NTP
National Toxicology Program

Update on the NTP Toxicology and Carcinogenicity Studies of Cell Phone Radiofrequency Radiation

Michael Wyde, Ph.D., D.A.B.T.

National Institute of Environmental Health Sciences

GLORE 2013
November 15, 2013

Objective

To identify potential toxic and carcinogenic effects associated with chronic exposure to modulated cell phone radiofrequency radiation (RFR) and to characterize dose-response relationships in animals

Critical Study Design Criteria

- Exposures to begin *in utero* (rats only)
- Unrestrained, individually-housed animals
- Maximum power levels at which animals capable of thermoregulation (non-thermal range)
- Frequencies and modulations that reflect those in use in the U.S.

Study Design

- Exposure to RFR in reverberation chambers for 18hr 20min per day (10 min on/10 min off)
  - Rats – 900 MHz, GSM & CDMA modulated signals (gestation/lactation)
  - Mice – 1900 MHz, GSM & CDMA modulated signals
- Three-phase studies: thermal pilot, subchronic, and chronic studies
- Power levels (SARs)
  - Thermal pilot studies
    - SARs of 4-12 W/kg in young, aged, pregnant (rats only)
  - Subchronic
    - Rats: 3, 6, 9 W/kg Mice: 5, 10, 15 W/kg
  - Chronic
    - Rats: 1.5, 3, 6 W/kg Mice: 2.5, 5, 10 W/kg

Reverberation Chambers

Chamber Interior

Chamber with cage racks

5-Day Thermal Pilot Studies

- Goal - determine the effect of RFR on body temperature, body weight, and survival
- Conducted in young and old rats and mice, and pregnant rats
  - Effects of size and pregnancy status
- Exposures of 0, 4, 6, 8, 10, 12 W/kg for 5 days (10 studies)
- Body temperatures collected via scanner from implanted microchips
  - Increase of >1°C considered excess thermal effect
  - Collected baseline before study initiation
  - Collected 3 times a day on Days 1, 3, and 5 during the 10-minute off period
  - Collected after daily shutdown for husbandry prior to initiation on Days 2 and 4

Thermal Pilot Study Results

Mouse Studies

- No thermal effects observed at SARs up to 12 W/kg regardless of age, sex, or modulation

Rat Studies

- Lethal effects and excessive increases in body temperatures were observed in rats at 10 and 12 W/kg
- Effects were observed in pregnant rats
  - Increase in early resorptions at 10 and 12 W/kg GSM
  - Decreased body weight gain (8%) at 12 W/kg GSM
- Based on these data, SARs of ≥ 10 W/kg are not recommended for further study in rats

Subchronic studies

- Perinatal study in Sprague-Dawley rats (900 MHz)
  - SAR exposures of 0, 3, 6, 9 W/kg
  - 10 pregnant rats per power level, per modulation beginning on gestation day (GD) 6
  - 18 hrs 20 min intermittent (10 min on/off) exposure/day 5 days/week
    - 7 days/week during gestation, lactation, and last week of study
  - At weaning (PND-21), litter size reduced to 2 male and 2 female pups and exposure continued for 28 more days (PND 49)
  - Animals individually housed on PND 35
- 28-day study in B6C3F1 mice (1900MHz)
  - SARs exposures of 0, 5, 10, and 15 W/kg
  - 10 male and female mice per power level, per modulation
  - 5-week old at study initiation

Subchronic Study Status

- In-life portion complete
- Currently in the data evaluation and review phase
- Complete histopathology undergoing standard NTP Pathology Data Review and Quality Assurance (QA) process
- Data from subchronic studies include:
  - Pregnancy/littering data
  - Body weight (dam gestation, litter weights, dam lactation, individual pup)
  - Body temperature (gestation, lactation, individual pups)
  - Organ weights (pups)
  - Special gene expression analysis for brain and liver

