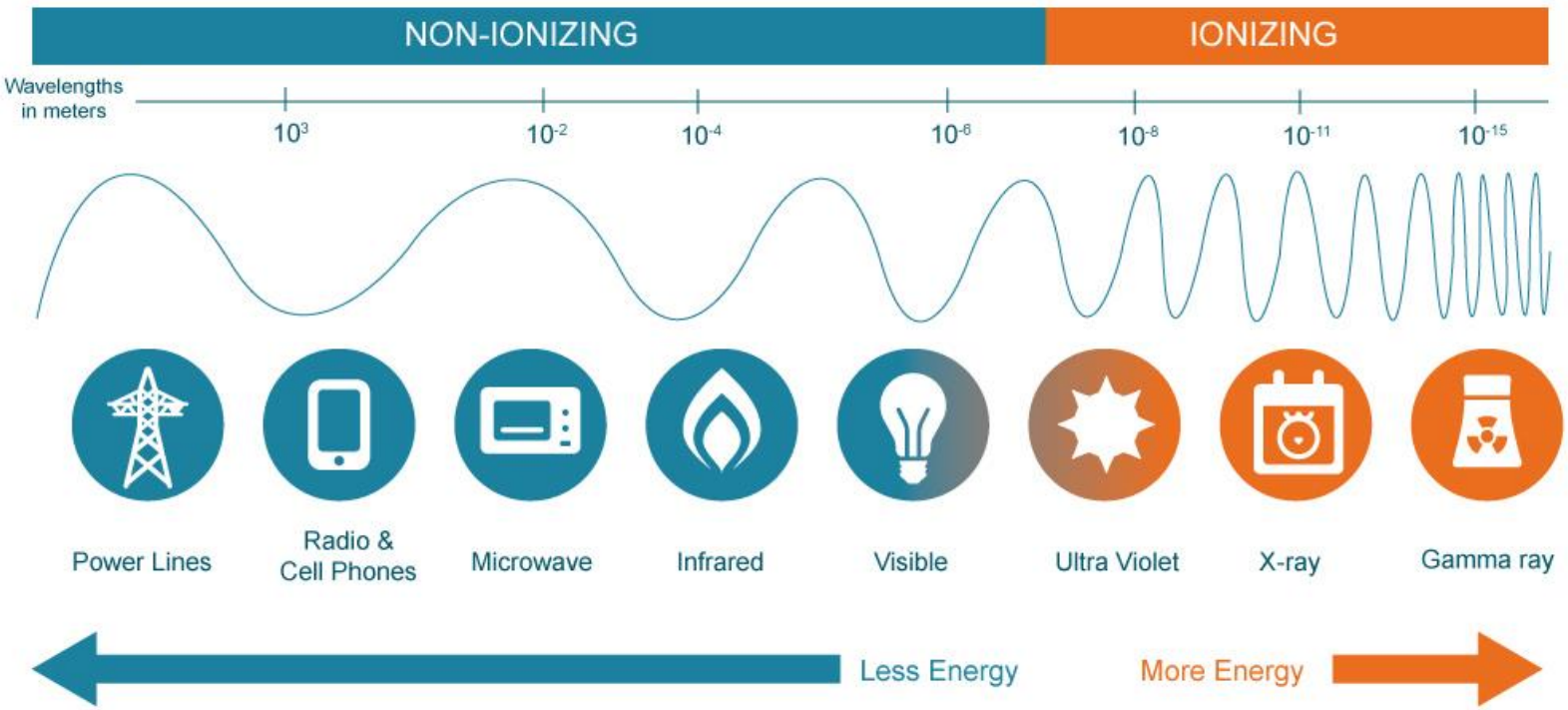
No evidence: No test agent related increase in neoplasms

