

# **Radiofrequency Radiation**

## **A Possible Human Carcinogen?**

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# IARC Evaluation in 2011 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)

# IARC Definitions

- **Limited evidence in humans:** a causal interpretation between exposure and cancer is credible, but chance, bias or confounding could not be reasonably ruled out
- **Limited evidence in experimental animals:** data suggest a carcinogenic effect, but not definitive (e.g., single experiment, only benign neoplasms or restricted to promoting activity)
- **Possibly carcinogenic to humans (2B):** limited evidence in humans and less than sufficient in animals
- **Probably carcinogenic to humans (2A):** limited evidence in humans and sufficient in animals; exceptionally based on limited evidence in humans or based on relevant mechanistic considerations

# Why use animals 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
- ~ one-third of human carcinogens identified first in animals
- Controlled exposures eliminate potential confounders
- Animal studies can eliminate the need to wait for high incidence of long latency human cancers before implementing public health protective strategies

# Animal Carcinogenicity Studies

## Reviewed by IARC

Type of study	Features	Positive	Negative
<b>2 years:</b> Rats Mice	Chou et al: increase in total tumors	0-1 0	4-5 1
<b>Transgenic or cancer prone mice</b>	Short exposure durations, low SARs, high background rates	2	10
<b>Initiation/promotion</b>			
skin	DMBA or B[α]P, low SAR	0	4
brain	ENU, low SAR, short duration	0	6
lymphoma	X-ray, low SAR	0	1
mammary gland	DMBA → 900 MHz GSM	1	3
<b>Co-carcinogenicity</b>			
skin	B[α]P or UV	2	1
colon	DMH for 5 wks		1
lung & liver	ENU given on GD-14	1	
vascular	MX in water, 104 wks	1	

# Animal Carcinogenicity Studies

## After IARC – Lerchl, 2015

Pregnant B6C3F1 mice were exposed to UMTS 1,966 MHz radiation beginning on GD-6; on GD-14 mice were injected with 40 mg/kg ENU. RF exposures in offspring were 23.5 hr/day, 7 d/wk for 72 wks

Lesion	0 (sham)	0.04 mW/g	0.4 mW/g	2 mW/g
<i>Incidence, %</i>				
Lung, A/B carcinoma	84	79	96*	81
Lung, A/B adenoma	23	46*	46*	39*
Liver, HC carcinoma	14	30*	25*	29*
Lymphoma	9	17	24*	9

\*  $p < 0.05$

# Animal Carcinogenicity Studies After IARC – NTP 2016

Rats were exposed 9 hr/day (continuous cycle of 10 min on and 10 min off for 18-hr/day), 7 day/wk, up to 110 wks of age. Exposures began on GD-5

Male Rats	Sham	GSM (SAR mW/g)			CDMA (SAR mW/g)		
Organ, lesion	0	1.5	3.0	6.0	1.5	3.0	6.0
Brain	Incidence, %						
glioma $\phi$	0	3.3	3.3	2.2	0	0	3.3
glial hyperplasia	0	2.2	3.3	1.1	2.2	0	2.2
Total proliferative	0	5.5	6.6	3.3	2.2	0	5.5
Heart	Incidence, %						
Schwannoma $\delta \phi$	0	2.2	1.1	5.5	2.2	3.3	6.6*
Schwann hyperpl	0	1.1	0	2.2	0	0	3.3
Total proliferative	0	3.3	1.1	7.7	2.2	3.3	9.9

\*  $p < 0.05$ ,  $\phi$  Significant trend CDMA  $\delta$  Significant trend GSM



