National Toxicology Program's Studies on Cell Phone Radiation: Utility for Assessing Human Health Risks

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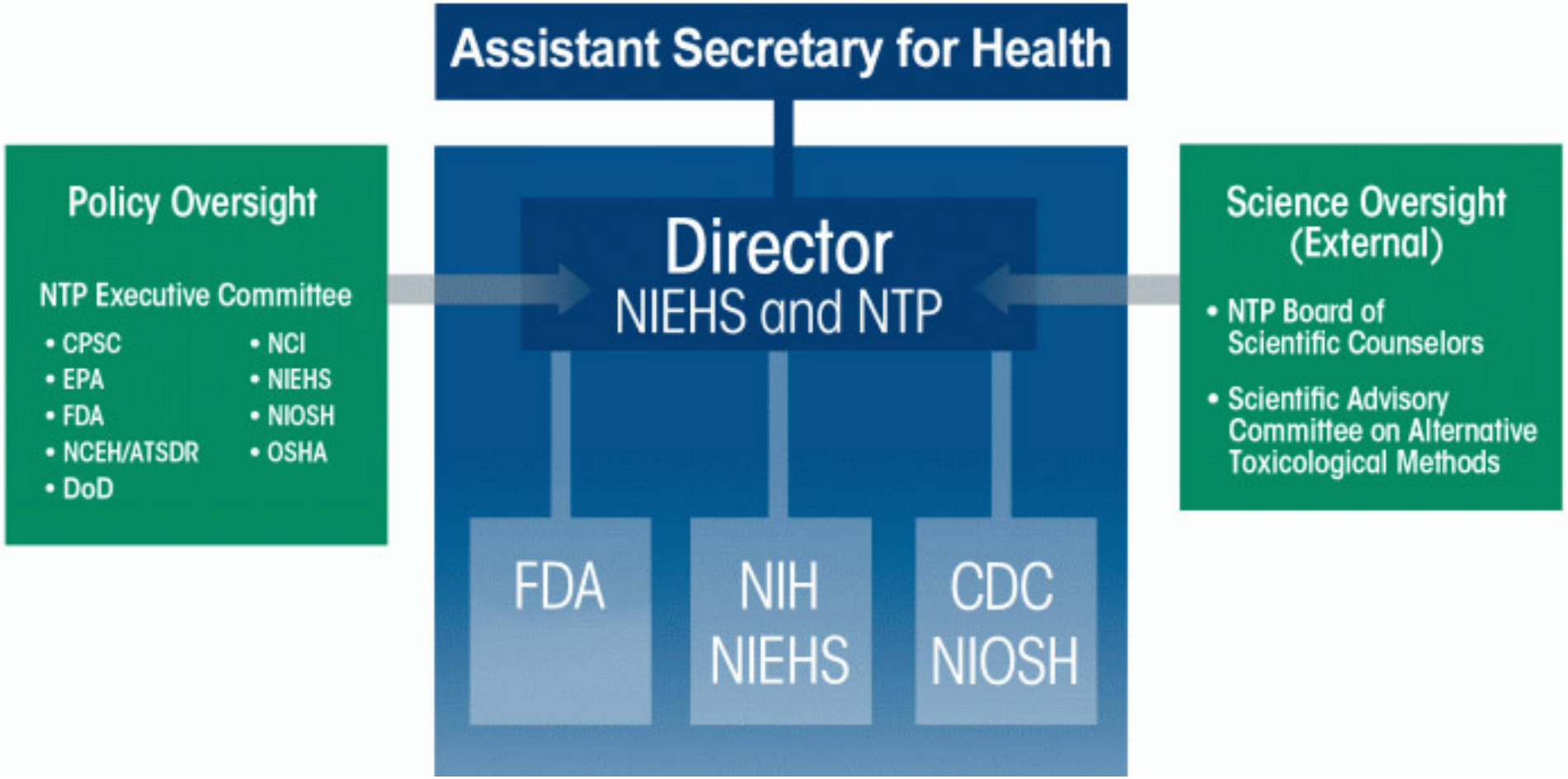
Outline

