



**Radiation Health 2019**  
**Can Wireless Communications Damage Your Health?**

The Ramazzini Institute Bioassay on RFR



**Radiation Health 2019**  
Get the Facts  
International Conference

**Can Wireless Communications Damage Your Health?**  
Sat 28<sup>th</sup> September 2019, Ramazzini Institute, Bologna, Italy



Cesare Maltoni Cancer Research Center

**Andrea Vornoli**  
 London, September 28<sup>th</sup>, 2019  
 Ramazzini Institute, Bologna, Italy

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*"It pays for more to prevent than to treat"*  
 Bernardino Ramazzini, physician  
 Carpi 1633 - Padova 1714

**Bernardino Ramazzini**



Carpi, 1633 – Padua, 1714



DE MORBIS ARTIFICUM DIATRIBA  
 BERNARDINI RAMAZZINI  
 ARCHI-LYCEI MODERATORIBUS

De morbis artificum diatriba, (1700)

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**The CMCR(1969)**

**History...**





**Castle built in 1475**  
 Domus Jucunditatis  
 of Bentivoglio family







**Cesare Maltoni**  
 (1930-2001)



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**...and Science**

- > 210 compounds/physical agents studied with more than 500 chronic studies in SD rats, Swiss mice and Chinese Hamster from 1969
- > This program is **second only to that of the United States' National Toxicology Program**
- > **Life span** (~3 years) experiments
- > **Breeding facility**
- > Family tree of SD rats from the 1970'.....until now (**more than 200.000**)

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## Ramazzini Institute

- The **Ramazzini Institute (RI)** is a **non-profit independent cooperative** located in Bologna, Italy



- Our work principally involves strategies based on prevention of **environmental diseases**, in particular cancer
- The RI depends on support from more than **27,000 associates**, each year covering about 30% of the budget
- The **budget is annually published on our website** and incomes include funds from national and international public institutions, liberal donations and contributions from private citizens and NGOs such as Environmental Health Trust

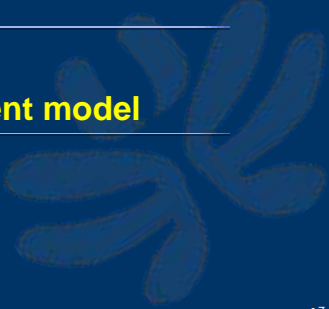
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## Ramazzini Institute: the support of the scientific committee

 <p>Professor <b>PHILIP J. LANDRIGAN</b>, Professor of Biology, Director, Global Public Health Program Schiller Institute for Integrated Science and Society, Boston College, Chestnut Hill, MA, USA</p>	 <p>Dr. <b>LINDA BIRNBAUM</b>, director of the NIEHS, and National Toxicology Program (NTP), USA</p>	 <p>Dr. <b>KURT STRAIF</b>, Head of Section of Evidence Synthesis and Classification, International Agency for Research on Cancer (IARC), Lyon, France</p>	 <p>Dr. <b>PIETRO COMBA</b>, Director, Unit of Environmental Epidemiology, National Institute of Health, Italy</p>
 <p>Dr. <b>ELLEN SILBERGELD</b>, Professor of Environmental Health Science at the Johns Hopkins Bloomberg School of Public Health, Baltimore, USA</p>	 <p>Dr. <b>MELISSA McDIARMID</b>, Professor of Medicine and Director of the University of Maryland School of Medicine's Occupational Health Program, USA</p>	 <p>Dr. <b>LENNART HARDELL</b>, Professor of Oncology and Epidemiology, Örebro University Hospital, Sweden</p>	 <p>Dr. <b>MARIE-NOEL BRUNE DRISSE</b>, Uruguay, Children Health Department, WHO</p>

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## Peculiarity: The human equivalent model



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## The Animal Model of The Ramazzini Institute



