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The carcinogenic potential of non-ionizing radiations: The cases of S-50 Hz MF and 1.8 GHz GSM radiofrequency radiation

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Abstract

Epidemiological studies have suggested that human exposure to extremely low-frequency electromagnetic fields from the electric power and to mobile phone radiofrequency electromagnetic fields induce an increased risk of developing malignant tumours. However, no adequate laboratory data, in particular long-term carcinogenicity bioassays to support the epidemiological evidence, have yet been available. This motivated the Ramazzini Institute to embark on a first project of four large life-span carcinogenic bioassays conducted on over 7000 Sprague Dawley rats exposed from prenatal life until natural death to S-50 Hz MF alone or combined with gamma radiation or formaldehyde or aflatoxin B1. Results now available from these studies, which started concurrently, have shown that exposure to Sinusoidal-50 Hz Magnetic Field (S-50 Hz MF) combined with acute exposure to gamma radiation or to chronic administration of formaldehyde in drinking water induces a significantly increased incidence of malignant tumours in males and females. A second project of two large life-span carcinogenic bioassays was conducted on over 3000 Sprague Dawley rats exposed from prenatal life until natural death to 1.8 GHz GSM of mobile phone radio base station, alone or combined with acute exposure to gamma radiation. Early results from the experiment on 1.8 GHz GSM alone show a statistically significant increase in the incidence of heart malignant schwannoma among males exposed at the highest dose.

KEYWORDS

cancer promotion, carcinogenicity, co-carcinogenesis, extremely low-frequency magnetic fields, mobile phone, radiofrequency radiation, schwannoma, Sprague Dawley rats

1 | INTRODUCTION

Much has long been known about the carcinogenic potential for human beings of short-wave/high-frequency electromagnetic fields, so-called ionizing radiation. No adequate scientific studies were conducted until the end of the 1970s on electromagnetic non-ionizing radiation carcinogenicity. The explanation was that because non-ionizing radiations do not have sufficient energy to alter the DNA directly, it was not "logical" to speculate on the existence of potential long-term effects, such as cancers, being induced by other possible biological mechanisms.

The first information on the potential carcinogenic risks associated with exposure to non-ionizing radiations arose in 1979 when Wertheimer and Leeper showed for the first time that children exposed residentially to extremely low-frequency electromagnetic fields (ELFEMF) had a significantly increased risk of developing leukaemia.[1] The perception that other types of non-ionizing radiations of higher frequency might induce potential carcinogenic risks focused

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the attention of public health and the scientific community in the 1990s particularly after the increased use of cell phones. In fact, in the past two decades, the rapid expansion of cell phones and cordless communication systems and of radio-television information networks has been without precedent. The use of these systems has brought about the diffusion of radiofrequency electromagnetic fields (RFEMF), generated by various sources, in both working and living environments.

After the paper of Wertheimer and Leeper, several other epidemiological studies were carried out around the world supporting the possible association between exposure to 50/60 Hz electromagnetic fields (EMF) and cancer risks in children and adults. In 1982, Milham reported a correlation between leukaemia and ELFEMF exposure in adults.[2] Subsequently, an excess of breast cancer was observed among males exposed to ELFEMF.[3-6] In 2000, a pooled analysis reported a significantly increased risk of leukaemia among children exposed to over 0.3-0.4 μT.[7] In 2002, the International Agency for Research on Cancer (IARC) considered 50/60 Hz EMF as a possible carcinogen for human being (group 2B).[8] Further, case-control studies and a pooled analysis based on primary data confirmed the evidence of an approximately two times increased risk of leukaemia in children exposed to magnetic field levels of 0.3-0.4 μT.[9-11]

Concerning the potential carcinogenic risks of mobile phone radiofrequency radiation (RFR), the first alert appeared at the end of the past century when Hardell reported the results from case-control studies on use of cellular phones and brain tumour risk[12,13] and later when he published a statistically significantly increased risk of schwannoma[14] for ipsilateral use of mobile phone. More recently, two epidemiological case-control studies proved more informative, showing that the risk of developing brain tumours and acoustic nerve schwannomas was higher than in controls when cumulative use was considered.[15,16] In 2011, as published in the Monograph 2013,[17] the IARC classified the RFR from mobile phones as a possible human carcinogen (group 2B) based on an association between high mobile phone use and glioma of the brain and acoustic neurinoma.

However, the epidemiological evidence was deemed not to provide sufficient qualitative and quantitative data for use as a guideline prompting action to safeguard public health. More adequate laboratory data were required, in particular long-term carcinogenicity bioassays in rodents reproducing human exposure situations as closely as possible, and short-term in vivo and in vitro studies performed with a view to understanding how non-ionizing radiations may induce carcinogenic effects or enhance the effects of known carcinogens or genotoxic agents.