Inadequate study: Major limitations preclude interpretation

Technical Reports

- TR-595: Toxicology and Carcinogenesis Studies in Hsd:Sprague Dawley SD Rats Exposed to Whole-Body Radio Frequency Radiation at a Frequency (900 MHz) and Modulations (GSM and CDMA) Used by Cell Phones
- TR-596: Toxicology and Carcinogenesis Studies in B6C3F1/N Mice Exposed to Whole-Body Radio Frequency Radiation at a Frequency (1,900 MHz) and Modulations (GSM and CDMA) Used by Cell Phones
- Leads:
  - Mike Wyde, PhD, DABT (Study Scientist)
  - Mark Cesta, DVM, PhD, DACVP (TR-595 Study Pathologist)
  - Amy Brix, DVM, PhD (TR-596 Study Pathologist)

Radio Frequency Radiation

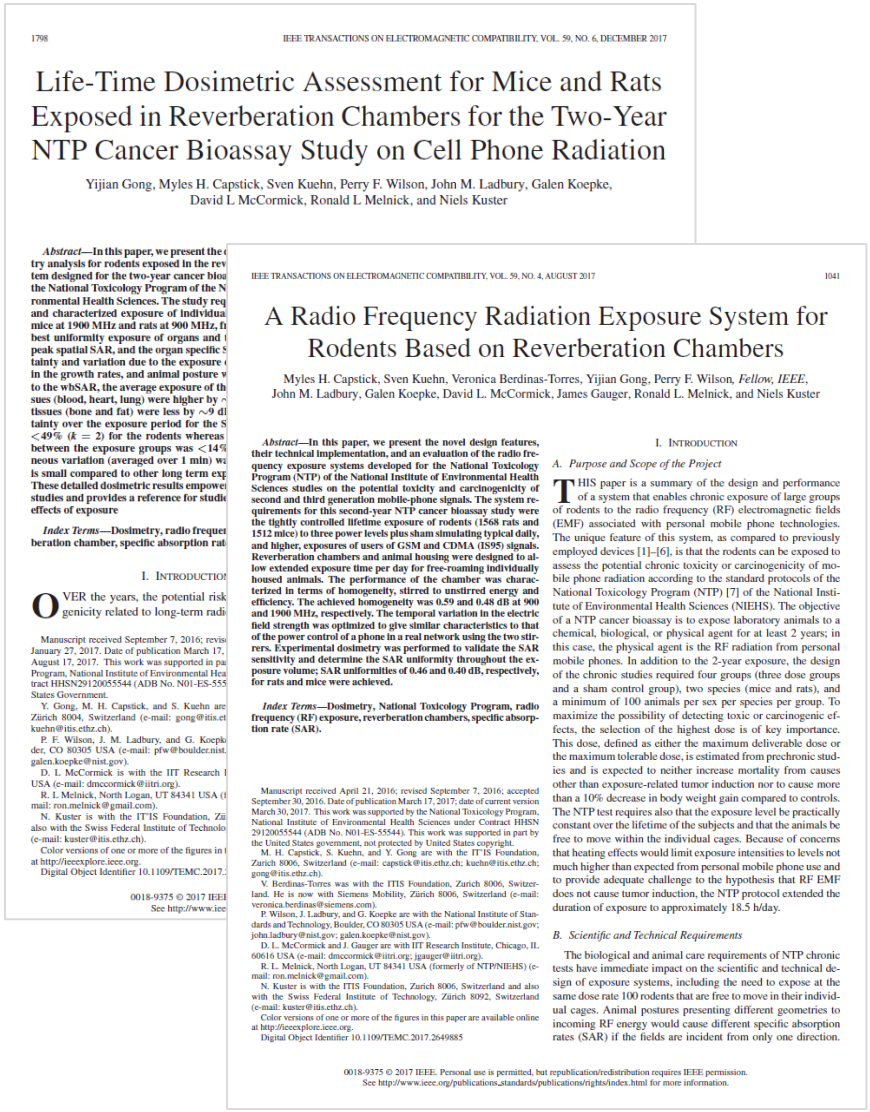


https://www.mirion.com/introduction-to-radiation-safety/what-is-radiation/

Exposure measured in Specific Absorption Rate (SAR): W/kg

NTP Program on Radio Frequency Radiation

- Nominated to NTP by the FDA due to concerns of wide spread exposure and possible carcinogenic activity
- Over several years NTP worked with NIST and IT'IS to design and validate reverberation exposure chambers.
- Exposure system method, validation, and dosimetric assessment were published in *IEEE Transactions on Electromagnetic Compatibility* in 2017