**Sprague-Dawley rats**

CMCRC 8

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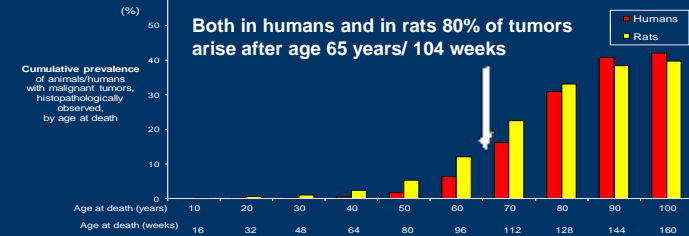
### CMCRC STUDY DESIGN: a human-equivalent model

Compared distribution by age at death:

- >1,114 people (1/2 both sexes) with malignant tumors (out of 2,560 autopsied men and women deceased at the Hospital of Trieste, in 1989)
- >1,212 Sprague-Dawley rats (1/2 both sexes) with malignant tumor (out of 3,051 necropsied male and female untreated rats, under control until spontaneous death, used as control groups 1984-1994)
- >10 human years are equivalent to 16 weeks in a rat

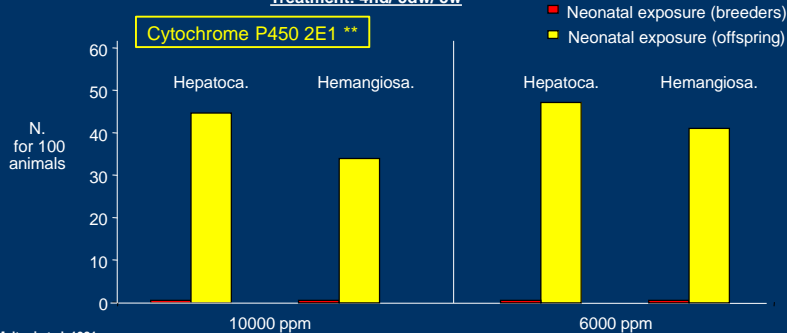


### A human-equivalent model



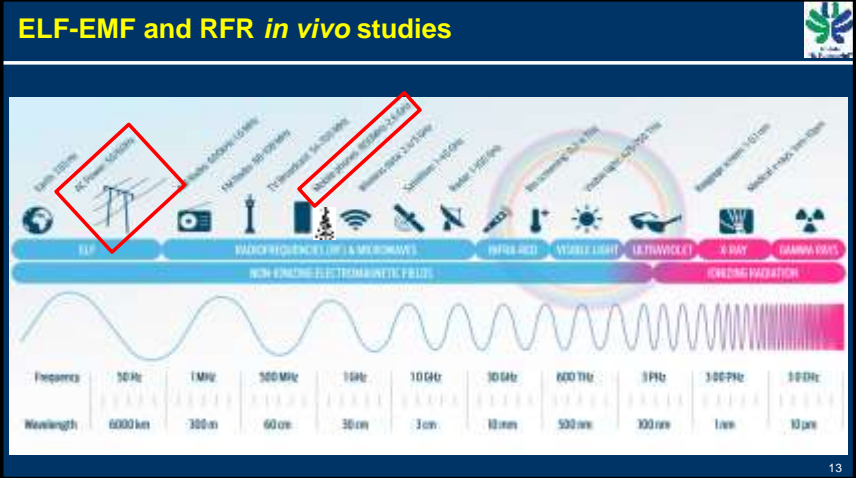
### Vinyl chloride: the importance of neonatal exposure, comparison between breeders and offspring

SPRAGUE-DAWLEY RATS (Exp. BT14, 1976)\*  
Treatment: 4hd/ 5dw/ 5w



Which were the Ramazzini Institute studies on EMF?





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### Integrated experimental project on extremely low frequency electromagnetic field (ELF-EMF)

