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The 1.5 GHz Electromagnetic Near-field Used for Cellular Phones Does Not Promote Rat Liver Carcinogenesis in a Medium-term Liver Bioassay

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We have recently established that local exposure to a 929.2 MHz electromagnetic near-field, used for cellular phones, does not promote rat liver carcinogenesis in a medium-term bioassay system. In the present study, a 1.439 GHz electromagnetic near-field (EMF), another microwave band employed for cellular phones in Japan, was similarly investigated. Time division multiple access (TDMA) signals for the Personal Digital Cellular (PDC) Japanese cellular telephone standard system were directed to rats through a quarter-wavelength monopole antenna. Numerical dosimetry showed that the peak SARs within the liver were 1.91–0.937 W/kg, while the whole-body average specific absorption rates (SARs) were 0.680–0.453 W/kg, when the time-averaged antenna radiation power was 0.33 W. Exposure was for 90 min a day, 5 days a week, over 6 weeks, to male F344 rats given a single dose of diethylnitrosamine (200 mg/kg, i.p.) 2 weeks previously. At week 3, all rats were subjected to a two-thirds partial hepatectomy. At week 8, the experiment was terminated and the animals were killed. Carcinogenic potential was scored by comparing the numbers and areas of the induced glutathione S-transferase placental form (GST-P)-positive foci in the livers of exposed (48) and sham-exposed rats (48). Despite increased serum levels of corticosterone, adrenocorticotropic hormone (ACTH) and melatonin, the numbers and the areas of GST-P-positive foci were not significantly altered by the exposure. These findings clearly indicated that local body exposure to a 1.439 GHz EMF, as in the case of a 929.2 MHz field, has no promoting effect on rat liver carcinogenesis in the present model.

Key words: Cellular phone — 1.5 GHz electromagnetic field — Rat — Medium-term liver bioassay — Promotion of carcinogenesis

Epidemiological studies have indicated that exposure to magnetic fields is associated with an increased cancer risk in the general population.[1–5] This may be particularly the case for industrial high exposure to electric and/or magnetic fields, derived not only from 50 or 60 Hz power frequency sources, but also from high-frequency transmitters.[6,7] Equivocal evidence of increased risk of brain tumors and leukemia development has been presented.[8–13]

The use of portable cellular phones is rapidly expanding in many countries, and the potential health hazards to humans of the electromagnetic waves that they use is therefore of great concern. Although the possibility of a link with brain tumors has been raised,[14] an experimental study did not show any adverse effect of the electromagnetic field used for cellular phones on rat brain carcinogenesis.[15]

In Japan, a digital cellular system operating at 800 MHz (Personal Digital Cellular (PDC)-800) started service in 1993, followed by a 1.5 GHz system (PDC-1500) in 1994. We have already demonstrated that local exposure to a 929.2 MHz field (PDC-800 system), modulated in a PDC wave form, used for cellular phones, has no significant effect on rat liver carcinogenesis.[16] In the present study, the effects of a 1.439 GHz field (PDC-1500 system) were analyzed in the same system and the data obtained from the two experiments were compared.

We selected the rat liver medium-term bioassay since it requires only 8 weeks experimental duration and has been extensively validated.[17–22] This bioassay is considered to be suitable for detecting the risk potential of electromagnetic near-fields in terms of the effect on liver carcinogenesis. Since several studies have shown a link between melatonin levels and electromagnetic near-fields, an assessment of this hormone and other stress hormones in the blood was also included.

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MATERIALS AND METHODS

The exposure apparatus was specially designed,[23] and fundamentally the same as that used in our previous study (929.2 MHz),[16] except that a cylinder was added from the center of the ceiling in order to provide better air ventilation. Fig. 1 shows a diagrammatic representation of the exposure apparatus used.

A 1.439 GHz electromagnetic near-field (EMF) of the time division multiple access (TDMA) signal for the PDC (Japanese cellular telephone standard) system (50 pulse per second with a duty ratio of 33%) was directed at rats through a quarter-wavelength mono-pole antenna.