1798 IEEE TRANSACTIONS ON ELECTROMAGNETIC COMPATIBILITY, VOL. 59, NO. 6, DECEMBER 2017

Life-Time Dosimetric Assessment for Mice and Rats Exposed in Reverberation Chambers for the Two-Year NTP Cancer Bioassay Study on Cell Phone Radiation

Yijian Gong, Myles H. Capstick, Sven Kuehn, Perry F. Wilson, John M. Ladbury, Galen Koepke, David L. McCormick, Ronald L. Melnick, and Niels Kuster

IEEE TRANSACTIONS ON ELECTROMAGNETIC COMPATIBILITY, VOL. 59, NO. 4, AUGUST 2017 1041

A Radio Frequency Radiation Exposure System for Rodents Based on Reverberation Chambers

Myles H. Capstick, Sven Kuehn, Veronica Berdinas-Torres, Yijian Gong, Perry F. Wilson, *Fellow, IEEE*, John M. Ladbury, Galen Koepke, David L. McCormick, James Gauger, Ronald L. Melnick, and Niels Kuster

Design Considerations

- Two frequencies were evaluated: Rats at 900 MHz; Mice at 1900 MHz
- Modulations of CDMA (IS-95) and GSM were evaluated
- Exposure was in intervals of ten minutes on and ten minutes off for a total exposure of 9 hours and 10 minutes per day
- In utero and lactational exposure was included for rats; required development of litter based statistics

NTP Program on Radio Frequency Radiation

- Animal exposure studies were conducted in three phases at IIT Research Institute:
  - Pilot study to determine heating tolerance in rats and mice (SAR 4-12 W/kg), published in *Bioelectromagnetics* in 2018
  - Twenty-eight day toxicity studies for exposure selection in chronic exposure study
  - Two-year bioassay to determine carcinogenicity and chronic toxicity in rats and mice
- Group size was increased from 50 to 90 animals to increase power in two-year study
- Due to logistics, a common control group was used between the GSM and CDMA modulations for each species

Peer Review Meeting Format

- Review meeting occurred over three days
- There were opportunities for public comment during the review
- Due to the technical nature of the exposure system, two panels were convened to review the system (Panel 1) and then the findings and conclusions (Panel 2)

Peer Review – Panels

- Panel 1: Reverberation Chamber Exposure System
  - Assess the reverberation chamber technology for evaluating the effects of cell phone radiofrequency radiation exposure in rats and mice
- Panel 2: NTP Findings in Rats and Mice
  - Review and evaluate the scientific and technical elements of the study and its presentation
  - Determine whether the study's experimental design, conduct, and findings support the NTP's conclusions regarding the carcinogenic activity and toxicity of the test agent

Technical Report Peer Review Panel 1

- David Eaton, PhD, DABT, ATS University of Washington (Panel Chair)
- Frank Barnes, PhD, University of Colorado
- James Lin, PhD, University of Illinois
- Asminia Kiourti, PhD, Ohio State University

Technical Report Peer Review Panel 2

- David Eaton, PhD, DABT, ATS University of Washington (Panel Chair)
- Rick Adler, DVM, PhD, DACVP, GlaxoSmithKline
- Lydia Andrews-Jones, DVM, PhD, DACVP, Allergan, Inc.
- J. Mark Cline, DVM, PhD, DACVP, Wake Forest School of Medicine
- George Corcoran, PhD, ATS, Wayne State University
- Susan Felter, PhD, Proctor & Gamble
- Jack Harkema, DVM, PhD, DACVP, Michigan State University
- Wolfgang Kaufmann, DVM, PhD, DECVP, Felow IATP, Merck (Retired)
- Tyler Malys, PhD, Data Management Services
- Kamala Pant, MS, BioReliance
- Matthias Rinke, DVM, PhD, FTA Pathology, CVP, Fellow IATP, Bayer Pharma AG (retired)
- Laurence Whiteley, DVM, PhD, DACVP, Pfizer