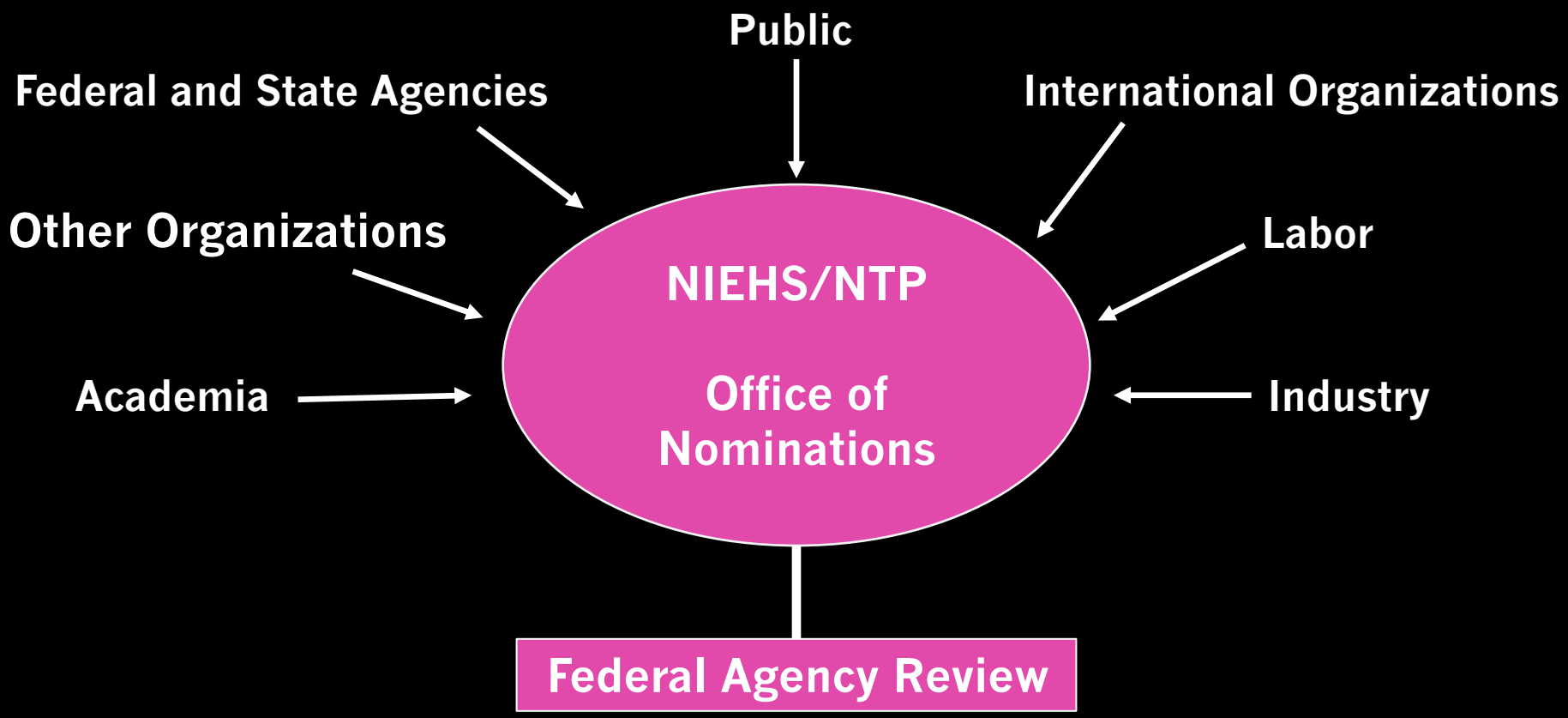
- The National Toxicology Program (NTP) and the nomination of cell phone radiofrequency radiation (RFR)
- RFR exposure system
- Design of the experimental studies
- Major findings from the NTP studies
- Application of NTP findings in future qualitative (IARC) and quantitative (US FDA) risk assessments for the development of health-based exposure standards

National Toxicology Program, HHS

(Headquartered at the NIEHS)



National Toxicology Program Nomination Process



FDA Nominated to NTP Cell Phone Radiofrequency Radiation Emitted from Wireless Communication Devices

- Request: toxicity and carcinogenicity studies in experimental animals “to provide the basis to assess the risk to human health”
- Reason – “existing exposure guidelines are based on protection from acute injury from thermal effects of RFR exposure, and may not be protective against any non-thermal effects of chronic exposures”

FCC Exposure Guidelines (1996) for Radiofrequency (RF) Radiation

- Designed to protect against adverse effects that might occur due to increases in tissue or body temperature of $1^{o}C$ (measured in monkeys, SAR of 4 W/kg averaged over the whole body)
  - SAR: rate of RF energy absorbed per unit mass
- Exposure limits for general population
  - 0.08 W/kg averaged over whole body (÷ 50)
  - 1.6 W/kg averaged over any 1 gram of tissue (US)
  - 2.0 W/kg averaged over 10 gram of tissue (Europe)

Why do Health Agencies Use Animal Studies to Assess Human Cancer Risk?

- Similar biological processes of disease induction
- Unethical to intentionally test for carcinogenicity in humans
- Every known human carcinogen is carcinogenic in animals when adequately tested
- Controlled exposures eliminate potential confounders
- Animal studies can eliminate the need to wait for sufficient human cancer data before implementing public health protective strategies

Objectives of NTP Studies

1) Test (challenge) the hypothesis/assumption that cell phone RF radiation at non-thermal exposure intensities is incapable of inducing adverse health effects

2) Provide data on tissue dose (SAR) and incidence of response that can be used to assess potential human health risks