Numerical dosimetry showed that the peak specific absorption rates (SARs) within the liver were 1.91–0.937 W/kg, those in other tissues were 6.20–7.60 W/kg, and whole-body average SARs were 0.680–0.453 W/kg when the time-averaged antenna radiation power was 0.33 W.[24] Exposure lasted 90 min a day, for 5 days a week, over 6 weeks.

Fig. 2 shows the protocol for the medium-term liver bioassay employed. Male F344 rats (Charles River Japan Inc., Atsugi) at 5 weeks of age were randomly divided into 3 groups and housed 3 per cage with wood-chip bedding in an air-conditioned animal room at 24±2°C and 55±5% humidity, with a 12 h light/dark cycle. At the age

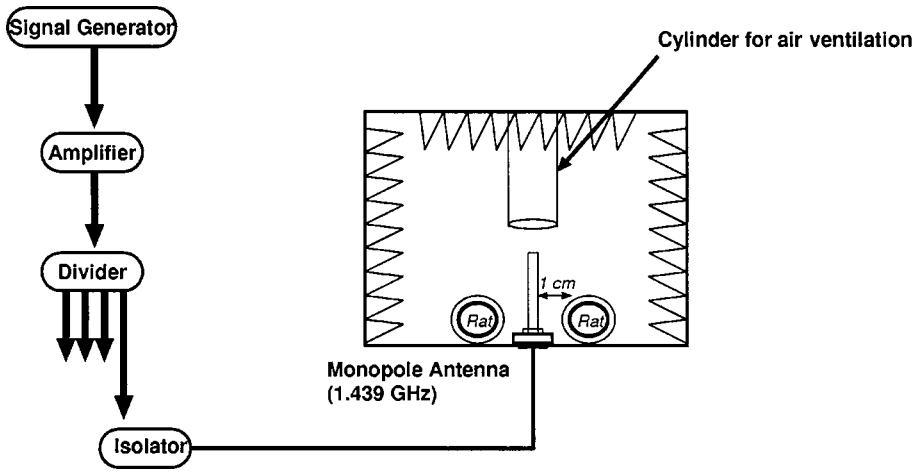

Fig. 1. Diagram of the exposure apparatus. Exposure conditions: frequency, 1.439 GHz; antenna input, 0.33 W (PDC modulation); animals, F344 male rats; duration, 90 min/day, 5 days/week, 6 weeks.

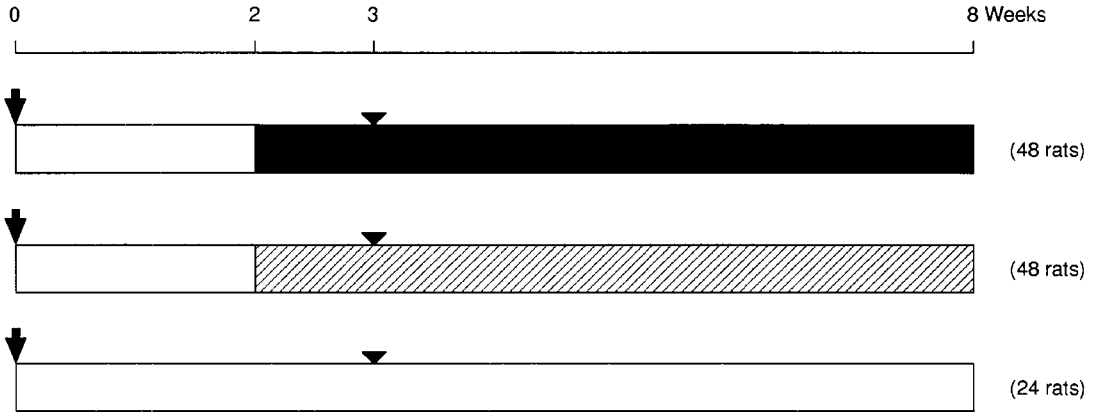

Fig. 2. Experimental protocol for assessment of electromagnetic near-field (1.439 GHz) effects in a medium-term liver bioassay. Animals, 6-week-old F344 male rats; ( ), number of animals examined; ■, exposure to the electromagnetic field (EMF, 1.439 GHz); ▨, sham exposure; ▼, diethylnitrosamine (DEN) 200 mg/5 ml saline/kg b.w., i.p.; ▼, two-thirds partial hepatectomy.