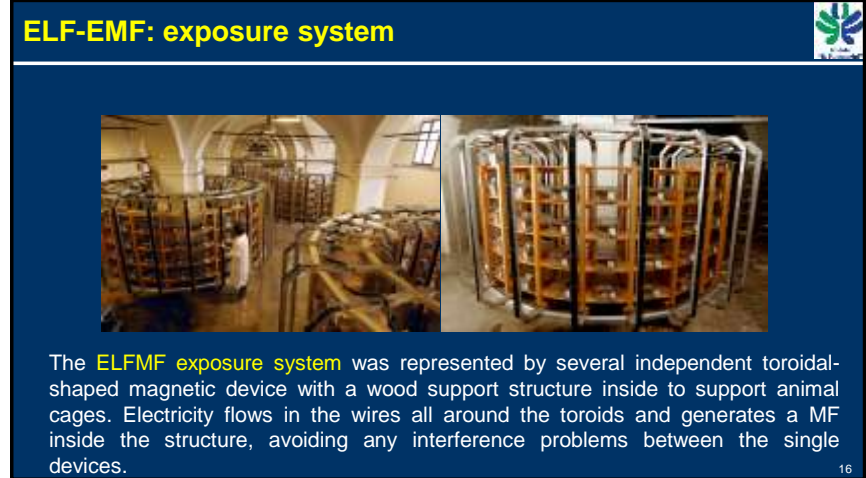
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### ELF-EMF: Long-term bioassays experimental project

All experiments started at the 12<sup>th</sup> day of pregnancy and continued life-span

Experiment	Number of animals (M+F)	Treatment
BT 1 CEM	5,029	ELF-EMF S-50 Hz
BT 2 CEM	805	ELF-EMF S-50 Hz + <i>formaldehyde</i>
BT 3 CEM	657	ELF-EMF S-50 Hz + <i>γ-radiation (0.1 Gy)</i>
<b>TOTAL</b>	<b>6,491</b>	

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### ELF-EMF + formaldehyde

**2016**

**Synergism Between Sinusoidal 50 Hz Magnetic Field and Formaldehyde in Triggering Carcinogenic Effects in Male Sprague-Dawley Rats**

Morando Soffritti, <sup>1,2</sup> Eva Tibaldi, <sup>1,2</sup> Michela Padovan, <sup>1,2</sup> David G. Hoel, <sup>1,2</sup> Livia Giuliano, <sup>1,2</sup> Luciano Bua, <sup>1,2</sup> Michela Lazzarini, <sup>1,2</sup> Laura Falcioni, <sup>1,2</sup> Marco Manservigi, <sup>1,2</sup> Fabiana Manservigi, <sup>1,2</sup> and Fiorella Balagoggi, <sup>1,2</sup>

**Background:** Experimental/animal bioassays performed up to now have failed to provide conclusive confirmation of the carcinogenicity of extremely low-frequency magnetic fields (ELF-MF).

**Hypothesis:** To evaluate the potential synergistic carcinogenic effects of concurrent exposure to ELF-MF and formaldehyde on two groups of male and female Sprague-Dawley rats.

**Methods:** The group was exposed from prenatal life until natural death to 50 Hz MF (microtesla) in addition with formaldehyde (0.1 mg/l) for 24 weeks. Two groups were treated only with formaldehyde or only with MF and one group served as untreated control.

**Results:** Compared to parental controls, exposure to MF and formaldehyde caused in males a statistically significant increased incidence of malignant cancer (P < 0.05), Malignant C-cell carcinomas (P < 0.05) and lymphomas/leukemias (P < 0.05) in significantly significant differences were observed among female groups.

**Conclusions:** Life-time exposure to MF and formaldehyde induced statistically significant carcinogenic effects in male rats. *Int J Rad Biol.* 2016;94(1):1-10.

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### ELF-EMF + formaldehyde: enhancing effects

The concurrent exposure to lifespan 50-Hz and 50 mg/l formaldehyde from 6 to 104 weeks of age determined:

- Significant increase in the incidence of **total malignant tumors, C-cell carcinomas and lymphomas/leukemias** in male Sprague-Dawley rats, compared to negative controls
- Significant increase in **C-cell carcinomas and lymphomas/leukemias**, compared to males exposed to EMF alone (positive control)
- Concerning C-cell carcinomas, our results **reinforce the biological significance** of the same increased incidence observed by US NTP and classified as an equivocal finding (Boorman et al, 1999)

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### ELF-EMF + $\gamma$ radiation

**2016**

**Life-span exposure to sinusoidal 50 Hz magnetic field and acute low-dose  $\gamma$  radiation induce carcinogenic effects in Sprague-Dawley rats**