Rat Study Results

Perinatal Results (PND1) – GSM

(n=20 dams)	0 W/kg	3 W/kg	6 W/kg	9 W/kg
Dams Littering	20	19	18	20
Mean Litter size	11.9 ± 1.8	11.6 ± 2.3	12.7 ± 1.5	12.2 ± 2.3
Mean # ♂	6.1 ± 1.9	5.9 ± 1.7	6.7 ± 2.2	5.8 ± 2.5
Mean # ♀	5.8 ± 1.9	5.7 ± 1.6	6.0 ± 1.9	6.4 ± 2.3
Litter weight total (g)	77.2 ± 11.7	76.3 ± 14.6	80.0 ± 8.8	72.2 ± 13.1
Mean litter wt ♂ (g)	40.8 ± 12.8	39.8 ± 10.9	41.8 ± 14.7	34.8 ± 15.0
Mean litter wt ♀ (g)	36.4 ± 11.6	36.6 ± 9.8	37.6 ± 11.3	37.4 ± 13.0

Rat Study Results

Perinatal Results (PND1) – CDMA

(n=20 dams)	0 W/kg	3 W/kg	6 W/kg	9 W/kg
Dams Littering	20	17	17	16
Mean Litter size	11.9 ± 1.8	11.6 ± 1.3	10.8 ± 4.4	11.6 ± 2.0
Mean # ♂	6.1 ± 1.9	5.7 ± 1.8	5.0 ± 2.8	6.4 ± 1.9
Mean # ♀	5.8 ± 1.9	5.9 ± 2.2	5.8 ± 3.0	5.2 ± 2.3
Litter weight total (g)	77.2 ± 11.7	77.1 ± 8.8	68.2 ± 26.4	69.4 ± 11.7
Mean litter wt ♂ (g)	40.8 ± 12.8	38.4 ± 11.7	32.2 ± 17.5	39.3 ± 10.7
Mean litter wt ♀ (g)	36.4 ± 11.6	38.2 ± 14.1	38.2 ± 15.6	34.4 ± 7.9

Rat Study Results

Dam Body Weights During Gestation

GSM

GD	0 W/kg	3 W/kg (900 MHz)		6 W/kg (900 MHz)		9 W/kg (900 MHz)	
	WT(G)	WT(G)	% OF CNTL	WT(G)	% OF CNTL	WT(G)	% OF CNTL
6	238.3	236.2	99.1	237.3	99.6	238.3	100.0
9	250.7	248.9	99.3	249.7	99.6	249.8	99.6
12	266.2	262.1	98.4	263.2	98.9	264.2	99.2
15	282.5	278.6	98.6	278.9	98.7	281.3	99.6
18	319.3	312.7	98.0	311.6	97.6	313.6	98.2
21	366.4	353.9	96.6	351.6	96.0	354.8	96.8

CDMA

GD	0 W/kg	3 W/kg (900 MHz)		6 W/kg (900 MHz)		9 W/kg (900 MHz)	
	WT(G)	WT(G)	% OF CNTL	WT(G)	% OF CNTL	WT(G)	% OF CNTL
6	238.3	237.5	99.7	237.0	99.5	236.1	99.1
9	250.7	250.2	99.8	251.5	100.3	248.0	98.9
12	266.2	263.3	98.9	263.8	99.1	260.5	97.9
15	282.5	277.0	98.0	277.8	98.3	272.5	96.5
18	319.3	306.6	96.0	307.0	96.2	300.2	94.0
21	366.4	343.3	93.7	342.1	93.4	333.1*	90.9
Pregnant Dams (on PND1)	20	17		17		16	

Decrease may reflect non-pregnants

Rat Study Results

Dam Body Weights During Lactation

GSM

PND	0 W/kg	3 W/kg (900 MHz)		6 W/kg (900 MHz)		9 W/kg (900 MHz)	
	WT(G)	WT(G)	% OF CNTL	WT(G)	% OF CNTL	WT(G)	% OF CNTL
1	272.7	267.8	98.2	271.6	99.6	263.5	96.6
4	263.8	265.1	100.5	269.9	102.3	264.1	100.1
7	284.1	280.3	98.7	281.8	99.2	270.0*	95.1
14	292.4	289.9	99.2	286.4	98.0	266.1*	91.0
21	279.7	267.3*	95.5	265.8*	95.0	248.5*	88.8

CDMA

PND	0 W/kg	3 W/kg (900 MHz)		6 W/kg (900 MHz)		9 W/kg (900 MHz)	
	WT(G)	WT(G)	% OF CNTL	WT(G)	% OF CNTL	WT(G)	% OF CNTL
1	272.7	268.9	98.6	271.7	99.6	263.8	96.7
4	263.8	264.1	100.1	269.3	102.1	264.6	100.3
7	284.1	282.5	99.4	282.1	99.3	269.6*	94.9
14	292.4	293.3	100.3	284.9	97.4	264.1*	90.3
21	279.7	282.6	101.0	272.9	97.5	245.9*	87.9