of 6 weeks, animals in Group 1 (EMF-exposed group) were given a single i.p. injection of diethylnitrosamine (DEN, >99% purity) at a dose of 200 mg/kg b.w., dissolved in saline, to initiate hepatocarcinogenesis and 2 weeks later, were exposed to EMF. Each animal was held in a narrow plastic cylinder (diameter 55 mm or 70 mm, depending on the animal's size) with many small holes for air ventilation. Two cylinders were placed on either side of the antenna, located at the center on the bottom of each exposure box (see Fig. 1), with a total of 12 boxes placed in separate rooms. Rats were not anesthetized during the exposure to EMF. All rats were subjected to two-thirds partial hepatectomy (PH) at week 3. On the day of the PH operation, the exposure procedure was not performed, but it was resumed on the next day (within 24 h). Animals in group 2 (sham-exposed group) were given DEN and PH, and served as a sham-exposure group, placed in the same cylinders in the exposure boxes in the same manner, but without actual exposure to EMF. Animals in group 3 (control group) received DEN and PH as in groups 1 and 2, but were kept in animal cages without being placed in the exposure boxes. The use of metals, which could influence the electromagnetic field, was avoided. Therefore, sutures instead of metal clips were used for the PH. Body weights were measured once a week. At the termination at week 8, animals were anesthetized with ether and blood samples were collected from the aorta (for hormone analysis) from 24 or 25 animals in each group before they were killed (between 9:30–12:00 in the morning). Then the livers were excised, weighed and cut into 2–3 mm thick sections. Four slices, one from each of the liver lobes, were fixed in ice-cold acetone for immunohistochemical demonstration of glutathione S-transferase placental form (GST-P)-positive foci. The following organs were weighed at autopsy and histopathologically analyzed; liver, spleen, kidneys, adrenal glands, thymus and testes. The organ weights relative to body weight (%) were calculated. Corticosterone, adrenocorticotropic hormone (ACTH) and melatonin were measured at SRL, Inc., Tachikawa, by radioimmunoassay. Melatonin was measured by a double-antibody radioimmunoassay based on the Kennaway G280 anti-melatonin antibody.[25)]

For analysis of preneoplastic lesion development, numbers and areas of GST-P-positive foci of more than 0.2 mm in diameter were measured using a color video image processor (SPICCA II, Nippon Avionics Co., Ltd., Tokyo), and data per cm^2 of liver section were calculated.

Statistical analysis was carried out using Student's t- or Welch's t-test after application of the preliminary *F*-test for equal variance.