Morando Soffritti<sup>1,2</sup>, Eva Tibaldi<sup>1,2</sup>, Michela Padovan<sup>1,2</sup>, David G. Hoel<sup>1,2</sup>, Livia Giuliano<sup>1,2</sup>, Luciano Bua<sup>1,2</sup>, Michela Lazzarini<sup>1,2</sup>, Laura Falcioni<sup>1,2</sup>, Marco Manservigi<sup>1,2</sup>, Fabiana Manservigi<sup>1,2</sup>, Fiorella Balagoggi<sup>1,2</sup>

**Abstract:** In 2002 the International Agency for Research on Cancer classified extremely low frequency magnetic fields (ELF-MF) as a possible carcinogen on the basis of epidemiological evidence. Experimental bioassays for rats and mice performed up to now on ELF-MF alone or in association with known carcinogens have failed to provide conclusive confirmation.

**Objectives:** To study the carcinogenic effects of combined exposure to sinusoidal 50 Hz (50-Hz) magnetic fields and acute  $\gamma$  radiation in Sprague-Dawley rats.

**Methods:** Life spanned groups of male and female Sprague-Dawley rats exposed from prenatal life until natural death to 10 or 1000 nT 50-Hz MF and also to 0.1 Gy  $\gamma$  radiation delivered as a single acute exposure at 6 weeks of age.

**Results:** The results of the study showed significant carcinogenic effects for the respiratory tract in males and females and a significant increased incidence of malignant schwannomas of the heart as well as increased incidence of lymphomas/leukemias in males.

**Conclusions:** These results call for a re-evaluation of the safety of non-ionizing radiation.

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### ELF-EMF + $\gamma$ radiation: enhancing effects

- Significant dose-related increased incidence of **mammary adenocarcinomas** in male and female rats compared to negative control
- Dose-related (significant at the higher EMF dose) increased incidence of **heart malignant Schwannomas** in males compared to negative control
- Significant increased incidence of **lymphomas/leukemias** in males compared to negative control
- significant increased incidence of **mammary adenocarcinomas** in female and **lymphomas/leukemias** in males compared to positive control ( $\gamma$ -radiation)

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### ELF-EMF alone

2018  
Environmental Research  
journal homepage: www.elsevier.com/locate/environres

Results of lifespan exposure to continuous and intermittent extremely low frequency electromagnetic fields (ELFEMF) administered alone to Sprague Dawley rats

L. Bua<sup>a</sup>, E. Tibaldi<sup>b</sup>, L. Falconi, M. Lauriola, L. De Angelis, F. Gaudi, M. Manservigi, F. Manservigi, I. Manzoli, I. Menghetti, R. Mottrella, S. Panzocchi, D. Spaggi, V. Stroilo, A. Vornoli, D. Zanfani<sup>a</sup>, F. Balpoggi<sup>a</sup>

<sup>a</sup> Centro Nazionale Studi Rischio Campi, Roma; <sup>b</sup> Università della Basilicata, Potenza, Italy

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### ELF-EMF alone

Summary of specific malignant tumors in the three experiments

Experiment	Chemical	Malignant tumors		Benign tumors		Malignant lymphomas		Total malignant tumors		
		No.	%	No.	%	No.	%	No.	%	
Malignant lymphomas	None	Control	0	0.0	0	0.0	0	0.0	0	0.0
		50 Hz	0	0.0	0	0.0	0	0.0	0	0.0
		60 Hz	0	0.0	0	0.0	0	0.0	0	0.0
		100 Hz	0	0.0	0	0.0	0	0.0	0	0.0
Squamous cell carcinomas	None	Control	0	0.0	0	0.0	0	0.0	0	0.0
		50 Hz	0	0.0	0	0.0	0	0.0	0	0.0
		60 Hz	0	0.0	0	0.0	0	0.0	0	0.0
		100 Hz	0	0.0	0	0.0	0	0.0	0	0.0
Adenocarcinomas	None	Control	0	0.0	0	0.0	0	0.0	0	0.0
		50 Hz	0	0.0	0	0.0	0	0.0	0	0.0
		60 Hz	0	0.0	0	0.0	0	0.0	0	0.0
		100 Hz	0	0.0	0	0.0	0	0.0	0	0.0