This background motivated the Italian Ramazzini Institute (RI) to embark on two large systematic and integrated projects of long-term bioassays on rodents to evaluate (a) the carcinogenic potential of non-ionizing radiations focusing on Sinusoidal-50 Hz magnetic field (S-50 Hz MF) from electric power and (b) the carcinogenic potential of the RFEMF 1.8 GHz GSM in a far field situation reproducing the environmental exposure generated by the antennae of mobile phone radio base stations. The distinctive common characteristics of these two projects were (a) the use of a large number of male and female rats per group in order to increase the sensitivity of the studies; (b) use in all experiments of Sprague Dawley rats from the colony of the Cesare Maltoni Cancer Research Center whose expected tumorigram and fluctuations are based on data deriving from more than 20 000 historical controls held in the same environmental and diet standards; (c) starting the exposure to S-50 Hz MF or 1.8 GHz GSM, 19 h/d, from prenatal life exposing the female breeders from the 12th day of pregnancy and continuing the exposure of the offspring until natural death; (d) inclusion of all rats in each litter in order to consider potential family effects.

Concerning the conduct of experiments, all the animals were kept in highly standardized environmental and diet conditions; feed and water consumptions as well as body-weight were measured every 2 weeks for the first 8 weeks and then every 4 weeks until the end of the experiments. All dead animals were submitted to complete necropsy, and the organs and tissues were collected and preserved in a 70% solution of Solvanol (a mixture of ethyl and isopropyl alcohol, 60% and 40%, respectively) and 30% of distilled water and finally embedded in paraffin blocks while 3-5 μm sections were cut and routinely stained with haematoxylin-eosin. All lesions were trimmed including adjacent normal tissue. Statistical evaluation of the difference in incidence of the various malignant tumours was based on the Cox proportional hazard regression model,[18] which was adjusted for possible differential survival, and on Fisher's exact test. The *P* values are given in the tables. For those end-points for which some dose groups had no cases, a simple Mantel-Haenszel test was used since there was no difference in survival between the exposed groups.

Up to now, the results of the experiments on S-50 Hz MF alone or combined with formaldehyde or γ radiation have already been published[19-21] as well early results on 1.8 GHz GSM.[22]

1.1 | Project on a sinusoidal-50 hz magnetic field (s-50 hz mf)

The study on the carcinogenic potential of S-50 Hz MF was planned as an integrated project including four experiments, trying to reproduce potential human exposure situations as exposure to S-50 Hz MF alone, to assess its potential qualitative and quantitative carcinogenic effects with reference to intensity and continuity/discontinuity of electric current; or to assess the capacity of S-50 Hz MF to enhance the carcinogenic effects of low exposure to known carcinogenic agents such as γ radiation or formaldehyde or aflatoxin B1.

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In all, the project encompassed four experiments performed with 7133 rats. The four experiments in this project started concurrently in order to compare the effects of the different exposure situations to which workers or the general population may be exposed. In order to provide the same environmental conditions, all rats in the four experiments were located in the same room, measuring 900 m^2. The details as to the generation of the experimental rats and of the exposure apparatus have already been reported[19].

The plan of the project is outlined in Table 1. The control group for experiment 1 is common to experiments 2 and 3. Experiment 4 had its own control group.

1.2 | Experiment on S-50 Hz MF alone

As reported in the literature, up to now four long-term carcinogenicity bioassays have been performed to assess the carcinogenic potential of 50-60 Hz MF on rats.[23-26]

Altogether, the results of these studies did not show any carcinogenic effects from ELFMF. However, some doubts were raised in the scientific community concerning the design and conduct of those studies, with particular regard to the number of animals per group and sex, the starting of exposure at mature age and the duration of the experiments, which was no more than 110 weeks (equivalent to two thirds of the life of the animals), too short to identify rare pathological lesions in later life. For this reason, the Ramazzini Institute planned an experiment with a large number of rats, starting the exposure from prenatal life and continuing observation until natural death. The plan and the results referring to the incidence of animals bearing malignant tumours are reported in Table 2. In the test conditions, as already reported,[21] the exposure to S-50 Hz MF alone did not show any statistically significant difference in the incidences of treated rats bearing malignant tumours compared to controls, or indeed for what concerns any target organs and tissues. These results

TABLE 1 The integrated project on S-50 Hz MF: overall design

Experiments	No. of Sprague Dawley rats	Treatment[a] (μ-T)	Other treatment	Duration	State of the art
Experiment[21] 1[b]	5029	0; 2; 20; 100; 1000	—	Life-span	Completed
Experiment[20] 2	805	0; 1000	Formaldehyde, 50 ppm in drinking water from 6 wk of age and continued for 104 wk	Life-span	Completed
Experiment[19] 3	657	0; 20; 1000	γ radiation, 0.1 Gy, one shot at 6 wk of age	Life-span	Completed
Experiment 4[c]	642	0; 1000	Aflatoxin B1, 70 μg/d × 9 d, between 6-7 wk of age	Life-span	In elaboration
Total	7133				

[a]The treatment with S-50 Hz MF started from foetal life and continued until spontaneous death.
[b]The first experimental control group was repeated in experiments 2 and 3.
[c]Experiment 4 had its own control group.