- BSC Liason: Donald G. Stump, PhD, DABT, WIL Research

Discussion Topics

- Design Considerations
- Monotonic vs Non-Monotonic Responses
- Reasons for Differential Survival and Interpretation Impact
- Historical Control Use & Presentation
- Environmental Stress to the Animals
- Assessment of Heating Tolerance
- Relationship to Human Exposure

RFR Mouse Findings (TR-596)

Sex	Mod	0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Male	GSM	73%	72%	89%*	80%
	CDMA		91%*	80%	79%
Female	GSM	74%	80%	77%	80%
	CDMA		84%	77%	79%

* $p < 0.05$

Body weights of exposed animals were within 10% of control values

RFR Mouse Findings (TR-596)

Sex	Mode	Site	Incidence[a]	Historical Control Range	NTP Call	Panel Vote
Male	GSM	Skin: Fibrosarcoma, Sarcoma, or Malignant Fibrous Histiocytoma	1, 0, 6, 4%	0-2%	**Equivocal**	8 Yes/ 3 No
		Lung: Alveolar/Bronchiolar Adenoma or Carcinoma	26*, 27, 36, 38%	16-34%	**Equivocal**	11 Yes
Female	GSM	Malignant Lymphoma	2, 14*, 10*, 7%	10-36%	**Equivocal**	9 Yes/ 2 No
Male	CDMA	Liver: Hepatoblastoma	7, 7, 18*, 8%	0-6%	**Equivocal**	10 Yes/ 1 No
Female	CDMA	Malignant Lymphoma	2, 10*, 7, 8%	10-36%	**Equivocal**	11 Yes

[a] Incidence of control, low, medium, and high exposure groups
* $p < 0.05$

Panel agreed with NTP's conclusions in the mouse report

RFR Rat Findings (TR-595)

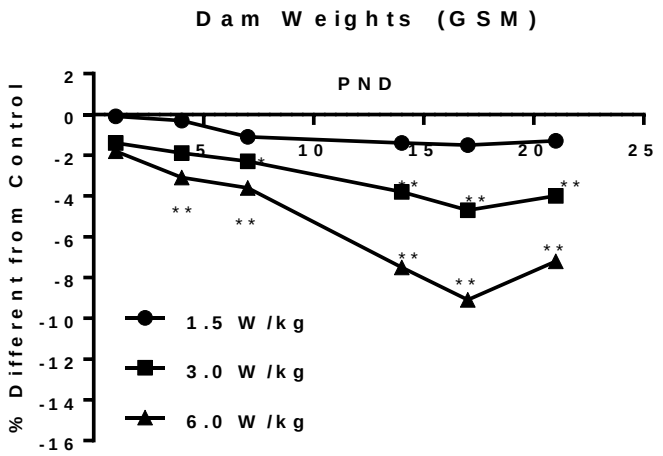
Sex	Mod	0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Male	GSM	28%	50%*	56%*	68%*
	CDMA		48%*	62%*	48%
Female	GSM	54%	59%	53%	63%
	CDMA		50%	56%	68%