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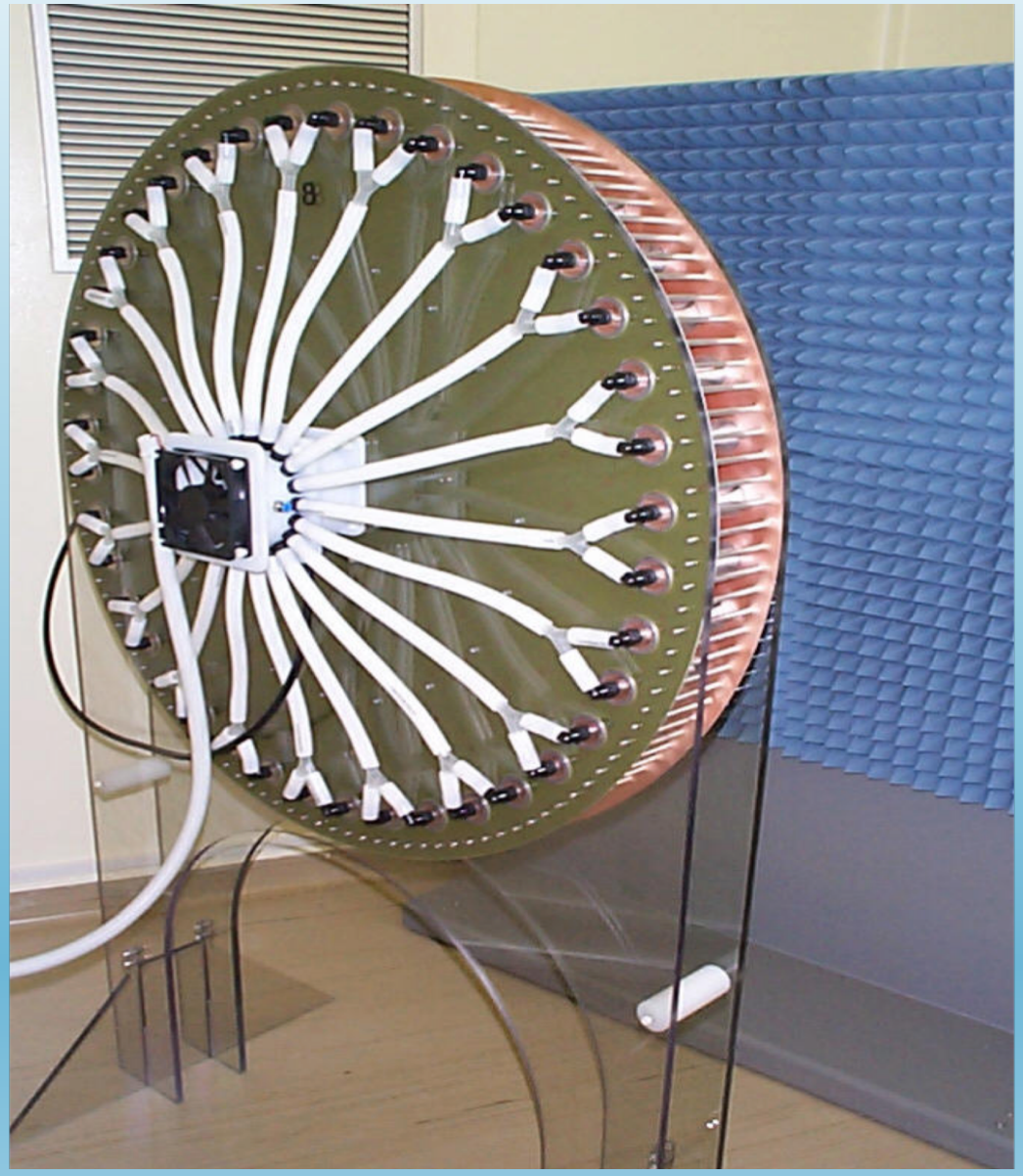
Ferris Wheel RF Exposure System