TABLE 2 Incidence of animals bearing malignant tumours in male (M) and female (F) Sprague Dawley rats exposed to S-50 Hz MF alone[21]

Group	Treatment[a] S-50 Hz MF (μT)	Animals		Animals bearing tumours	
		Sex	No.	Benign %	Malignant %
I	0 (control)	M	500	50.6	35.0
		F	501	68.1	42.5
II	2 C	M	500	50.2	35.0
		F	502	71.1	41.2
III	20 C	M	501	44.9	36.9
		F	502	69.7	41.8
IV	100 C	M	500	52.0	26.6
		F	500	73.0	40.6
V	1000 (on/off)	M	250	51.2	39.2
		F	250	70.8	48.0
VI	1000 C	M	253	52.4	34.1
		F	270	72.6	43.7

[a]Treatment for 19 h/d, intermittent (on/off) or continuous (C), starting on 12th day of pregnancy and continuing until natural death

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are consistent with the ones published by the US National Toxicology Program.[26]

1.3 | Experiment on S-50 Hz MF and formaldehyde

The intent of this study was to test whether exposure to S-50 Hz MF starting from prenatal life and continuing until natural death of the rats could enhance the carcinogenic effects of formaldehyde, a widely produced and used chemical agent considered by IARC to be carcinogenic for human beings, causing cancer of the nasopharynx and leukaemia.[27] Occupational formaldehyde exposure occurs in formaldehyde factories, disinfection in hospitals, in embalming and anatomy laboratories, furniture factories, paper mills, the building and construction industry, and foundries. Formaldehyde is produced by automobile oxygenated fuel combustion; it is present in offices and public buildings, in residential indoor air, in some foods as a biostatic agent, such as cheese, and in cigarette smoke. Indeed, hundreds of millions of people may be exposed at a very low dose of formaldehyde during their working life or in the general environment and concurrently be exposed to ELFEMF from electric power.

In this experiment, groups of 200 male and 203 female Sprague Dawley rats were exposed to 1000 μT from day 12 of foetal life until natural death and to 50 ppm of formaldehyde in drinking water starting from 6 weeks of age and continuing for 104 weeks, and then observed until natural death. Moreover, a group of 253 males and 270 females were exposed to 1000 μT alone, a group of 200 males and 202 females were exposed to formaldehyde alone, and one group of 500 males and 501 females served as a negative control group. All rats were observed until natural death. The concentration of 50 ppm of formaldehyde in drinking water was selected because in a previous experiment, conducted at the RI on Sprague Dawley rats to test the carcinogenic potential of this agent administered in drinking water at various concentrations, this dose did not show any significantly increased carcinogenic effect.[28,29]

In this experiment, males exposed to formaldehyde or to S-50 Hz MF alone compared to negative controls did not show any significant differences in the incidence of rats bearing malignant tumours and hemolymphoreticular neoplasias (HLRN); when rats were treated with formaldehyde and S-50 Hz MF combined, a statistically significantly increased incidence in males bearing malignant tumours ($P \leq 0.05$) and HLRN ($P \leq 0.05$) was observed (Table 3).

Concerning C-cell carcinomas of the thyroid (Table 4), a statistically significantly increased incidence was observed in males treated with formaldehyde and S-50 Hz MF compared to negative controls ($P \leq 0.01$) and compared to the group treated only with S-50 Hz MF ($P \leq 0.05$). When C-cell carcinomas were aggregated to adenomas, a significantly increased incidence ($P \leq 0.01$) was observed in females treated with formaldehyde compared to negative controls.

1.4 | Experiment on S-50 Hz MF and acute exposure to γ radiation

The aim of this study was to test whether the long-term carcinogenic risks of acute low-dose γ radiation (0.1 Gy) delivered to rats at a young age (6 weeks) may be enhanced by exposure to S-50 Hz MF starting from prenatal life and continuing until natural death.

TABLE 3 Incidence of animals bearing malignant tumours and hemolymphoreticular neoplasias (HLRN) in male (M) and female (F) Sprague Dawley rats exposed to S-50 Hz MF and/or formaldehyde[20]

	Treatment		Animals			
Group	S-50 Hz MF[a] (μT)	Formaldehyde[b] (mg/L)	Sex	No.	Animals bearing malignant tumours %	HLRN %
I	0 (negative control)[c]	0	M	500	35.0	16.6
			F	501	42.5	13.6
II	0 (positive control)	50	M	200	41.5	22.0
			F	202	47.0	11.4
III	1000 C	0	M	253	34.0	14.2
			F	270	43.7	16.3
IV	1000 C	50	M	200	48.5*,**	23.5**
			F	203	37.9	12.3

[a]Treatment for 19 h/d, continuous (C), starting on 12th day of pregnancy and continuing until natural death.
[b]Formaldehyde was administered in drinking water for 104 wk, starting at 6 wk of age.
[c]The negative control group is common with Experiment 1.
*Statistically significant ($P \leq 0.01$) compared to negative control.
**Statistically significant ($P \leq 0.05$) compared to males treated to 1000 μT alone (group III).