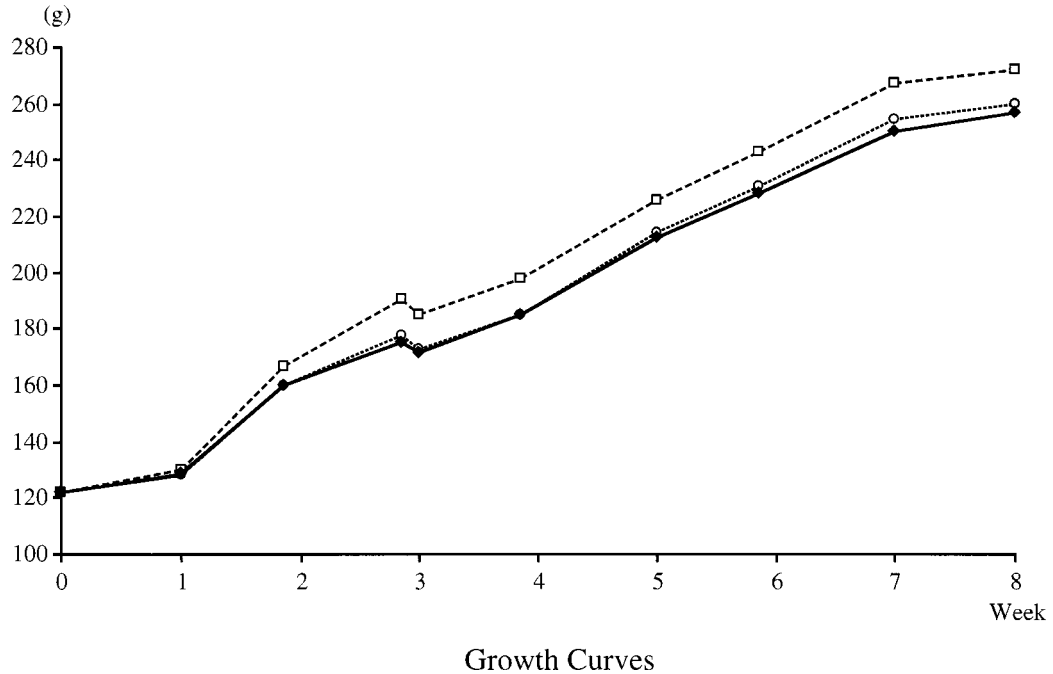

Fig. 3. Growth curves of rats in EMF-exposed, sham-exposed and control groups. Note the loss of body weight in each group apparent at week 3 after partial hepatectomy. ◆, EMF-exposure; ○, sham exposure; □, control.

Table I. Final Body (g), Absolute (g) and Relative (%) Organ Weights

Group No.	Treatment	No. of rats	Body weight	Liver (%)	Spleen (%)	Kidney (%)	Thymus (%)	Testes (%)	Adrenals (%)
1	EMF	47	257.2±12.6***	7.83±0.54*** (3.04±0.14*)	0.64±0.04$^{**,\#}$ (0.25±0.02)	1.61±0.10*** (0.63±0.03)	0.24±0.04* (0.09±0.02*)	2.72±0.29$^{*,\#}$ (1.06±0.12)	0.032±0.003 (0.013±0.001$^{***,\#\#}$)
2	Sham	45	260.5±10.0***	8.02±0.53*** (3.08±0.15)	0.66±0.04* (0.25±0.02)	1.64±0.08** (0.63±0.02)	0.23±0.03* (0.09±0.01*)	2.82±0.10 (1.08±0.05**)	0.031±0.004 (0.012±0.002**)
3	Control	24	272.8±9.5	8.58±0.66 (3.14±0.20)	0.69±0.07 (0.25±0.03)	1.70±0.10 (0.62±0.03)	0.25±0.02 (0.09±0.01)	2.84±0.13 (1.04±0.05)	0.031±0.002 (0.011±0.001)

*, **, *** Significantly different from the control group values at $P<0.05$, $P<0.01$ and $P<0.001$, respectively.
#, ## Significantly different from the sham group values at $P<0.05$ and $P<0.001$, respectively.

Table II. Corticosterone, ACTH and Melatonin Serum Levels in Rats Exposed to an Electromagnetic Near-field

Group No.	Treatment	No. of rats	Corticosterone (ng/ml)	ACTH (pg/ml)	Melatonin (pg/ml)
1	EMF	24	398.6±92.6$^{***,\#\#\#}$	141.4±24.0$^{*,\#\#\#}$	4.5±0.9$^{\#}$
2	Sham	24	181.8±47.1**	104.1±33.6*	3.9±0.6
3	Control	24	226.4±65.7	123.2±23.5	4.2±0.8

*, **, *** Significantly different from the control group value at $P<0.05$, $P<0.01$ and $P<0.001$, respectively.
#, ### Significantly different from the sham group value at $P<0.05$ and $P<0.001$, respectively.