➤ No statistically significant increase in benign and/or malignant tumors incidence was observed in Sprague Dawley rats treated with ELF-EMF alone, compared to controls

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### ELF-EMF: conclusions

The results of our studies demonstrate that:

- In our experimental conditions, when administered alone S-50 Hz ELF-EMF are not carcinogenic
- In light of our results on the carcinogenic effects of ELF-EMF in combination with formaldehyde and  $\gamma$ -radiation, ELF-EMF act as cancer enhancer in presence of other chemical and physical carcinogens.

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### Integrated experimental project on radiofrequency radiation (RFR)

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### RFR experimental projects

All experiments started at the 12<sup>o</sup> day of pregnancy and continued life-span


Experiment	Number of animals (M+F)	Treatment	State of the art *
BT 1 CEMRF	2,448	RFR/MW 1.8 GHz	Partially published
BT 3 CEMRF	617	RFR/MW 1.8 GHz + $\gamma$ -radiation (0.1 Gy)	Ongoing
<b>TOTAL</b>	<b>3,065</b>		

• STATE OF THE ART:

- RFR alone: heart and brain results published. For all the other tissues, slides evaluation at microscope is still ongoing, and complete evaluation at end of 2019, followed by PWG. Publication of results expected for end 2019
- RFR +  $\gamma$  radiation : all tissues embedded, preparation of all the slides is ongoing

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### The Ramazzini RFR exposure system



- The rats were located in 4 rooms totally shielded in order to minimize the effect of field non-uniformity due to reflections and interferences caused by the walls
- The cages were located in wooden circular-shaped devices with a single exposure device in the center, each serving at least 400 rats
- All devices were identical and a different intensity of RFR was provided as reported by the experimental design

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### The Ramazzini RFR exposure system



Antenna      Probe      Software


The exposure system included :

- ✓ main generator unit
- ✓ external control panel
- ✓ main radiator system (transmitting antenna)
- ✓ feedback probe

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### Radio Frequency radiation *in vivo* studies

#### AIM OF THE STUDIES



The nomination for NTP to study cell phone RF radiation was made by the U.S. Food and Drug Administration



Animals were exposed to frequencies and modulations currently used in cellular communications in the United States

The nomination for the RI study was performed on the basis of the number of people exposed and the inadequacy of information on the possible hazards



Animals were exposed to frequencies and modulations that mimic the commonly human population exposure to radiobase-station antennas in the world

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### Radio Frequency radiation *in vivo* studies


**GSM (Global System for Mobile Communication)**  
CDMA (Code Division Multiple Access)  
*Near Field*

**GSM (Global System for Mobile Communication)**  
*Far Field*

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### Radio Frequency radiation *in vivo* studies




**Prenatal** | **Postnatal**

Total animals: 720

start of treatment ↑

Sacrifice (106 weeks)



**Prenatal** | **Postnatal**



Total animals: 2448

start of treatment ↑

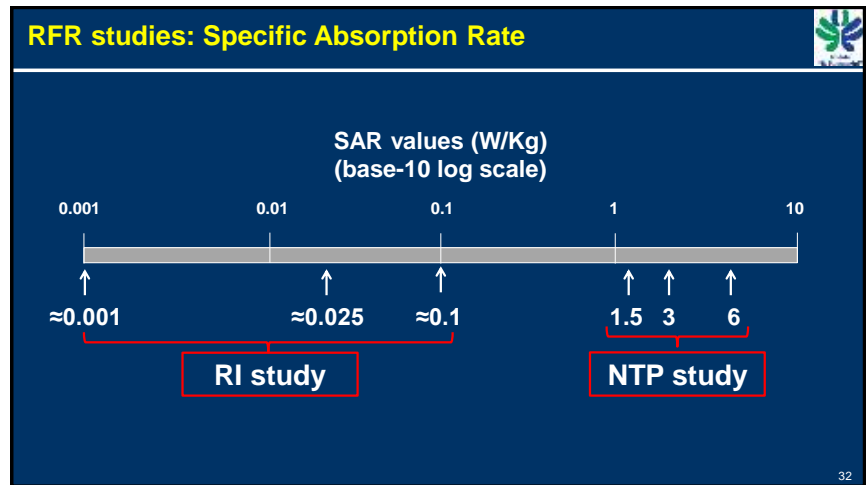
Lifespan

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### Radio Frequency radiation *in vivo* studies