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This type of combined exposure is not unusual in the human workplace or in general life. Thus, during a computed tomography (CT) test, adults may receive a radiation dose of at least 15 mGy per scan and children more or less 30 mGy, while if we consider that on average each examination entails 2-4 scans,[30] the cumulative exposure in children corresponds to more or less 120 mGy (≥0.1 Gy).

In this experiment, groups of 223 (group II), 212 (group III), 222 (group IV) male and female rats were exposed to 0.1 Gy at 6 weeks of age and to 0, 20, 1000 S-50 Hz MF, respectively, from prenatal life until natural death. One group of 500 males and 501 females (group I) served as negative controls. All the four experimental groups encompassed 1658 rats. The dose of the positive controls (0.1 Gy) was selected so as to have a comparison with the results of a previous larger experiment on the carcinogenicity of γ radiation, in which the lowest dose tested was 0.1 Gy.[31] The results of the study are reported in Tables 5-8.

Table 5 shows that exposure to 1000 μT S-50 Hz MF plus 0.1 Gy induces a statistically significant dose-related increase ($P \leq 0.01$) in males bearing malignant tumours compared to negative controls, in particular at the highest

TABLE 4 Incidence of animals bearing C-cell tumours of thyroid in male (M) and female (F) Sprague Dawley rats exposed to S-50 Hz MF and /or formaldehyde[20]

	Treatment		Animals		C-cell tumours		
Group	S-50 Hz MF[a] (μT)	Formaldehyde[b] (mg/L)	Sex	No.	Adenomas %	Carcinomas %	Adenomas plus carcinomas %
I	0 (negative control)	0	M	500	4.0	1.0	5.0
			F	501	2.0	1.6	4.0
II	0 (positive control)	50	M	200	6.0	1.5	8.0
			F	202	7.0	2.5	9.9*
III	1000 C	0	M	253	4.3	1.2	5.5
			F	270	5.0	1.1	6.3
IV	1000 C	50	M	200	4.0	4.0*****	8.0
			F	203	3.0	1.5	4.4

[a]Treatment for 19 h/d, continuous (C), starting on 12th day of pregnancy and continuing until natural death.
[b]Formaldehyde was administered in drinking water for 104 wk, starting at 6 wk of age.
*Statistically significant ($P \leq 0.01$) compared to negative control (group I).
**Statistically significant ($P \leq 0.01$) compared to negative control.
***Statistically significant ($P \leq 0.05$) compared to males exposed to 1000 μT alone (group III).

TABLE 5 Incidence of animals bearing malignant tumours and hemolymphoreticular neoplasias (HLRN), compared to negative controls, in male (M) and female (F) Sprague Dawley rats exposed to S-50 Hz MF and/or γ radiation[19]

	Treatment		Animals		Animals bearing malignant tumours	
Group	S-50 Hz MF[a] (μT)	γ radiation[b] (Gy)	Sex	No.	%	HLRN %
I	0 (negative control)	0	M	500	35.0**	16.6
			F	501	42.5*	13.6
II	0 (positive control)	0.1	M	118	39.0	15.3
			F	105	44.8	12.4
III	20 C	0.1	M	105	51.4	18.1
			F	107	59.8	19.6
IV	1000 C	0.1	M	110	54.5[†]	25.5[††]
			F	112	51.8	14.3

[a]Treatment for 19 h/d, continuous (C), starting on 12th day of pregnancy and continuing until natural death.
[b]Administered one off at 6 wk of age.
*Near negative control incidence are *P*-values ($P \leq 0.05$) or
**($P \leq 0.01$) associated with the Cox regression model for trend analysis.
[†]Statistically significant ($P \leq 0.01$) compared to negative control;
[††]($P \leq 0.05$) compared to negative control performed with Cox proportional hazard model.