RESULTS

Retardation in body weight gain was observed in the EMF-exposed (group 1) and sham-exposed (group 2) groups after week 2 of this experiment, following the onset of restraint in cylinders. However, no differences were evident between the two groups (Fig. 3). Food consumption levels at week 3 (before partial hepatectomy) were 12.4±1.0, 12.8±0.3 and 14.0±0.6 g/day/animal, and body weights at the same period were 175.4±10.5, 177.7±8.2 and 190.5±8.0 g in the EMF-exposed, sham-exposed and control groups, respectively. The values in the EMF-exposed and the sham-exposed groups were significantly decreased from those of the control ($P<0.001$). This was also the case for the final body weights (Table I).

One rat in group 1 and 2 rats in group 2 died after partial hepatectomy in group 1 (EMF), due to operation errors. In view of the need to place two rats in parallel near the antenna in the exposure box in order to ensure an equal exposure pattern, extra rats were substituted during the exposure period, but were not included as effective animals for any analysis.

Data for final body and absolute and relative organ weights are summarized in Table I. Absolute organ weights of the spleen and testes were significantly decreased in the EMF-exposed as compared to the sham-exposed group ($P<0.05$). However, the relative weights were not significantly different, except for the adrenal value, which was significantly increased in the EMF-exposed group over the sham-exposure group (Table I).

Table III. Quantitative Values for GST-P-positive Foci

Group No.	Treatment	No. of rats	GST-P-positive foci	
			No./cm^2	Area (mm^2)/cm^2
1	EMF	47	6.906±1.803$^{\#}$	0.455±0.165
2	Sham	45	7.711±2.007*	0.514±0.173
3	Control	24	6.729±1.687	0.462±0.170

* Significantly different from the control group value at $P<0.05$.
# Significantly different from the sham group value at $P<0.05$.

Serum hormone levels Data for serum levels of corticosterone and ACTH, markers of stress, and melatonin are summarized in Table II. Significant increases were observed for all three in the EMF-exposed group as compared to sham-exposed group. However, corticosterone and ACTH values in the sham-exposed group were significantly lower than the control values.

GST-P analysis Quantitative data for GST-P-positive liver foci are summarized in Table III. EMF exposure did not enhance GST-P-positive liver foci development; both numbers and areas (mm^2) per unit area of the liver in the EMF-exposed group (group 1) were less than in the sham-

exposed case, the former being statistically significant ($P<0.05$). However, the number of the lesions in sham-exposed animals (group 2) was significantly increased as compared to the control value.

Histopathological analysis Histopathological analyses of the liver, spleen, thymus and adrenal glands were performed for all killed animals. In the liver, altered hepatocellular foci (38/47, 34/45, 15/24 in each group, respectively) and a micro-granuloma (1/45 in sham-exposed group) were observed. Slight atrophy of the testes was evident in the EMF-exposed group (2/47). In the spleen, thymus and adrenal glands, no histopathological changes were observed.

DISCUSSION

In Japan, both 900 MHz and 1.5 GHz microwave bands are used for cellular phones, whereas in European countries and the US, only 900 MHz bands are used. Our previous data for 929.2 MHz pulse modulated microwaves