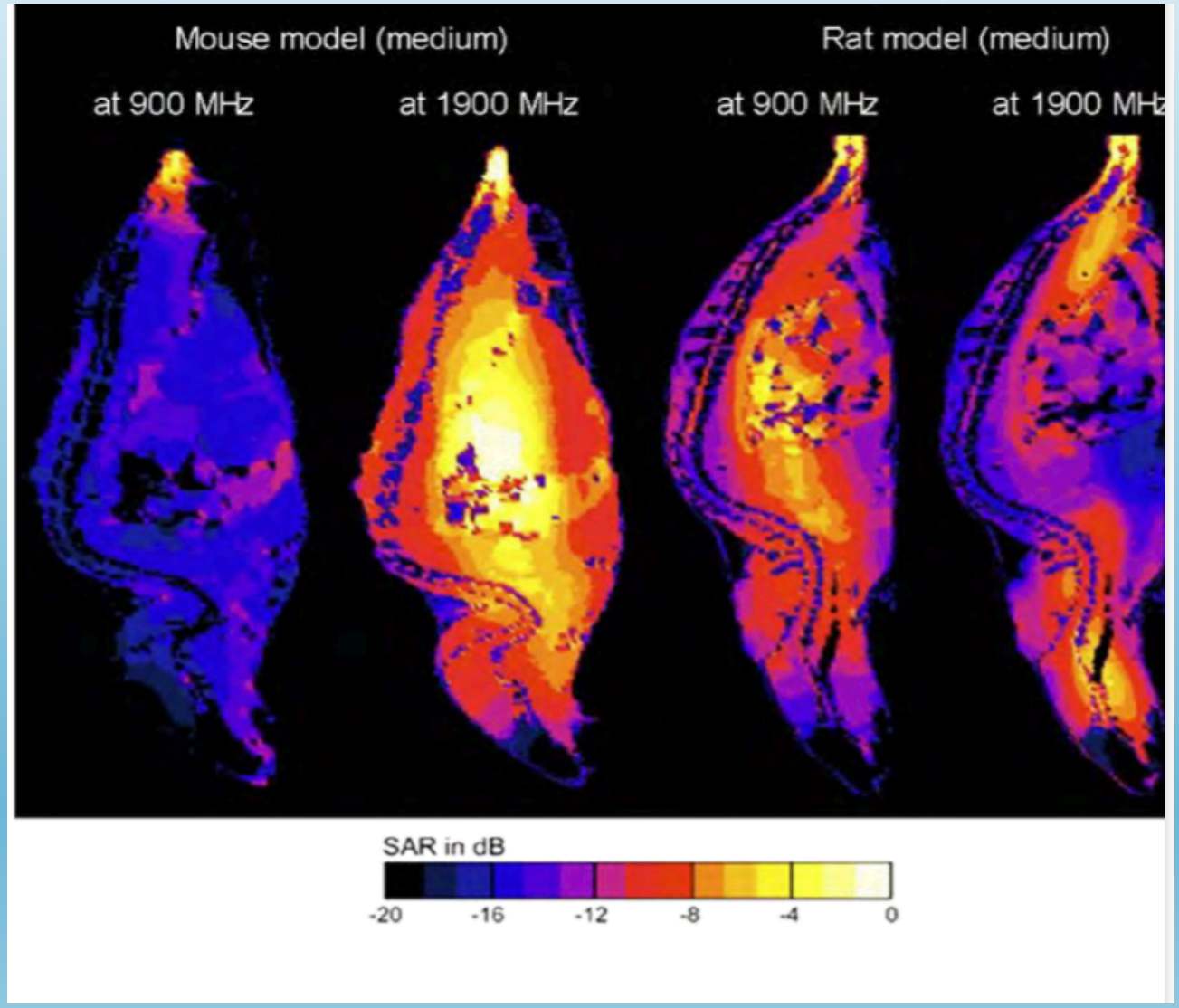
NTP Exposure System Requirements

- Animals (100/group) must be unrestrained, individually housed, with full access to feed and water
- Shielded system, homogeneous EMF environment, uniform in all directions
- Power levels not to exceed animals' ability to thermoregulate
- Cage racks, cages, lids minimal RF absorption; ventilation; temperature, humidity, and noise control
- Frequencies and modulations reflect those in use
  - 900 and 1900 MHz
  - CDMA and GSM modulation
- Chronic studies to include three power levels and sham chamber per sex per species

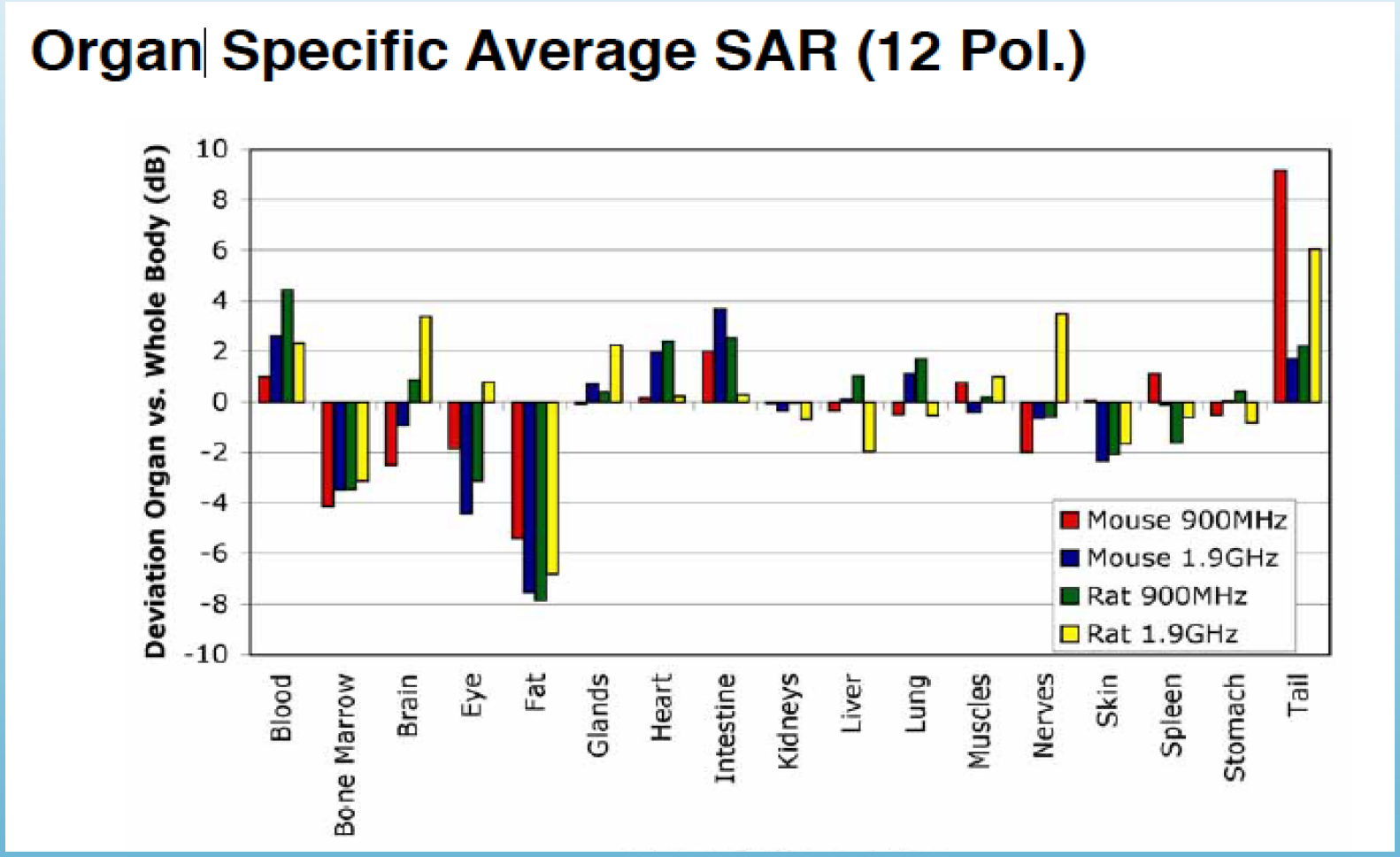
NTP Study in Reverberation Chambers

A room shielded from penetrating EMFs containing an excitation antennae and ventilation panels. Field exposures emanate from multiple angles (all directions), while rotating paddles distribute the fields to create a statistically homogeneous electromagnetic environment. No limit on daily exposure time, no comparable historical control.