	NTP National Toxicology Program	Instituto Ramazzoni COOPERATIVA SOCIALE ONLUS
<b>ANIMAL MODELS</b>	 Sprague-Dawley rats    B6C3F <sub>1</sub> mice	 Sprague-Dawley rats
<b>FREQUENCY OF SIGNAL MODULATION</b>	1900 MHz    900 MHz	1800 MHz
<b>STUDY GROUPS AND EXPOSURE</b>	I group: 0 W/Kg (90 F, 90 M) II group: 1.5 W/Kg (90 F, 90 M) III group: 3 W/Kg (90 F, 90 M) IV group: 6 W/Kg (90 F, 90 M)	I group: 0 V/m (405 F, 412M) II group: 5 V/m (410F, 401M) III group: 25 V/m (202 F, 209 M) IV group: 50 V/m (202F, 207M)
<b>TIME OF EXPOSURE</b>	10-min on, 10-min off increments 9 hours/day, 7 days/week	continuous exposure 19 hours/day, 7 days/week

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### RFR studies: results



- **Brain**  
Significant increase in malignant glioma and glial cell hyperplasia in male rats
- **Heart**  
Significant dose-related increase in malignant schwannoma and Schwann cells hyperplasia in males
- **Adrenal gland**  
Significant increase in (combined) pheochromocytomas of adrenal marrow in males



- **Brain**  
Slight, not significant, dose-related increase in malignant glioma in female rats
- **Heart**  
Significant dose-related increase in malignant schwannoma in males; slight, not significant, increase in hyperplasia of Schwann cells in both males and females

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### RI study on RFR : first results

Report of final results regarding brain and heart tumors in Sprague-Dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8 GHz GSM base station environmental emission

2018

L. Faltoni, L. Bui, E. Tibaldi, M. Lazzarini, L. De Angelis, F. Genik, D. Mandrilli, M. Manuveliti, F. Marrovisi, I. Manzoli, I. Mesghem, E. Miondici, S. Panzavolta, D. Sangi, V. Senilo, A. Vornoli, F. Delgado

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### NTP study on RFR : results

Peer Review meeting:

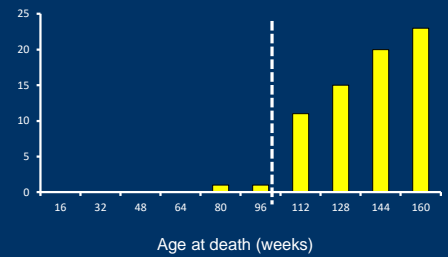
**CLEAR EVIDENCE OF CARCINOGENICITY**

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### The importance of the RI lifespan model

Cumulative prevalence of animals (all groups, males and females) with **HEART** malignant Schwannomas by age at death



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### RI study on RFR: fertility and litter preliminary evaluations

Group	Treatment (PND-RFR Level) (Days*)	PND 9		PND 10		PND 11		PND 12		PND 13	
		Mean BW	SD	Mean BW	SD	Mean BW	SD	Mean BW	SD	Mean BW	SD
I	0	16.5 ± 1.7		16.7 ± 1.8		18.4 ± 2.0		20.9 ± 1.2		20.5 ± 2.8	
II	5	16.2 ± 1.8		17.1 ± 1.9		18.7 ± 1.9		20.4 ± 2.3		20.4 ± 2.7	
III	25	16.7 ± 1.6		17.9 ± 2.1		18.9 ± 2.4		20.1 ± 1.3		19.5 ± 2.4	
IV	50	13.4 ± 1.8**		15.2 ± 1.7**		16.7 ± 2.3**		18.4 ± 2.0**		17.9 ± 2.2**	

Table 2: Mean body weights of F1 rats during lactation. \*\*: statistically significant decrease, (p < .01) using linear regression models (one for each value of PND) that take into account the decreases of the litter.