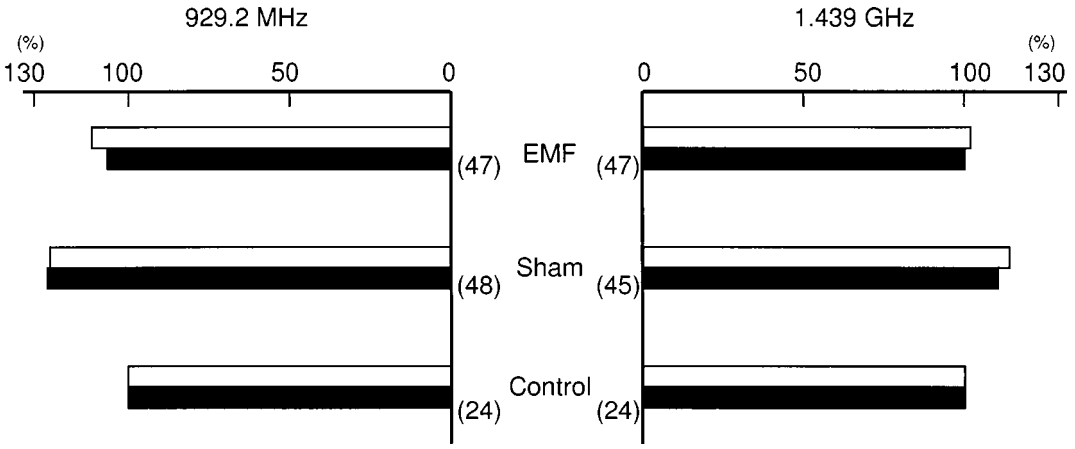

Fig. 4. Comparison of numbers and areas of GST-P-positive liver foci in rats exposed to 929.2 MHz and 1.439 GHz EMF, relative (%) to control values. (Data for the 929.2 MHz experiment were published in *Carcinogenesis*, **19**: 311–314, 1998 [Ref. 16].) ▭, No./cm^2; ■, area (mm^2/cm^2); ( ), No. of rats.

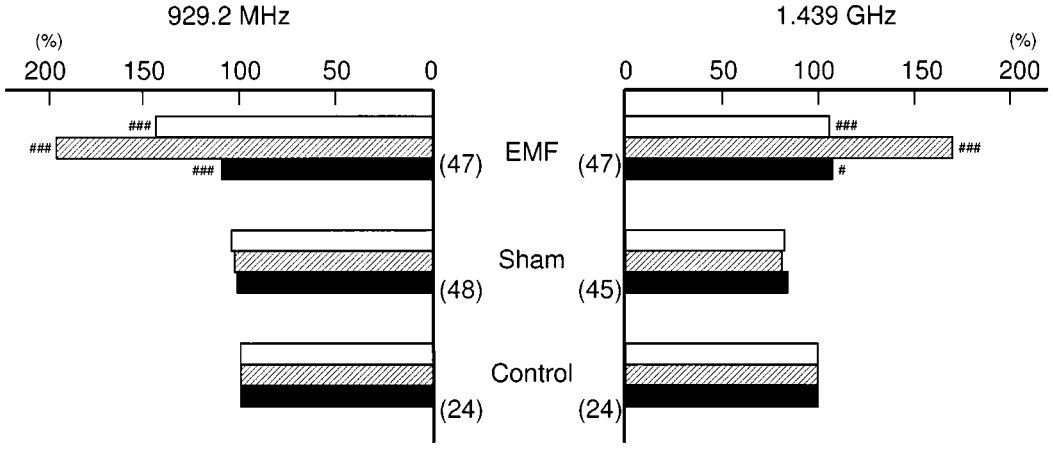

Fig. 5. Comparison of serum hormone levels in rats exposed to 929.2 MHz and 1.439 GHz EMF, relative (%) to control values. ###, # Significantly different from the sham group values at $P<0.001$ and $P<0.05$, respectively, with comparison of absolute values. (Data for the 929.2 MHz experiment were published in *Carcinogenesis*, **19**: 311–314, 1998 [Ref. 16].) ▭, ACTH; ▨, corticosterone; ■, melatonin; ( ), No. of rats.

using the same rat liver medium-term bioassay did not demonstrate any enhancement of preneoplastic lesion development.[16] In the present study, an EMF of 1.439 GHz pulse modulated microwaves also did not enhance the appearance of GST-P-positive liver foci, the numbers in the EMF-exposed group, in fact, being significantly lower than in the sham-exposed group. These data clearly showed that exposure to an EMF of either 929.2 MHz or 1.439 GHz as used in cellular phones in Japan does not have any promoting potential on rat liver preneoplastic lesion development. Similar negative data for the effect of a 50 Hz magnetic field on rat liver preneoplastic lesion development have also been reported.[26, 27] Fig. 4 shows a comparison of the GST-P-positive liver foci values in the previous (929.2 MHz) and the present (1.439 GHz) studies.