# NTP Study in Reverberation Chambers

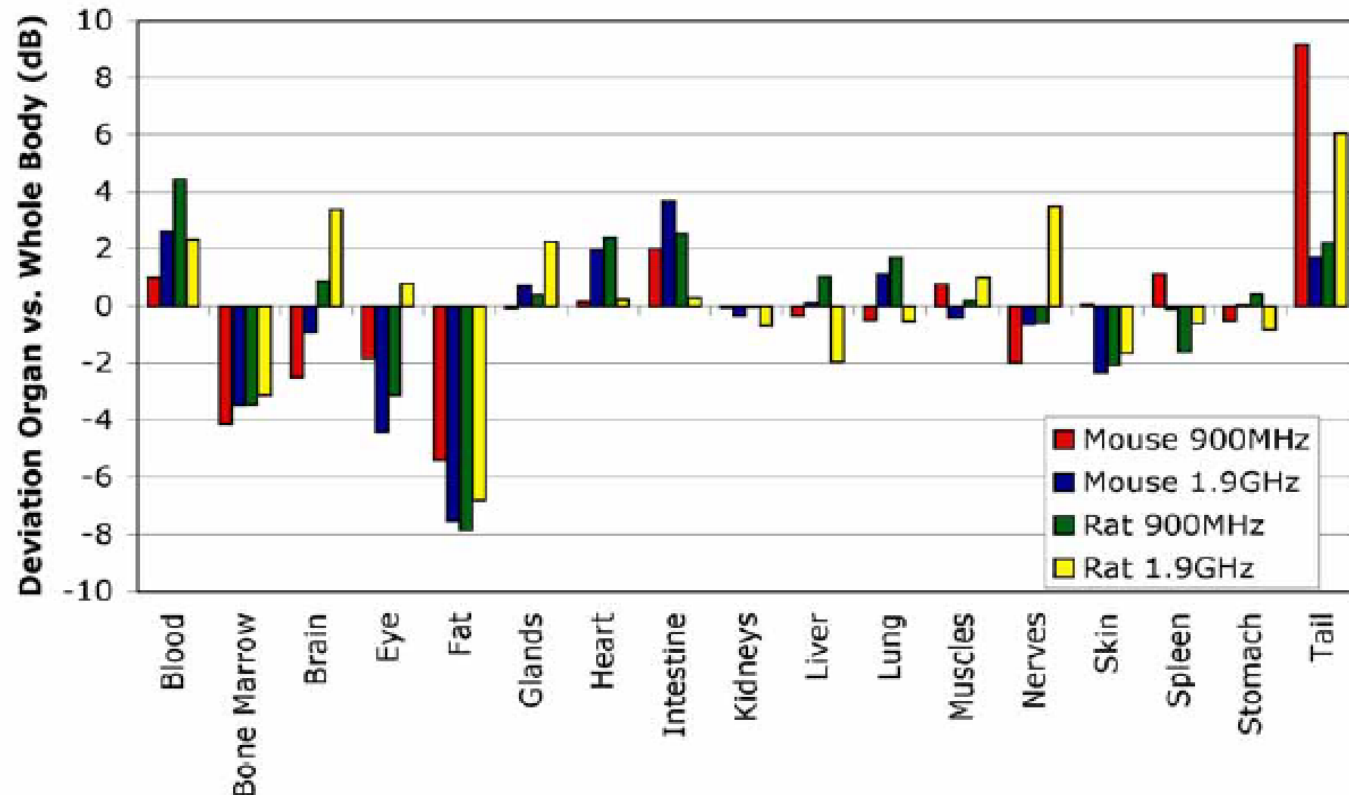


**A shielded room from penetrating EMFs containing an excitation antennae and ventilation panels. Field exposures emanate from multiple angles (all directions), while rotating paddles distribute the fields to create a statistically homogeneous electromagnetic environment. No limit on daily exposure time,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