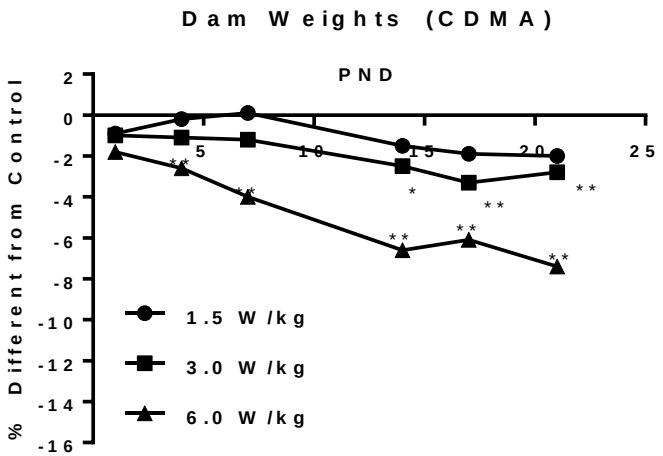
p = < 0.05

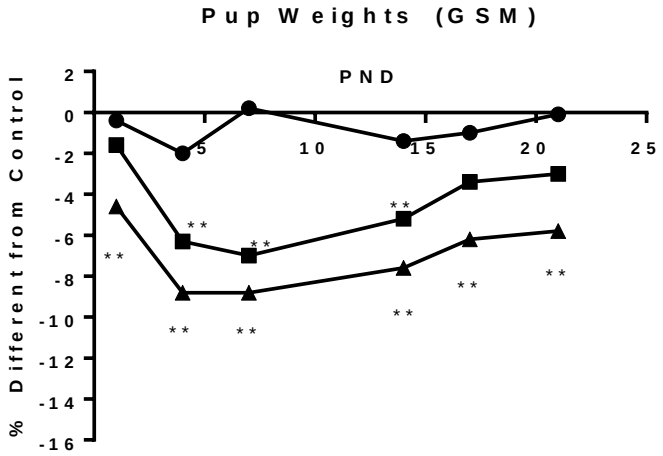
Low survival in male rat control attributed to high severity of chronic nephropathy