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TABLE 6 Incidence of animals bearing atypical precursors or mammary adenocarcinomas compared to negative controls in male (M) and female (F) Sprague Dawley rats exposed to S-50 Hz MF and/or γ radiation[19]

Group	Treatment S-50 Hz MF[a] (μT)	γ radiation[b] (Gy)	Animals		Animals bearing atypical precursors[c] %	Animals bearing adenocarcinomas %	Animals bearing atypical precursors or adenocarcinomas[d] %
			Sex	No.			
I	0 (negative control)	0	M	500	0.0‡	0.2§	0.2‡‡
			F	501	3.0‡‡	6.4§	9.4‡‡
II	0 (positive control)	0.1	M	118	0.8	—	0.8
			F	105	3.8	7.6	11.4
III	20 C	0.1	M	105	1.0	2.9*	3.8††
			F	107	13.1††	7.5	20.6††
IV	1000 C	0.1	M	110	1.8†	0.9	2.7†
			F	112	11.6†	16.1*	27.7††

[a]Treatment for 19 h/d, continuous (C), starting on 12th day of pregnancy and continuing until natural death.
[b]Administered one off at 6 wk of age.
[c]Mammary gland atypical precursors include atypical hyperplasia in single mammary gland or in fibroadenoma; they are counted only once according to the most severe lesion.
[d]Animals bearing more than one type of lesion are plotted only once according to the most severe lesion.
*Statistically significant ($P \leq 0.01$) performed with Cox proportional hazard model.
†Statistically significant ($P \leq 0.05$) or
††($P \leq 0.01$) performed with the Mantel-Haenszel test for the analysis.
‡Near the control incidence are the *P*-values ($P \leq 0.05$) or
‡‡($P \leq 0.01$) for the trend analysis (excluding the 0.1 Gy group).
§Near the control incidence is the *P*-value ($P \leq 0.01$) (excluding the 0.1 Gy group) performed with Cox regression model for trend analysis.

exposure. A significantly increased incidence of HLRN was also observed in males treated with 1000 μT S-50 Hz MF plus 0.1 Gy ($P \leq 0.05$).

The incidences of mammary lesions are reported in Table 6. No statistically significant differences in atypical precursors or adenocarcinomas were observed in males and females treated with 0.1 Gy compared to negative controls. Comparing untreated controls (excluding group II) with animals treated with 1000 μT or 20 μT plus 0.1 Gy, we observed in the mammary gland: (a) a significantly increased, dose-related incidence of atypical precursors in males ($P \leq 0.05$) and females ($P \leq 0.01$), in particular in females treated with 20 μT plus 0.1 Gy ($P \leq 0.01$) and in both males and females treated with 1000 μT plus 0.1 Gy ($P \leq 0.05$); (b) a statistically significantly increased, dose-related incidence of adenocarcinomas in males ($P \leq 0.01$) and females ($P \leq 0.01$), in particular in males exposed to 20 μT plus 0.1 Gy ($P \leq 0.01$) and in females exposed to 1000 μT plus 0.1 Gy ($P \leq 0.01$); (c) when rats bearing atypical precursors were combined with rats bearing adenocarcinomas, a significantly increased, dose-related incidence was observed in both males ($P \leq 0.01$) and females ($P \leq 0.01$), in particular in males and females exposed to 20 μT plus γ radiation ($P \leq 0.01$, respectively) and in males and females exposed to 1000 μT plus γ radiation ($P \leq 0.05$ and $P \leq 0.01$, respectively).

Table 7 reports the incidences of animals bearing mammary gland atypical precursors or aggregated adenocarcinomas, and the incidence of HLRN compared to the group of male and female rats exposed only to 0.1 Gy. The data show a still significantly increased dose-related incidence of animals bearing mammary gland atypical precursors or adenocarcinomas in males and females ($P \leq 0.01$, respectively) and in particular in males exposed to 20 μT plus γ radiation ($P \leq 0.01$) as well as in males and females exposed to 1000 μT plus γ radiation ($P \leq 0.05$ and $P \leq 0.01$, respectively). Concerning HLRN, a statistically significant increased incidence was observed in males exposed to 1000 μT plus γ radiation ($P \leq 0.05$).

The incidences of malignant schwannomas of the heart are reported in Table 8. When compared to untreated controls, the data show a significantly increased incidence of malignant heart schwannomas in males exposed to 20 or 1000 μT plus γ radiation ($P \leq 0.05$ or $P \leq 0.01$, respectively) with a statistically significantly positive trend ($P \leq 0.01$).

1.5 | The RI project on 1.8 GHz GSM base station RFR

In 2005, the Ramazzini Institute started the experimental project to evaluate the potential carcinogenic effects of far field 1.8 GHz GSM RFR generated by radio base stations for the mobile phone. The reason why it was chosen to study the effects of environmental exposure to RFR was to draw attention to the possible consequences for the public caused by diffuse environmental exposure to RFR in the workplace and in various outdoor/indoor domestic/public micro-environments. As reported, in fact, the mean total RFR exposure in various outdoor micro-environments

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lies between 0.23 V/m in non-central residential areas, to 1.85 V/m in a university area, which means that exposure levels tend to increase with increasing urban density and, as reported, that mobile phone base stations are the most important contributors.[32]

The RI project on RFR encompasses two long-term bioassays on Sprague Dawley rats. The plan of the project is reported in Table 9. In the first study, the rats were exposed to only 1.8 GHz GSM radiation; in the second study, the animals were exposed to 1.8 GHz GSM radiation and to an acute dose of ionizing radiation. Here are the early results of the experiment on 1.8 GHz GSM RFR alone.