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

## Organ Specific Average SAR (12 Pol.)

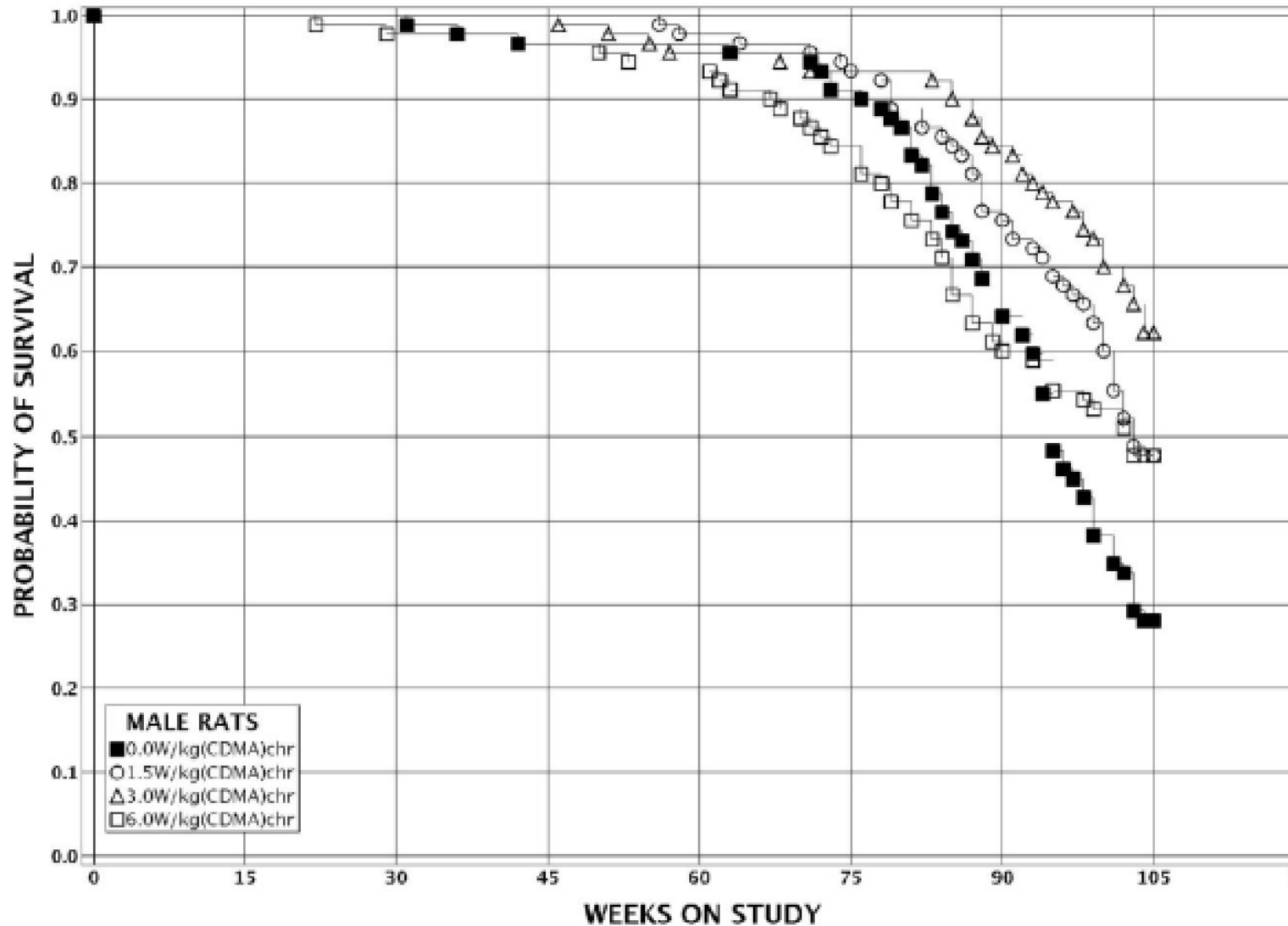


Based on high relative absorption in tail of rats at 1900 MHz and mice at 900 MHz, frequencies in NTP studies were 900 MHz for rats and 1900 MHz for mice

# Importance of NTP Results

- Increases in the incidence of brain tumors (gliomas) and malignant Schwannomas of the heart, and exposure related increases in DNA damage in brain cells of exposed rats and mice support IARC classification based on gliomas and acoustic neuromas among long term users of cell phone
- Exposure intensities, which were limited by potential heat effects at higher levels, are similar to or slightly higher than RF emissions from cell phones
- Survival was sufficient to detect tumors or pre-cancerous lesions in the brain and heart of control rats
  - ▶ no statistical difference in survival between control male rats and the exposure group with the highest rate of gliomas and heart schwannomas
  - ▶ 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