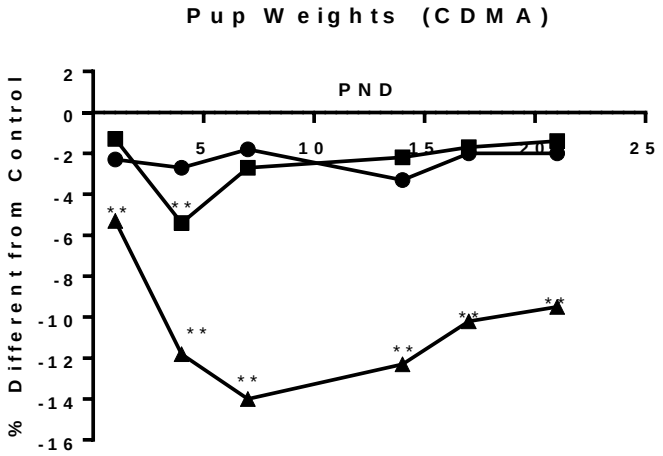
RFR Rat Perinatal Findings

Chronic – Lower Weights During Lactation









* $p < 0.05$
** $p < 0.01$

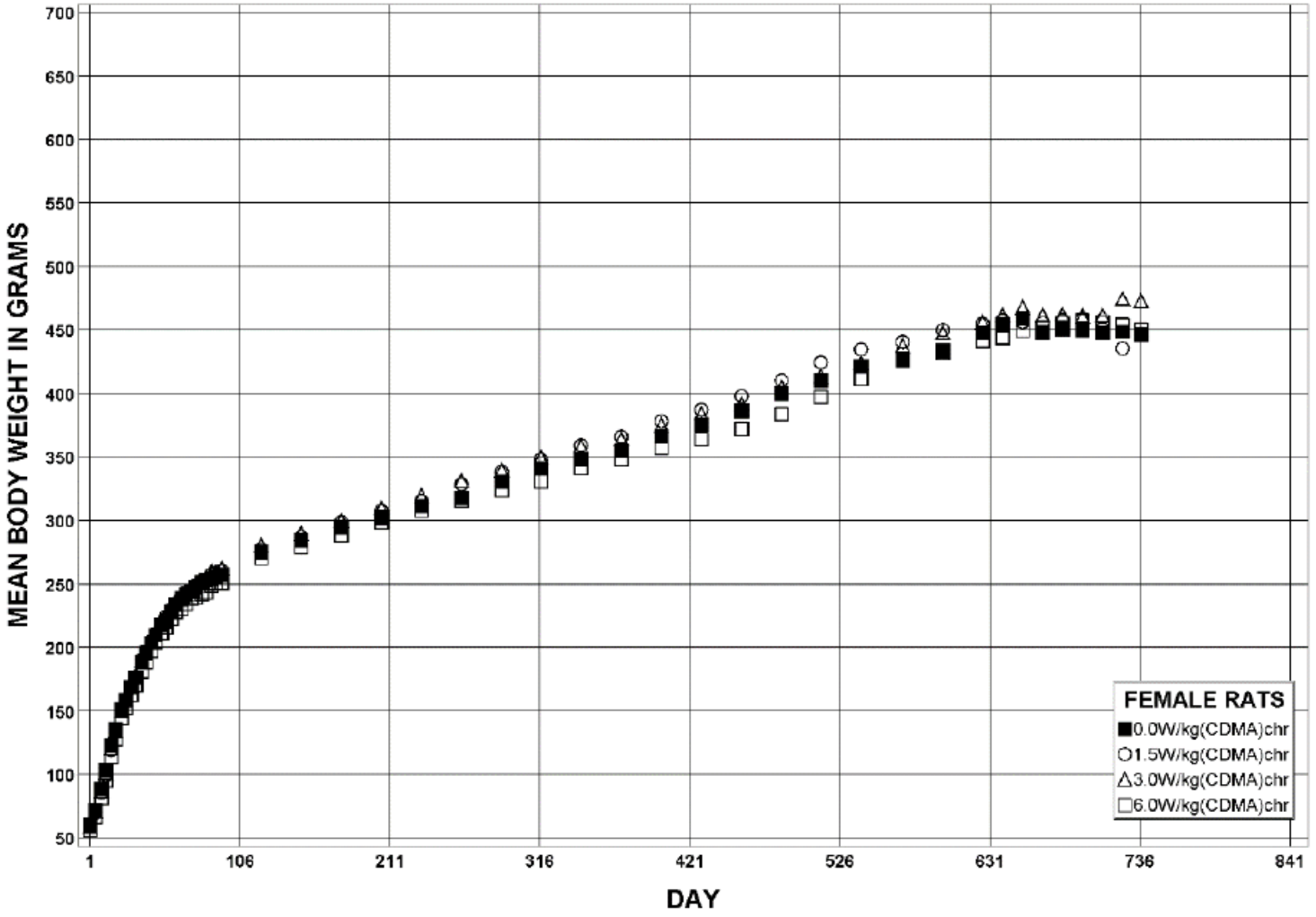
Pup Survival (%) during lactation (Two-Year Study)

Mode	Timepoint	0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
GSM	PND 1-4	98.6	99.4	98.1	98.5
	PND 4-21	100.0	99.7	99.1	99.7
CDMA	PND 1-4		99.1	98.9	97.5
	PND 4-21		99.7	99.7	94.0**

** $p < 0.01$

RFR Rat Growth Curves

CDMA



Heart Nonneoplastic Findings in Rats

Two-Year Study

Sex	Mode	Lesion	0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Male	GSM	Cardiomyopathy, Right Ventricle	60% (1.1)	69% (1.5)	80%* (1.9)	82%* (1.8)
		Cardiomyopathy, All Sites	88% (1.9)	93% (1.8)	87% (2.1)	88% (1.6)
Female	GSM	Cardiomyopathy, Right Ventricle	4% (1.0)	10% (1.1)	16%* (1.1)	17%* (1.2)
		Cardiomyopathy, All Sites	44% (1.1)	33%* (1.2)	43% (1.1)	30%* (1.1)

p = < 0.05

Severity = 1 (minimal); 2 (mild); 3 (moderate); 4 (marked)

Heart Nonneoplastic Findings in Rats

Two-Year Study

Sex	Mode	Lesion	0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Male	CDMA	Cardiomyopathy, Right Ventricle	60% (1.1)	50% (1.2)	69% (1.3)	82%* (1.7)
		Cardiomyopathy, All Sites	88% (1.9)	93% (1.9)	92% (1.8)	94% (1.3)
Female	CDMA	Cardiomyopathy, Right Ventricle	4% (1.0)	8% (1.0)	10% (1.0)	10% (1.0)
		Cardiomyopathy, All Sites	44% (1.1)	48% (1.1)	37% (1.2)	50% (1.1)

p = < 0.05

Severity = 1 (minimal); 2 (mild); 3 (moderate); 4 (marked)