Simulated RF Dosimetry in Rats and Mice Exposed to 900 or 1900 MHz



Organ SAR vs Whole Body SAR in Rats and Mice exposed in Reverberation Chambers



Based on high relative absorption in tail of rats at 1900 MHz and mice at 900 MHz, frequencies selected for NTP studies were 900 MHz for rats and 1900 MHz for mice

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Design of NTP Studies

- Demonstrate/validate average field uniformity (less than +/-1 dB Std Dev) at 900 MHz and 1900 MHz in reverberation chambers loaded with cage racks, cages, and bottles containing simulation fluid
- Continuous monitoring of field uniformity throughout all experimental studies
- Exposures: 10 minutes on and 10 minutes off, 18 hour/day
- Thermal pilot study: to determine the effects of different SAR levels of RFR (GSM and CDMA modulations) on body temperature (<1 ^{O}C) of Sprague-Dawley rats and B6C3F1 mice of different age and pregnancy status using sc implanted temperature microchips (5 days, 9 hr/day)

Design of NTP Toxicity Studies

- Prechronic study: to determine power levels for the chronic toxicity/carcinogenicity studies. Exposures from GD-6 (rats), and after weaning for 4 weeks. SAR: rats =3, 6, 9 W/kg, mice = 5, 10, 15 W/kg

- Chronic studies (N=90)
  - Exposures from GD-5 (rats), and after weaning for 2 years
  - GSM- and CDMA-modulations
  - SAR: Sprague-Dawley rats = 0, 1.5, 3, and 6 W/kg;
    B6C3F1 mice = 0, 2.5, 5, and 10 W/kg.
  - Complete necropsy/histopathology on all chronic study animals

- 14-week interim sacrifice animals
  - Brain DNA strand breaks
  - Hematology
  - Micronuclei (peripheral erythrocytes)

Finished System: 21 Chambers

NTP Levels of Evidence of Carcinogenic Activity

- **Clear evidence**: dose-related increase of malignant tumors, increase of combination of malignant and benign tumors, or marked increase of tumors that have ability to progress to malignancy*
- **Some evidence**: agent-related increase of malignant, benign or combined incidence of tumors*
- **Equivocal evidence**: marginal increase of tumors that may be agent related

* Other factors can influence the evaluation, e.g., uncommon tumors, or proliferative lesions (hyperplasia) at same site

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Pup Weights (PND 1) After Exposure of Pregnant Rats (GD 5-21)

	Sham	GSM (SAR W/kg)			CDMA (SAR W/kg)		
	0	1.5	3.0	6.0	1.5	3.0	6.0
	Mean Body Weight (grams)						
Male pups	7.22** 7.19** ±0.07	7.18 ±0.06	7.06 ±0.07	6.84** ±0.08	7.02 ±0.07	7.09 ±0.06	6.78** ±0.06
Female pups	6.83** 6.79** ±0.06	6.84 ±0.08	6.68 ±0.09	6.54** ±0.07	6.65 ±0.09	6.73 ±0.06	6.44** ±0.05

** p<0.01, trend if shown in sham control group, and pairwise comparison if in exposure group

Cardiomyopathy (Right Ventricle) in Male and Female Rats

	Sham	GSM (SAR W/kg)			CDMA (SAR W/kg)		
	0	1.5	3.0	6.0	1.5	3.0	6.0
Male: Incidence, %	60	69	80*	82*	50	69	82*
severity	1.1	1.5	1.9	1.8	1.2	1.3	1.7
Female: Incidence, %	4	10	16*	17*	8	10	10
severity	1	1.1	1.1	1.2	1.0	1.0	1.0

* $p<0.05$

DNA Damage in Brains of Rats and Mice

	Male rats		Female rats	
Region	**GSM**	**CDMA**	**GSM**	**CDMA**
Frontal cortex				
Cerebellum				
Hippocampus				
	Male mice		**Female mice**	
Frontal cortex				
Cerebellum				
Hippocampus				

Significant increase $p<0.05$ in one or more exposure groups and trend

Significant trend

Non-significant increase (>2-fold) in at least one exposure group

Proliferative Lesions (Tumors and Hyperplasias) in the Heart of Male Rats

Male Rats	Sham	GSM (SAR W/kg)			CDMA (SAR W/kg)		
	0	1.5	3.0	6.0	1.5	3.0	6.0
Lesion	Incidence, %						
Schwannoma[a]	0[b]	2.2	1.1	5.6	2.2	3.3	6.7*
Schwann cell hyperpl.	0	1.1	0	2.2	0	0	3.3
Total proliferative	0	3.3	1.1	7.8*	2.2	3.3	10*

*** p<0.05**

[a] Historical control rate = 1.3%

[b] Significant trend (GSM and CDMA), p<0.05

Proliferative Lesions (Tumors and Hyperplasias) in the Brain of Male Rats

Male Rats	Sham	GSM (SAR W/kg)			CDMA (SAR W/kg)		
	0	1.5	3.0	6.0	1.5	3.0	6.0
Lesion	Incidence, %						
Glioma[a]	0	3.3	3.3	2.2	0	0	3.3
Glial cell hyperplasia	0	2.2	3.3[b]	1.1[b]	2.2	0	2.2[b]
Total proliferative	0	5.5*	6.6*	3.3	2.2	0	5.5*