The exposure apparatus representative of an environmental exposure to a far field 1.8 GHz mobile phone base station included the following parts: (a) the main generator unit; (b) an external control group; (c) the transmitting antenna and (d) a feedback probe. The details of the exposure apparatus have already been reported.[22] The rats were located in four rooms totally shielded with RFR absorbent material.

1.6 | Experiment on far field 1.8 GHz GSM base station RFR alone

Results of long-term carcinogenicity studies on experimental animals, rats and mice, exposed to RFR have been summarized by IARC.[17] Several studies on mice undergoing whole-body exposure to RFR did not show any statistically significantly increased incidence of tumours at any sites compared to controls. The few long-term carcinogenicity studies on rats conducted in the past failed to show any carcinogenic effects,[33-36] apart from one study in which 100 male Sprague Dawley rats exposed to RFR as pulsed microwaves showed an increased incidence in total malignant tumours.[37] Overall, these bioassays did not show any evidence that RFR induces an increase in the incidence of malignant tumours in the test conditions. However, it must be noted that most of these experiments suffered from some form of inadequacy regarding the study design, in particular concerning the number of animals, the duration of exposure and of observation.

Recently, the US National Toxicology Program (NTP) published two Technical Reports on the results of carcinogenesis studies in HSD: Sprague Dawley rats[38] and B6C3F1/N mice exposed to whole-body near-field CDMA or GSM RFR[39] modulated at two frequencies (900 and 1900 MHz) as used by mobile phones in the USA. The study design, the conduct of the experiments and the results were reviewed by an external panel of pathologists and other scientific experts. Overall, the NTP studies found (a) clear evidence of malignant schwannomas in the hearts of male rats; (b) some evidence of malignant gliomas in the brain of male rats; (c) some evidence of tumours in the adrenal glands of male rats; (d) there was equivocal evidence of carcinogenic effects of GSM-modulated cell phone RFR at 900 MHz in female rats (schwannoma of the hearth); (e) equivocal evidence of CDMA-modulated cell phone RFR at 900 MHz in female rats (regarding malignant schwannoma of the heart, malignant glioma of the brain, benign, malignant or complex pheochromocytoma (combined) of adrenal medulla. Equivocal evidence of carcinogenicity of GSM-modulated cell phone RFR at 1900 MHz was observed in male B6C3F1/N (combined incidences of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma in the skin and combined alveolar/bronchiolar adenoma or carcinoma of the lung) and

TABLE 7 Incidence of animals bearing atypical precursors or mammary adenocarcinomas and haemolymphoreticular neoplasias (HLRN) compared to 0.1 Gy positive control in male (M) and female (F) Sprague Dawley rats exposed to S-50 Hz MF and/or γ radiation[19]

Group	Treatment S-50 Hz MF[a] (μT)	γ radiation[b] (Gy)	Animals		Animals bearing mammary gland atypical precursors or adenocarcinomas %	Animals bearing HLRN %
			Sex	No.		
I	0 (positive control)	0.1	M	118	0.8[†]	15.3
			F	105	11.4[†]	12.4
II	20 C	0.1	M	105	3.8[**]	18.1
			F	107	20.6	19.6
III	1000 C	0.1	M	110	2.7[*]	25.5[‡]
			F	112	27.7[**]	14.3

[a]Treatment for 19 h/d, continuous (C), starting on 12th day of pregnancy and continuing until natural death.

[b]Administered one off at 6 wk of age.

[c]Mammary gland atypical precursors include atypical hyperplasia in single mammary gland or in fibroadenoma; they are counted only once according to the most severe lesion.

*Statistically significant ($P \leq 0.05$) or

**($P \leq 0.01$) performed with the Mantel-Haenszel model for the analysis (used for incidental lesions).

[†]Near the 0.1 Gy group (positive control) incidence is the P-value ($P \leq 0.01$) performed with the Mantel-Haenszel model for trend analysis.

[‡]Statistically significant compared to 0.1 Gy group ($P \leq 0.05$)

[‡‡]performed with Cox proportional hazard model.

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TABLE 8 Incidence of animals bearing heart malignant schwannomas in male (M) and female (F) Sprague Dawley rats exposed to S-50 Hz MF and/or γ radiation compared to untreated controls[19]

Group	Treatment S-50 Hz MF[a] (μT)	γ radiation[b] (Gy)	Animals		Animals bearing heart malignant Schwannomas	
			Sex	No.	No.	%
I	0 (negative control)	0	M	500	1	0.2[†]
			F	501	0	—
II	0 (positive control)	0.1	M	118	0	—
			F	105	1	1.0
III	20 C	0.1	M	105	2	1.9*
			F	107	1	0.9
IV	1000 C	0.1	M	110	3	2.7**
			F	112	0	—

[a]Treatment for 19 h/d, continuous (C), starting on 12th day of pregnancy and continuing until natural death.
[b]Administered one off at 6 wk of age.
*Statistically significant ($P \leq 0.05$) or
**($P \leq 0.01$) performed with Cox proportional hazard model.
[†]Near control incidence is the P-value ($P \leq 0.01$) (excluding the 0.1 Gy group) performed with Cox regression model for trend analysis.

in females (malignant lymphoma, all organs). Equivocal evidence of carcinogenicity of CDMA-modulated cell phone RFR at 1900 MHz was also observed in males (hepatoblastoma of the liver) and in female B6C3F1/N (malignant lymphoma, all organs). These conclusions, as reported by NTP, represent the consensus between NTP and the external panel of scientific experts.