Heart Nonneoplastic Findings in Rats

Two-Year Study

Sex	Mode	Lesion	0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Male	GSM	Schwann Cell Hyperplasia	0%	1% (1.0)	0%	2% (2.0)
Female	GSM	Schwann Cell Hyperplasia	0%	0%	0%	0%
Male	CDMA	Schwann Cell Hyperplasia		0%	0%	3% (2.0)
Female	CDMA	Schwann Cell Hyperplasia		1% (3.0)	1% (1.0)	1% (1.0)

Severity = 1 (minimal); 2 (mild); 3 (moderate); 4 (marked)

Brain Nonneoplastic Findings in Rats

Two-Year Study

Sex	Mode	Lesion	0 W/kg	1.5 W/kg	3.0 W/kg	6.0 W/kg
Male	GSM	Glial Cell Hyperplasia	0%	2% (2.0)	3% (3.0)	1% (4.0)
Female	GSM	Glial Cell Hyperplasia	0%	0%	1% (4.0)	0%
Male	CDMA	Glial Cell Hyperplasia		2% (1.5)	0%	2% (2.5)
Female	CDMA	Glial Cell Hyperplasia		0%	1% (2.0)	1% (2.0)

Severity = 1 (minimal); 2 (mild); 3 (moderate); 4 (marked)

RFR Rat GSM Findings (TR-595)

Sex	Site	Incidence[a]	Historical Controls	NTP Call	Panel Call
Male	Heart: Malignant Schwannoma	0*, 2, 1, 6%	0, 2, 2%	Some	**Clear (8 Yes/3 No)**
	Brain: Malignant Glioma	0, 3, 3, 2%	0, 4%	Equivocal	**Some (7 Yes/4 No)**
	Brain: Granular Cell Tumor	1, 3, 4, 3%	0, 4%	Equivocal	11 Yes
	Adrenal: Pheochromocytomas	13, 27*, 31*, 16%	16, 24, 28%	Equivocal	**Some (6 Yes/4 No/1 Abs)**
	Prostate: Adenoma or Carcinoma	2, 2, 8, 3%	0, 0, 0%	Equivocal	11 Yes
	Pituitary: Adenoma	19, 31, 29, 29%	10, 22, 28%	Equivocal	10 Yes/1 No
	Pancreatic Islet: Adenoma or Carcinoma	14, 30*, 22, 19%	4, 6, 16%	Equivocal	11 Yes
Female	Heart: Malignant Schwannoma	0, 0, 2, 0%	0, 0, 0%	None	**Equivocal (9 Yes/2 No)**

[a] Incidence of control, low, medium, and high exposure groups

* $p < 0.05$

RFR Rat CDMA Findings (TR-595)

Sex	Site	Incidence[a]	Historical Controls	NTP Call	Panel Call
Male	Heart: Malignant Schwannoma	0*, 2, 3, 7*%	0, 2, 2%	Some	**Clear (8 Yes/3 No)**
	Brain: Malignant Glioma	0, 0, 0, 3%	0, 4%	Equivocal	**Some (6 Yes/4 No/1 Abs)**
	Pituitary: Adenoma	19, 28, 38*, 14%	10, 22, 28%	Equivocal	11 Yes
	Liver: Hepatocelluar Adenoma or Carcinoma	0, 2, 4, 1%	0, 0, 2%	Equivocal	11 Yes
Female	Heart: Malignant Schwannoma	0, 2, 0, 2%	0, 0, 0%	None	**Equivocal (9 Yes/2 No)**
	Brain: Malignant Glioma	0, 3, 0, 0%	0, 2%	Equivocal	8 Yes/3 No
	Adrenal: Pheochromocytomas	1, 10*, 6, 5%	0, 0, 10%	Equivocal	10 Yes/1 Abs

[a] Incidence of control, low, medium, and high exposure groups

* $p < 0.05$

Next Steps

- Reviewing the recommendations from the panel
- Final edits will be made to the draft Technical Reports
- Publication later this year

Questions