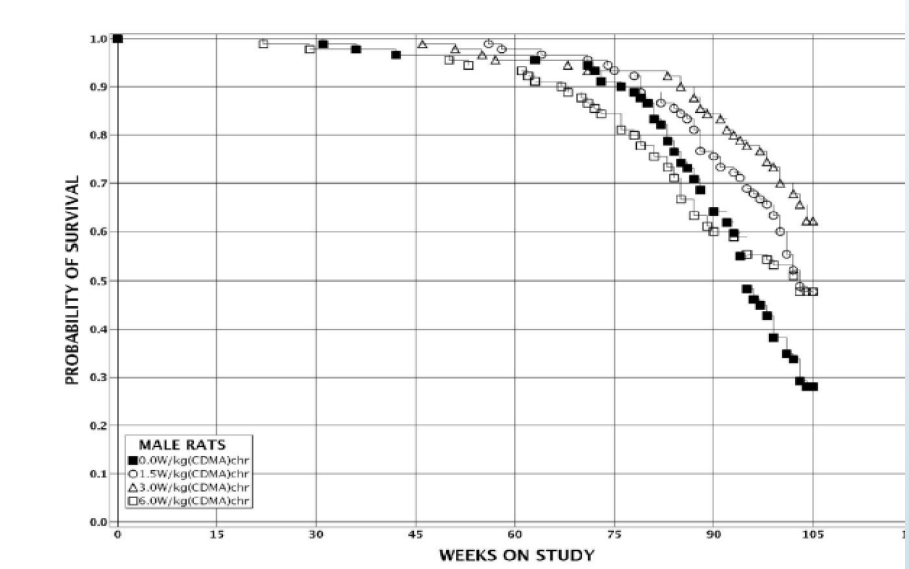
*** $p<0.05$**

[a] Historical control rate = 1.1%

[b] Marked severity of glial cell hyperplasia for one rat in these dose groups; "the hyperplastic lesions are within a continuum leading to malignant glioma"

Are Tumor Responses Due to Survival Differences?

1)



No significant difference in mean survival between controls and 6 W/kg CDMA male rats (same survival at 93 weeks)

2) No glial cell hyperplasias (potential precancerous lesions) or heart schwannomas were observed in any control rat, even though glial cell hyperplasia was detected in exposed rats as early at week 58 of the 2-year study and heart schwannomas were detected as early as week 70 in exposed rats. Therefore, survival was sufficient to detect tumors or pre-cancerous lesions in the brain and heart of control rats

Proliferative Lesions (Tumors and Hyperplasias) in the Prostate Gland of Male Rats

Male Rats	Sham	GSM (SAR W/kg)			CDMA (SAR W/kg)		
	0	1.5	3.0	6.0	1.5	3.0	6.0
Lesion	**Incidence, %**						
Adenoma/carcinoma[a]	2.2	2.2	7.8[b]	3.3	0	2.2	1.1
Epithelial hyperplasia[c] (severity)	5.5 (1.2)	14.4 (1.6)	12.2 (1.9)	12.2 (2.4)	12.2 (1.6)	10.0 (1.7)	17.6* (2.2)
Total proliferative	7.7	16.6	20.0*	14.4[d]	12.2	12.2	18.7*

*** $p<0.05$**

[a] Historical control rate for adenomas = 0.8%,

[b] Exceeded historical control range for all rat strains used by NTP

[c] Increased severity with increasing SAR (GSM or CDMA)

[d] One animal diagnosed with adenoma and hyperplasia

Proliferative Lesions (Tumors and Hyperplasias) in the Adrenal Medulla of Male and Female Rats

	Sham	GSM (SAR W/kg)			CDMA (SAR W/kg)		
	0	1.5	3.0	6.0	1.5	3.0	6.0
Male Rats, Lesion	**Incidence, %**						
Pheochromocytoma[a]	13	27*	31*	16	23	26*	16
Hyperplasia	48	27	29	40	38	36	23
Female rats, Lesion							
Pheochromocytoma[b]	1	3	3	2	10*	6	5
Hyperplasia	15	21	16	29*	22	23	20

*** $p<0.05$**

[a] Historical control rate = 23%

[b] Historical control rate = 3.3%

Lung Tumors in Male Mice Exposed to GSM

	Sham	GSM (SAR W/kg)		
	0	2.5	5	10
LUNG	Incidence, (%)			
Alveolar/Bronchiolar adenoma or carcinoma[a]	26*	27	36	38
A/B carcinoma	14	13	18	20

* $p<0.05$

[a] Historical control rate = 14%, range 8 – 24%

Evidence of Carcinogenic Activity in Rats

Tumor site	Male rat	Female rat
Heart, schwannoma	Clear: GSM* Clear: CDMA*	Equivocal: GSM Equivocal: CDMA
Brain, glioma	Some: GSM* Some: CDMA*	Equivocal, CDMA*
Adrenal gland	Some: GSM	Equivocal: CDMA
Prostate gland	Equivocal: GSM*	
Pituitary gland	Equivocal: GSM Equivocal: CDMA	
Pancreas	Equivocal: GSM	
Liver	Equivocal: CDMA	

* Hyperplasias also occurred

Key Findings from the NTP Studies

- Cell phone radiation caused
  - Cancers and preneoplastic lesions in the heart and brain
  - Proliferative lesions in the prostate gland
  - DNA damage in brain cells of rats and mice
  - Heart muscle disease
  - Reduced birth weights
- The assumption that non-ionizing radiation cannot cause cancer or other adverse health effects, other than by tissue heating, is wrong.