# Survival of CDMA-Exposed Male Rats



# Mechanistic Studies Reviewed by IARC

Effects of RF radiation exposures		In vivo studies		In vitro studies	
		Positive	Negative	Positive	Negative
<b>Genotoxicity<sup>A</sup></b>	<b>human</b>	<b>16</b>	<b>8</b>	<b>23</b>	<b>75</b>
	<b>animal</b>	<b>15</b>	<b>15</b>	<b>8</b>	<b>17</b>
<b>Oxidative stress<sup>B</sup></b>		<b>13</b>	<b>2</b>	<b>6</b>	<b>9</b>
<b>Immunotropic effects</b>		<b>9</b> <b>5↑ 4↓</b>	<b>3</b>	<b>7</b> <b>4↑ 3↓</b>	<b>1</b>
<b>Cell cycle, apoptosis</b>				<b>8</b>	<b>8</b>
<b>Altered gene or protein expression</b>		<b>16</b>	<b>17</b>	<b>21</b>	<b>29</b>

<sup>A</sup> Genotoxicity includes mutation, chromosome aberrations, micronuclei, DNA strand breaks, aneuploidy

<sup>B</sup> Oxidative stress includes formation of reactive oxygen species, lipid peroxidation, oxidative DNA damage

↑: stimulation, ↓:suppression

# Mechanistic Studies Reviewed by IARC

- Evidence was weak for RF radiation causing genotoxic effects, altering gene or protein expression, causing oxidative stress and altering levels of reactive oxygen species, or altering cell cycling
- Mechanistic data had limited impact on the overall cancer evaluation of RF radiation
- Mixed results or inconsistency in response to RF exposures may have been due to:
  - ▶ differences in susceptibility by species, strain, and tissue or cell-type evaluated
  - ▶ different sensitivity of the analytical method
  - ▶ insufficient exposure intensity, or insufficient exposure duration
  - ▶ different exposure systems
  - ▶ inaccurate determination of dose
  - ▶ inadequate control of temperature

# Mechanistic Studies after IARC, 2011

Effects of RF radiation exposures	In vivo studies		In vitro studies	
	Positive	Negative	Positive	Negative
Genotoxicity <sup>A</sup>	7	2	5	4
Neoplastic transformation			1	
Oxidative stress <sup>B</sup>	13	2	12	4
Inflammation Immunosuppression				
Cell cycle, apoptosis	3	4	9	4
Altered gene or protein expression	7	2	6	2
Brain alterations	7	2	1	

<sup>A</sup> Genotoxicity includes mutation, chromosome aberrations, micronuclei, DNA strand breaks, aneuploidy

<sup>B</sup> Oxidative stress includes formation of reactive oxygen species, lipid peroxidation, oxidative DNA damage

## Oxidative Stress – *in vivo*

Reference	Species; tissue	Exposure			ROS	Measured Effects		
		Modulation, Frequency, WB-SAR	Hr/day	# day		Lipid perox	8OH-dG	GSH, AA enz
Khalil '14	Human; saliva	Cell phone users	0.5	1	NE	NE	NE	
Avci '12	Rat; brain, serum	1800 MHz, 0.4 mW/g	1	21	↑	NE		
Saikhedkar '14	Rat; brain	900 MHz mobile phone	4	15		↑		↓
Bilgici '13	Rat; brain, serum	900 MHz, 1.08 mW/g	1	21		↑		
Sahin '16	Rat; brain	UMTS 2100 MHz, 0.4 mW/g	6	10		NE	↑	
Akbari '14	Rat; brain	Radiofrequency waves		45		↑		↓
Hussein '16	Rat; brain	GSM 1800 MHz, 0.6 mW/g	2	90		↑		↓
Chauhan '17	Rat; liver, brain, spleen	2450 MHz, 0.4 mW/g	2	35		↑		
Esmekaya '11	Rat; liver, lung, testis, heart	GSM 900 MHz, 1.2 mW/g	0.3	21		↑		↓
Kesari '11	Rat; sperm cells	GSM 900 MHz, 0.9 mW/g	2	35	↑	↑		↓
Güler '16	Rabbit; brain	GSM 1800 MHz, 0.018 mW/g: prenatal +/- postnatal	0.25	7-14		↑	↑	
Güler '12	Rabbit; liver	GSM 1800 MHz, prenatal +/- postnatal	0.25	7-14		↑	↑	
Kismali '12	Rabbit; blood	GSM 1800 MHz, 0.052 mW/cm <sup>2</sup>	0.25	7		NE		
Ozgur '13	Rabbit; blood	GSM 1800 MHz, prenatal +/- postnatal	0.25	7-14		↑		
Manta '16	Drosophila, ovary	Cell phone; 0.15 mW/g	0.5	1	↑			