The results of the NTP study on rats motivated the Ramazzini Institute to publish the early results of its study on 1.8 GHz GSM dealing with the evaluation of the preneoplastic and neoplastic lesions of the heart and of the brain.[22]

The experiment encompasses three groups of 817, 811 and 411 male and female Sprague Dawley rats exposed, respectively, to 5, 25 and 50 V/m for 19 h/d from prenatal life (exposing the female breeders from the 12th day of pregnancy) and continuing the exposure of the offspring until natural death. A fourth group of 412 male and 405 female rats served as controls. In Table 10, the data show a significantly increased incidence ($P \leq 0.05$) of malignant schwannoma of the heart in males exposed to 50 V/m. When, at this dose level, the incidences of preneoplastic hyperplasia of Schwann cells are combined with malignant schwannomas, the statistical significance proves to be much higher ($P \leq 0.01$). These findings are consistent with the results from the NTP study and demonstrate the reproducibility of the carcinogenic effects of RFR on the Schwann cells of the heart.[40]

Table 11 shows the results of a histopathological evaluation of the benign and malignant lesions of the meninges and the brain. The data show a non-statistically, significantly increased, dose-related incidence in malignant tumours of the brain, which include oligodendroglioma, astrocytoma and mixed glioma.

The histopathological evaluation of all experimental animals is still in progress and is expected to be finalized at the end of this year.

1.7 | Experiment on 1.8 GHz GSM base station RFR and acute exposure to γ radiation

Several studies have been conducted to investigate the potential promotional and co-carcinogenic effects of RFR combined with exposure to chemical or, physical agents.[17] The majority of

TABLE 9 The RI integrated project on 1.8 GHz GSM base station RFR signal: overall design

Experiments	No. of Sprague Dawley Rats	Treatment[a] (V/m)	Other treatments	Duration	State of the art
Experiment[22] 1	2448	0; 5; 25; 50	—	Life-span	Early results
Experiment 2	617	0; 25; 50	γ radiations, 0.1 Gy one shot at 6 wk of age	Life-span	In elaboration
Total	3065				

[a]The 19 h/d treatment started the 12th day of pregnancy and continued until natural death.

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such studies did not show an enhancement of the carcinogenic effects. However, in one study of co-carcinogenesis, pregnant mice were exposed to RFR from day 6 of gestation and to ethylnitrosourea (ENU), injected intraperitoneally, on day 14 of gestation; the exposure of the offspring to RFR then continued for 2 years. The mice exposed to ENU and RFR showed an increased incidence of bronchiole-alveolar carcinoma and hepatocellular adenoma.[41] Later, the same results were replicated by Lerchl et al[42] in a study reproducing the same experimental design. These results demonstrated the reproducibility of the long-term tumour-promoting effects of RFR at non-thermal exposure levels.

On the basis of the results obtained with studies on ELFMF combined with exposure to formaldehyde or γ radiation, the RI planned an experiment in which Sprague Dawley rats were exposed to 1.8 GHz GSM far field RFR from prenatal life until natural death as well as to an acute low dose of γ radiation. In this experiment, two groups of 224 and 184 male and female Sprague Dawley rats were exposed to γ radiation (0.1 Gy) at 6 weeks of age and to 25 or 50 V/m, respectively, from prenatal life (12th day of gestation) until natural death; one group of 209 male and female rats served as negative controls. The biophase has ended, and histopathological evaluation of all rats is in progress; the final elaboration of the results being expected for the end of this year.

2 | DISCUSSION

All the experiments conducted by the RI on S-50 Hz MF and 1.8 GHz GSM RFR proceeded smoothly without any critical setbacks despite the large dimension of the projects.

The study on S-50 Hz MF alone confirmed the results of the NTP, despite the higher sensitivity of the RI study design, which consisted of a larger number of animals per group and above all a prenatal start to exposure and the life-span duration of the study.