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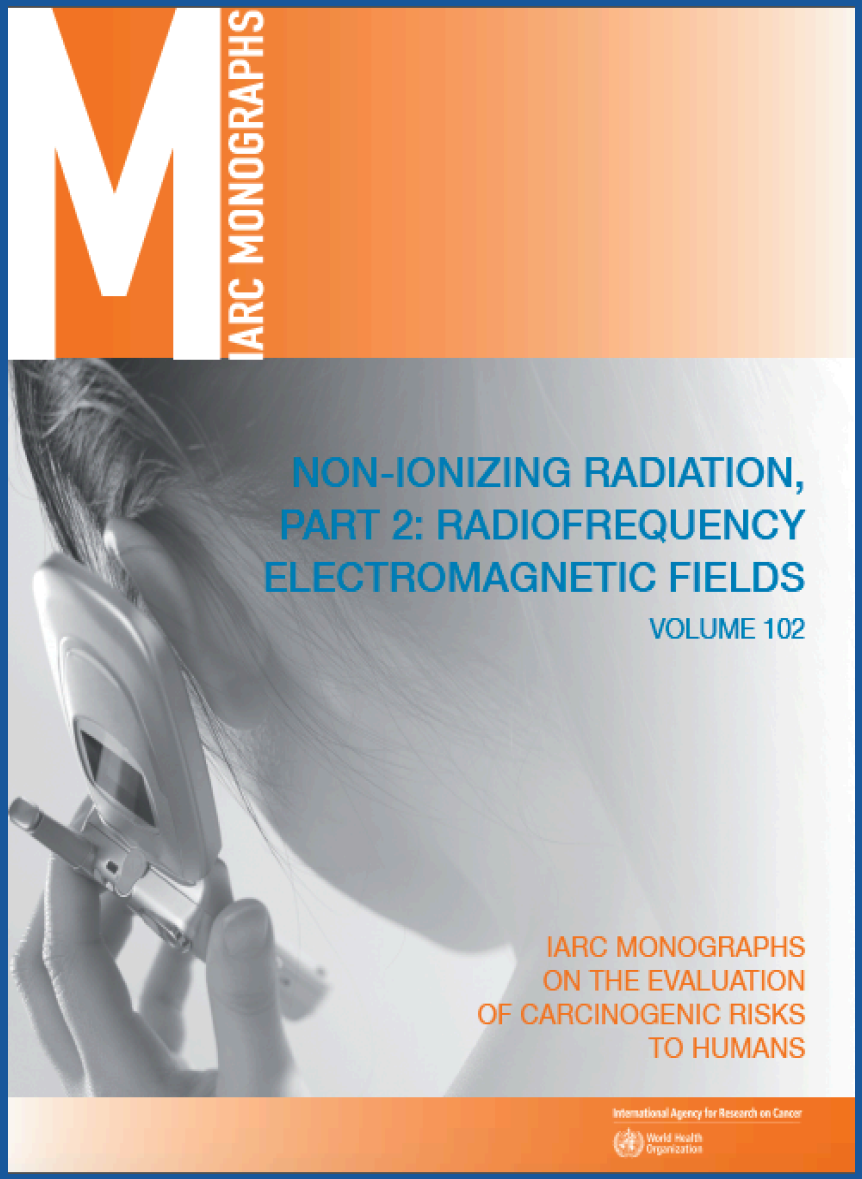
IARC Evaluation of RF-EMF, 2011



IARC Evaluation on the Carcinogenicity of RF Radiation

Monograph Volume 102 (2013)

- **Limited evidence in humans: positive associations have been observed from exposure to RF radiation from wireless phone and glioma and acoustic neuroma**
  - **Negative cohort studies: potential misclassifications of exposure**
  - **Positive case-control studies: potential selection and recall bias**
- **Limited evidence in experimental animals**
- **Overall: RF-EMFs are possibly carcinogenic to humans (Group 2B)**

Concordance Between Rats and Humans in Cell Types Affected

- NTP: cancers in the heart (schwannoma) and brain (glioma)
- International Agency for Research on Cancer: radiofrequency radiation is possibly carcinogenic to humans based largely on increases in glioma and acoustic neuroma (vestibular schwannoma) in both the Interphone and Swedish case-control studies

IARC's Levels of Evidence of Carcinogenicity

- **Humans**
  - **Sufficient evidence:** a causal relationship established between exposure and human cancer, with chance, bias and confounding ruled out with reasonable confidence
  - **Limited evidence:** a causal interpretation between exposure and cancer is credible, but chance, bias or confounding could not be reasonably ruled out
- **Experimental animals**
  - **Sufficient evidence:** increased incidence of malignant or benign and malignant neoplasms in two or more species, two or more independent studies, or an unusual degree with regard to incidence, site, or type of tumor
  - **Limited evidence:** data suggest a carcinogenic effect, but not definitive (e.g., single experiment, only benign neoplasms or restricted to studies that demonstrate only promoting activity)