* Statistically significant difference from time-matched control group (0 W/kg), $p \leq 0.05$

Rat Study Results

Pup Body Weights During Lactational Phase – GSM

PND	0 W/kg	3 W/kg (900 MHz)		6 W/kg (900 MHz)		9 W/kg (900 MHz)	
	WT(G)	WT(G)	% OF CNTL	WT(G)	% OF CNTL	WT(G)	% OF CNTL
Males							
4	9.8	9.7	98.4	9.1*	92.2	8.2*	83.5
7	16.3	15.6*	95.6	14.7*	90.1	13.1*	80.3
14	31.6	31.3	99.1	30.0*	94.8	26.7*	84.4
21	53.3	52.9	99.3	51.1*	95.9	45.5*	85.3

* Statistically significant difference from time-matched control group (0 W/kg), $p \leq 0.05$

- Body weights were lower in 6 and 9 W/kg male and female pups at PND4
- SAR-dependent decrease
- Indication of a potential “recovery” by PND 21

Rat Study Results

Pup Body Weights During Lactational Phase – CDMA

PND	0 W/kg	3 W/kg (900 MHz)		6 W/kg (900 MHz)		9 W/kg (900 MHz)	
	WT(G)	WT(G)	% OF CNTL	WT(G)	% OF CNTL	WT(G)	% OF CNTL
Males							
4	9.8	9.5	96.9	9.1*	92.2	8.1*	82.0
7	16.3	15.2*	93.2	14.3*	87.4	12.9*	79.2
14	31.6	30.9	97.7	29.7*	93.9	26.8*	84.9
21	53.3	52.6	98.8	51.4*	96.4	45.3*	84.9

* Statistically significant difference from time-matched control group (0 W/kg), $p \leq 0.05$

- Body weights were lower in 6 and 9 W/kg male and female pups at PND4
- SAR-dependent decrease
- Indication of a potential “recovery” by PND 21

Rat Study Results

Body Weights in Males During the Prechronic Phase

GSM Modulation

PND	0 W/kg	3 W/kg (900 MHz)		6 W/kg (900 MHz)		9 W/kg (900 MHz)	
	WT(G)	WT(G)	% OF CNTL	WT(G)	% OF CNTL	WT(G)	% OF CNTL
21	61.0	60.1	98.5	57.2*	93.8	50.6*	82.9
28	95.0	91.6	96.4	86.7*	91.2	78.3*	82.4
35	144.3	138.2	95.8	130.8*	90.6	119.8*	83.0
42	193.4	185.3*	95.8	176.4*	91.2	162.1*	83.9

CDMA Modulation

PND	0 W/kg	3 W/kg (900 MHz)		6 W/kg (900 MHz)		9 W/kg (900 MHz)	
	WT(G)	WT(G)	% OF CNTL	WT(G)	% OF CNTL	WT(G)	% OF CNTL
21	61.0	58.8	96.4	56.9*	93.2	50.5*	82.8
28	95.0	89.7*	94.4	88.0*	92.6	77.8*	81.9
35	144.3	136.0*	94.3	132.9*	92.1	118.8*	82.4
42	193.4	183.5*	94.9	182.0*	94.1	163.8*	84.7

Rat Study Results

Summary of RF Effects on Body Weight

- Gestation
  - Decrease body weight in dams at 9 W/kg **CDMA** only
- Lactation
  - Decreased body weight in **dams** at 9 W/kg **GSM** and **CDMA**
  - SAR-dependent decrease in body weight of male and female **pups** at 6 and 9 W/kg throughout lactation for both GSM and CDMA
- Perchronic Study Phase
  - Continued lower body weights in both sexes at 6 and 9 W/kg GSM and CDMA

Rat Study Results

Body Temperature in Dams – GSM

Power Level (W/kg)	Body Temperature (°C)							
	Gestational Day (GD)[a]				Postnatal Day (PND)[b]			
	GD 6	GD 7	GD 11	GD 16	PND 1	PND 4	PND 7	PND 14
0	36.7	36.6	36.7	36.5	37.7	36.7	36.8	36.9
3	37.3	36.7+	36.5+	36.6+	37.8	37.1	37.1	37.1
6	36.5	37.1*,+	37.1+	36.8	38.1	37.5*	37.2	37.8*
9	36.8	37.2*	37.2*	37.0*	38.4*	37.9*	37.2	38.3*