Our studies on S-50 Hz MF combined with exposure to a known carcinogen demonstrated for the first time that: (a) concurrent exposure to S-50 Hz MF from prenatal life until natural death and to formaldehyde in drinking water for 104 weeks induces a significantly increased incidence of animals bearing malignant tumours and HLRN in males; thyroid C-cell carcinomas were significantly increased in males and also in females when carcinomas were aggregated to adenomas; (b) the exposure to S-50 Hz MF from prenatal life until death enhanced the carcinogenic effects of acute exposure to γ radiation in mature age, namely animals bearing malignant tumours, HLRN and malignant schwannomas of the heart in males. Concerning mammary neoplasias, a significantly increased incidence was observed in males and females when exposed to 1000 μT as well as 20 μT MF.

All in all, these results clearly show the carcinogenic potential of the interaction between S-50 Hz MF and known carcinogens. This interaction is evident also at the lower intensity of 20 μT MF. These results cannot be compared to studies conducted in the past because of the different experimental design, the large number of rats per group, the exposure starting from prenatal life and the life-span duration of the study. Moreover, the fact that S-50 Hz MF may enhance the progression of a number of lesions from benign to malignant in situations where exposure to MF is combined with exposure to low doses of well-known carcinogens, as may happen in many workplaces, is very important from a public health viewpoint.

Another interesting fact is that, unlike other past experiments suggesting no effects of promotion or co-carcinogenesis where the exposure to MF started after the treatment with the carcinogen, our studies started the exposure to MF much earlier than the treatment with the carcinogen. This might be a critical issue explaining the different effects and is worth investigating.

Our first results of the experiment on environmental exposure to 1.8 GHz GSM RFR in Sprague Dawley rats have

TABLE 10 Incidence of animals bearing hyperplasia Schwann cells or malignant Schwannoma of the heart in male (M) and female (F) Sprague Dawley rats exposed to far field 1.8 GHz GSM base station RFR signal[22]

Group	Treatment[a] (Volt/metre)	Animals		Hyperplasia Schwann cells %	Malignant Schwannoma %
		Sex	No.		
I	0 (control)	M	412	0.7	0.0
		F	405	0.5	1.0
II	5	M	401	0.5	0.7
		F	410	0.0	2.2
III	25	M	209	0.5	0.5
		F	202	0.0	0.5
IV	50	M	207	2.4	1.4*
		F	202	1.0	1.0

[a]Treatment for 19 h/d starting on the 12th day of pregnancy and continuing until natural death.
*Statistically significant ($P \leq 0.05$) performed with Fisher's exact test.

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TABLE 11 Incidence of animals bearing preneoplastic or neoplastic lesions of the brain in male (M) and female (F) Sprague Dawley rats exposed to far field 1.8 GHz GSM base station RFR signal[22]

		Animals		Tumours of meninges[b]		Brain lesions	
Group	Treatment[a] (V/m)	Sex	No.	Benign %	Malignant %	Glial cell hyperplasia %	Malignant tumours[c] %
I	0	M	412	0.5	0.2	0.0	0.0
		F	405	0.0	0.2	0.2	0.5
II	5	M	401	1.0	1.0	0.0	0.7
		F	410	1.0	0.2	0.0	0.7
III	25	M	209	0.5	0.5	0.5	1.0
		F	202	1.0	0.0	0.0	1.0
IV	50	M	207	1.0	0.0	0.0	0.0
		F	202	1.0	0.0	0.0	1.5

[a]Treatment for 19 h/d, starting on 12th day of pregnancy and continuing until natural death.
[b]Tumour of the meninges include meningioma and granular cell tumours benign and malignant.
[c]Malignant tumours of the brain include oligodendroglioma, astrocytoma, mixed glioma.

shown a significantly increased incidence of malignant heart schwannomas. The fact that the same type of tumour was also observed in the NTP study simulating exposure to mobile phone antenna cannot be considered accidental. Completion of the histopathological examination of all rats in the study will add more information on the carcinogenic potential of RFR.

In conclusion, almost 40 years after the epidemiological demonstration of the carcinogenic effects of ELFEMF, the RI coming on top of the NTP studies should put an end to the fallacy that non-ionizing radiation may be considered safe for want of any demonstration of carcinogenicity in animal studies.

In 2007, at the first Prenatal Programming and Toxicity (PPTOX) Conference, and then in the MiniReview paper published in BCPT,[43] we recommended "to take into serious consideration the warnings provided by long-term experimental carcinogenic bioassays and in particular the ample epidemiological and experimental evidence demonstrating that developmental in conjunction with adult exposure to carcinogenic risks produce an overall increase in the incidence of malignant tumours."

Indeed, from what we already know as to the carcinogenic potential of ELFEMF and RFR, we must emphatically advocate caution, especially now that we are thinking of generalized electric forms of transportation and are at the fifth generation (5G) of mobile phones for wireless communication. Moreover, the new data available must prompt IARC, the WHO and other international regulatory agencies to re-evaluate their conclusions as to the carcinogenic risks of non-ionizing radiations. Nor should we forget what David Rall, past Director of NIEHS, predicted many years ago, long before cell phones: "Microwaves will be the environmental challenge of the 21st century."

CONFLICT OF INTEREST

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