## Oxidative Stress – *in vitro*

Reference	Cell type	Exposure		ROS	Measured Effects		
		Modulation, Frequency, SAR	Hours		Lipid perox	8OH-dG	GSH, AA enz
Ni '13	Human lens epithelial	GSM 1800 MHz 0-4 mW/g	0.5-24	↑	↑		↓
Liu '12	Human blood mononuclear	GSM 900 MHz, 0-0.43 mW/g	1-8	↑			
Kazemi '15	Human blood mononuclear	GSM 900 MHz, 0-2mW/g	2	↑			
Naziroglu '12	Human leukemia	2450 MHz			↑		
Liu '14	Mouse spermatocyte line	GSM 1800 MHz, 0-4 mW/g	24 inter-mittent	↑			
Duan '15	Mouse sperm-atocyte line	GSM 1800 MHz, 0-4 mW/g	8 inter-mittent			↑	
Liu '13	Mouse spermatocyte line	GSM 1800 MHz, 0-4 mW/g	8 inter-mittent			↑	
Wang '15	Mouse neuroblast	GSM 900 MHz, 0-2 mW/g	24	↑		↑	
Kim '16	Mouse neuronal			↑			
Zuo '15	Rat neonatal neurons	GSM 1800 MHz, 0-4 mW/g	24 inter-mittent	↑			
Marjanovic '15	V79	1800 MHz, 1.6 mW/kg	0.16	↑			
Burlaka '13	Quail embryo	GSM 900 MHz,0-0.003 mW/g	19	↑	↑	↑	↓
Hong '12	Human mammary line	CDMA 837 MHz ± CDMA 1950 MHz 0-4 mW/g	2	NE			NE
Poullietier '11	Human brain lines	GSM 1800 MHz; 2, 10 mW/g	1 or 24	NE			
Xu '13	6 different human types	GSM 1800 MHz, 0-3 mW/g	24 inter-mittent	NE			
Kang '14	Mouse neuronal	CDMA 837 MHz ± CDMA 1950 MHz 0-4 mW/g	2	NE			

# Neoplastic Transformation Induced by RF Radiation, (Yang et al., 2012)

- NIH/3T3 cells exposed to 916 MHz (cw) EMF: 2 hr/d at 0, 10, 50, or 90 W/m<sup>2</sup>
- After 8-12 weeks exposure, cells formed clones in soft agar; this represents anchorage independent growth
- Tumors formed on backs of immunodeficient mice inoculated with RF-exposed cells



1. Mechanistic updates and new approaches
  1. Recent findings from in vitro and animal studies; what non-thermal molecular and cellular changes are reproducible?
  2. What areas need further study, and what hypotheses need to be researched?
  3. How can mechanistic studies address differences in susceptibility with age and underlying vulnerabilities?
  4. How to identify and validate potential biomarkers of exposure?
  5. What are the most important co-exposures for future research (i.e., toxicants, and beneficial compounds such as nutrients)?
2. What is the biological basis for medical uses of RFR?
3. What studies of newer technologies exist, e.g., 4G, 5G
4. Is there adequate data on reproduction, development, and neurological effects to assess human health risks?
5. What evidence is for hypersensitivity and methods to evaluate the phenomenon?
6. What are the major data gaps, research needs, research priorities and opportunities?