>1°C

\+ Statistically significant difference from pre-exposure (GD 6) time point, $p \leq 0.05$
* Statistically significant difference from time-matched control group (0 W/kg), $p \leq 0.05$

- Increased body temperatures were observed at 6 and 9 W/kg GSM during gestation and lactation
- Excessive increases (>1˚C) observed in dams exposed to 9 W/kg during lactation

Rat Study Results

Body Temperature in Dams – CDMA

Power Level (W/kg)	Body Temperature (°C)							
	Gestational Day (GD)[a]				Postnatal Day (PND)[b]			
	GD 6	GD 7	GD 11	GD 16	PND 1	PND 4	PND 7	PND 14
0	36.7	36.6	36.7	36.5	37.7	36.7	36.8	36.9
3	36.8	36.3	36.4	36.4	37.3	37.0	37.0	37.0
6	36.6	36.6	36.2*	36.7	37.7	37.3	37.4	37.6
9	36.4	37.1+	36.8	37.2*,+	37.9	38.1*	37.5	38.3*

+ Statistically significant difference from pre-exposure (GD 6) time point, $p \leq 0.05$
* Statistically significant difference from time-matched control group (0 W/kg), $p \leq 0.05$

- Increased body temperatures were observed at 9 W/kg CDMA during late gestation and lactation
- Excessive increases (>1˚C) observed during lactation

Rat Study Results

No RF Effect on Body Temperature During Prechronic Phase

GSM Modulation

Power Level (W/kg)	Body Temperature (°C)[a]					
	Male			Female		
	Day 16	Day 20	Day 27	Day 16	Day 20	Day 27
0	37.3	37.6	37.2	37.9	38.0	37.9
3	37.1	37.0*	37.0	37.0*	37.5	38.0
6	37.3	37.3	37.2	37.1*	37.1*	37.4
9	37.3	37.4	37.4	37.4*	37.6	37.6

CDMA Modulation

Power Level (W/kg)	Body Temperature (°C)[a]					
	Male			Female		
	Day 16	Day 20	Day 27	Day 16	Day 20	Day 27
0	37.3	37.6	37.2	37.9	38.0	37.9
3	37.0	37.2	36.5*	37.2*	38.0	37.1
6	37.1	37.1	37.0	37.5	37.6	38.0
9	37.3	37.5	37.4	37.5	37.6	38.0

* Statistically significant difference from time-matched control group (0 W/kg), $p \leq 0.05$

Summary of Rat Prechronic Study Results

- Body Weights
  - Decreased body weight in **dams** at 9 W/kg **CDMA** during **gestation**
  - Decreased body weight in **dams** at 9 W/kg **GSM** and **CDMA** during **lactation**
  - SAR-dependent decrease in body weight of male and female **pups** at 6 and 9 W/kg **GSM** and **CDMA** throughout lactation and prechronic phase
    - Started small and stayed small; no increasing effect with continued exposure
- Body Temperature
  - Increases that exceeded 1˚C in 9 W/kg **GSM** and **CDMA** dams during lactation
  - Slightly increased temperature at 6 W/kg **GSM**

Chronic toxicology and carcinogenicity studies

- Male and female Harlan Sprague-Dawley rats and B6C3F$_1$ mice
  - Perinatal exposure in rats (GD-6) with litters reduced to 4 males and 4 females at weaning
  - Exposures in mice beginning at 5 weeks of age
- SARs selected based on prechronic studies
  - Maximum achievable SARs for mice will be limited by the power output of the system
- 18 hrs 20 min of intermittent (10 min on/off) exposure/day, 7 days/week
- Interim time point at 19 weeks (n = 15) and study termination at 110 weeks of age (n = 90)
  - Micronucleus, **comet assay**, and clinical pathology

Acknowledgements

NIEHS
National Institute of Environmental Health Sciences
Research Triangle Park, NC

NIST
Boulder, CO

IITRI
Chicago, Il

ITIS FOUNDATION
Zurich, Switzerland