- Litter mean body weight in group IV was significantly decreased compared to those of the unexposed controls, on PND 1 and throughout the lactation period, particularly from postnatal day (PND) 9 to 13
- The lack of further decreases in body weight over the course of the lifespan carcinogenicity study suggests that the RFR-mediated effects on body weight in the F1 offspring may be specific to the perinatal period
- This results will be included in the publication of final results, planned by the end of 2019

### IR study on RFR: conclusions and perspectives

- The RI findings on far field exposure to RFR are consistent with the results of the NTP study on near field exposure
- The tumors of the brain and heart observed in rats exposed to RFR in both studies have the same histological origin of those observed in some epidemiological studies on cell phone users
- These experimental studies provide sufficient evidence to call for the re-evaluation of IARC, and in fact RFR were included among the high priorities for IARC Monographs Programme 2020–2024

### The danger for humans



Brain Tumours: Rise in Glioblastoma Multiforme Incidence in England 1995–2015 Suggests an Adverse Environmental or Lifestyle Factor  
A. Phillips, D.L. Henshaw, G. Lamburn, and M.J. O'Carroll

Red line represents the incidence rate across the years of glioblastoma multiforme in temporal and frontal lobes, those most exposed during a phone call

Green line represents the incidence rate of the other brain regions

### The danger for humans



### What are the next steps?

- Complete **histopathology** for the RFR studies
- Perform an external **PWG**
- Understand the **mutational landscape** of the glial tumors and any early molecular changes of the RFR study, **in comparison to that of humans** (in collaboration with the US NTP/NIEHS)

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### What are the next steps?

- **targeted resequencing** on rat tumor DNA (in collaboration with the US NTP/NIEHS)

#### Genetic Profiling of Radiofrequency Radiation Exposed Rat Gliomas using a Targeted Next-Generation Sequencing Panel (rGlioSeq)

**Ramesh C. Kovi**<sup>1,2</sup>, **Andrea Vornoli**<sup>3</sup>, **Ashley Brooks**<sup>1</sup>, **Thai Vu T. Ton**<sup>1</sup>, **Ahmed A. Mashal**<sup>1</sup>, **Miaofei Xu**<sup>1</sup>, **Eva Tibaldi**<sup>3</sup>, **Federica Gnudi**<sup>3</sup>, **Jian-Liang Li**<sup>4</sup>, **Robert C. Sills**<sup>1</sup>, **John R. Bucher**<sup>1</sup>, **Fiorella Belpoggi**<sup>3</sup>, and **Arun R. Pandiri**<sup>1</sup>

<sup>1</sup>Division of National Toxicology Program (DNTP), NIEHS, Research Triangle Park, NC, USA.  
<sup>2</sup>Experimental Pathology Laboratories Inc., Research Triangle Park, NC, USA  
<sup>3</sup>Cesare Maltoni Cancer Research Center (CMCRC), Ramazzini Institute (RI), Bologna, Italy  
<sup>4</sup>Integrative Bioinformatics Support Group, DIR, NIEHS, Research Triangle Park, NC, USA

STP meeting, Raleigh, NC, June 2019

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### What are the next steps?