IARC's Overall Evaluations

- **Possibly carcinogenic to humans (Group 2B)**
  - limited evidence in humans; or
  - sufficient evidence in animals; or
  - strong mechanistic evidence
- **Probably carcinogenic to humans (Group 2A)**
  - limited evidence in humans and sufficient in animals; or
  - limited evidence in humans and strong mechanistic evidence
- **Carcinogenic to humans (Group 1)**
  - sufficient evidence of cancer in humans; or
  - sufficient evidence of cancer in animals and strong mechanistic evidence in exposed humans

Other Relevant Studies After IARC, 2011

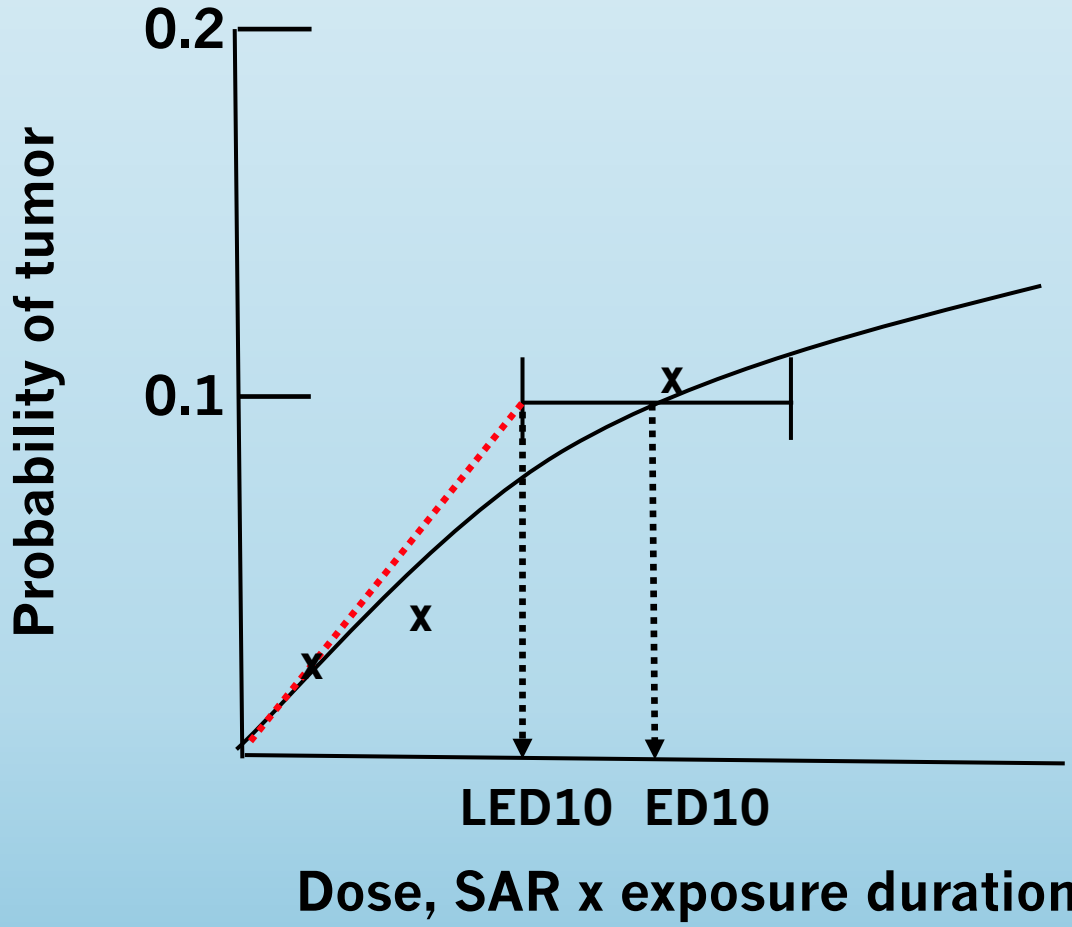
- **Human studies**:
  - Increased risk of glioma in French national study (CERENAT) of mobile phone use (Coureau et al., 2014)
  - Risk of glioma was not affected by selection or recall bias in the Canadian component of the Interphone study (Momoli et al., 2017)
  - Incidence of glioblastoma (frontal and temporal lobes) doubled in England between 1995 and 2015 (Philips et al., 2018),

- **Animal studies (in addition to NTP study)**:
  - Ramazzini study also finds increase in heart schwannomas in male rats exposed to GSM-modulated RFR Falcioni, et al. (2018)
  - Lerchl et al. (2015) reproduces co-carcinogenic effects of RF radiation at SARs of 0.04, 0.4, and 2 W/kg in ENU-treated mice (reported previously by Tillman et al. in 2010)

- **Mechanistic studies:**
  - Oxidative stress, which can lead to mutations chromosomal translocations, and genomic instability, detected in 93 of 100 studies dealing with oxidative effects of low-intensity RFR (Yakymenko et al., 2016)

Expected Next Steps for FDA and FCC

FDA needs to fulfill the intent of their nomination to the NTP and conduct a quantitative risk assessment so that the FCC can establish *health-protective* exposure standards



Slope factor = 0.1/LED10, or 0.05/LED05

Public Needs to Know

- Multiple studies have found increases in cancer incidence associated with exposure to RFR in animals and humans
- Because of the widespread use of cell phones, even a small increase in cancer risk would have a serious public health impact
- Precautionary principles should be promoted by health and regulatory agencies, especially for children and pregnant women:
  - Cancer risks may be greater for children than adults due to increased penetration of cell phone radiation within brains of children, and
  - the developing nervous system is more susceptible to tissue damaging agents

Lesson Learned

We should no longer assume that any current or future wireless technology, including 5G, is safe without adequate testing