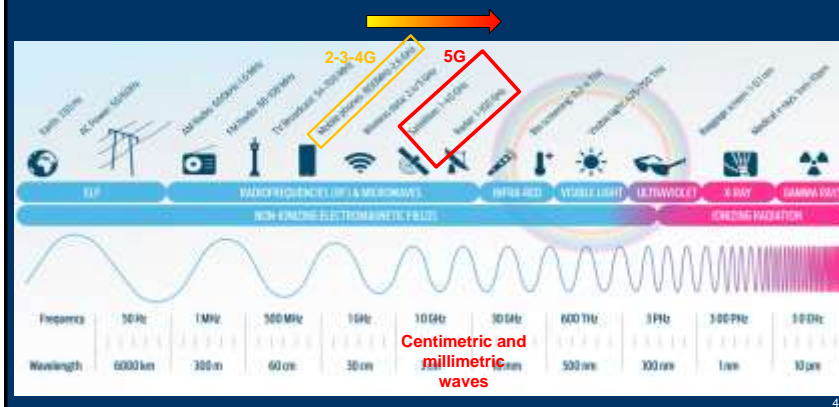
- In this study, we designed, developed and validated the targeted amplification-based next generation sequencing (NGS) panel for rat gliomas (rGlioSeq) for detecting genetic alterations in most common cancer-related genes in rat brain tumors.
- In contrast to most human gliomas which harbor mutations in *IDH1*, *IDH2* and/or *Tert* promoter region, the rat gliomas seem to be predominantly *idh1* wild type with mutations in the other glioma-related genes including *Setd2*, *Nf1*, *Egfr*, *Tp53*, *Arid1a* ecc.

STP meeting, Raleigh, NC, June 2019

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### 5G and the Internet of Things



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### 5G and the Internet of Things

- 5G is the term used to describe the **next generation of mobile networks** that goes beyond the 4G LTE mobile networks commonly used today
- 5G is the technology **that allows the existence of the Internet of Things (IOT)**, which connects all our devices and objects in wireless mode to Internet
- The 5G **will exploit a new "channel"** untapped until now: the frequencies to/beyond the 26 Ghz that guarantee more speed and less latency
- The 5G diffusion at extremely high frequencies (millimeter waves) is expected for the next two to three years

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### 5G and the Internet of Things

The 2G, 3G and 4G wireless technologies, used ubiquitously for decades with our mobile phones, computers, and various other devices create RFR exposures that **represent a serious risk to human, animal and environmental health**, as demonstrated by hundreds of studies

**There is an urgent need to assess 5G health effects now, before millions of people are exposed**

**...without repeating the mistakes of the past...**

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### Ignored early warnings from the RI

Agent/Compound	CMCRC-RI*	IARC Group/year	Prediction
Vinyl Chloride	1974	1 /1979	5 years
Chromium (VI) Compounds	1974	1/2012	38 years
Benzene	1979	1 /2012	33 years
Erionite	1982	1/2012	30 years
Trichloroethylene	1986	1 /2014	28 years

\* first evidence as experimental carcinogen

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### Ignored early warnings of the RI

Agent/Compound	CMCRC-RI*	IARC Group/year	Prediction
Styrene-7,8-oxide	1988	2A/1994	6 years
Dichloromethane	1988	2A/2016	28 years
Silica dust	1988	1/2012	24 years
Asbestos (all forms)	1989	1/2012	23 years
Formaldehyde	1989	1 /2012	23 years

\* first evidence as experimental carcinogen

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### Ignored early warnings of the RI

Agent/Compound	CMCRC-RI*	IARC Group/year	Prediction
Tamoxifen	1997	1/2012	15 years
Diesel (engine exhaust)	1997	1/2013	16 years
Ethanol (alcoholic beverages)	2002	1/2012	10 years
Acetaldehyde (alcoholic beverages)	2002	1/2012	10 years
Fluoro-edenite	2004	1/2017	13 years

\* first evidence as experimental carcinogen

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### ELF-EMF and RFR: Funding

The projects on ELFEMF and RFR (about € 10.000.000) up to now were supported by:

- Ramazzini Institute Associates, Bologna, Italy (≈ 60%)
- Ministry of Health, Italy
- National Institute for Insurance Against Injuries at Work (INAIL, ex ISPESL), Italy
- Regional Agency for Prevention and the Environment (ARPA) of the Emilia-Romagna Region, Italy
- Monte of Bologna and Ravenna Bank Foundation, Bologna, Italy
- Cassa di Risparmio Bank Foundation, Bologna, Italy
- Liberal donations from private NGOs, philanthropist and citizens: among them, Environmental Health Trust and Children With Cancer, UK

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### Thanks for your attention



*“The reward of great men is that, long after they have died, one is not quite sure that they are dead”*

Jules Renard, 1864 -1910

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