In our previous experiment,[16] corticosterone and ACTH levels in serum were significantly increased in both EMF-exposed and sham-exposed groups. The reason for this was speculated to be the elevation of body temperature of the rats in the exposure box. Therefore, in the present experiment, the air ventilation system in the box was improved. This is presumably why the serum levels of corticosterone and ACTH were not elevated in the sham-exposed group in the present study, although the reason for the decrease is unclear. On the other hand, the increase in the EMF-exposed group was in line with the adrenal weight data. These results indicate that exposure to EMF, regardless of the wave frequency, influences hormonal status, but exposure itself does not promote liver preneoplastic lesion development.

Melatonin, a hormone produced by the pineal gland, demonstrates a circadian rhythm (low during the day and elevated at night). Several reports have been published regarding the relationship between melatonin levels and mammary carcinogenesis,[28–30] colon carcinogenesis,[31] cell proliferation,[32] and DNA synthesis in cultured cells.[33] Since EMF has been reported to depress melatonin production,[34, 35] this parameter was also assessed in the present study. Since the blood samples were collected at autopsy (between 9:30 to 12:00 am), the levels were expected to be relatively low. However, as seen in the previous (929.2 MHz) study, exposure to a 1.439 GHz electromagnetic field did increase the melatonin level (Fig. 5).[16] The relationship, if any, between this elevation and preneoplastic lesion development is unclear.

Rapacholi *et al*. reported that exposure to a pulsed 900 MHz electromagnetic field, somewhat similar to that used in the present study, enhanced lymphoma development in Eμ-*pim1* transgenic mouse with long-term intermittent exposure.[36] They noted SARs of 0.008–4.2 W/kg, and employed a "far-field." In contrast, in the present study we applied a "near-field," which is more in line with the actual exposure conditions of cellular telephone users.

The bioassay system, used in the present study, is well established for detecting carcinogens and promoters of hepatocarcinogenesis.[17, 21, 22, 37, 38] It can detect carcinogenic and preventive potential in a short period,[39] and is also a useful tool for analyzing the underlying processes. Furthermore, since this bioassay system requires only 8 weeks experimental duration, it is suitable for time-consuming experiments involving special techniques, such as the present study.

In conclusion, the present study clearly demonstrated that a 1.439 GHz EMF, modulated in a PDC wave form, does not show any significant promoting effect on rat liver carcinogenesis under the experimental present conditions.

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REFERENCES

1) Savitz, D. A., Wachtel, H., Barnes, F. A., John, E. M. and Tvrdik, J. G. Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. *Am. J. Epidemiol.*, **128**, 21–38 (1988).
2) Tomenius, L. 50-Hz electromagnetic environment and the incidence of childhood tumors in Stockholm County. *Bioelectromagnetics*, **7**, 191–207 (1986).
3) Wertheimer, N. and Leeper, E. Adult cancer related to electrical wires near the home. *Int. J. Epidemiol.*, **11**, 345–355 (1982).
4) Preston-Martin, S., Navidi, W., Thomas, D., Lee, P. J., Bowman, J. and Pogoda, J. Los Angeles study of residential magnetic fields and childhood brain tumors. *Am. J. Epidemiol.*, **143**, 105–119 (1996).
5) Gurney, J. G., Mueller, B. A., Davis, S., Schwartz, S. M., Stevens, R. G. and Kopeckey, K. J. Childhood brain tumor occurrence in relation to residential power line configurations, electric heating sources, and electric appliance use. *Am. J. Epidemiol.*, **143**, 120–128 (1996).
6) Miller, A. B., To, T., Agnew, D. A., Wall, C. and Green, L. M. Leukemia following occupational exposure to 60-Hz electric and magnetic fields among Ontario electric utility workers. *Am. J. Epidemiol.*, **144**, 150–160 (1996).
7) Milham, S., Jr. Mortality from leukemia in workers

exposed to electrical and magnetic fields. *N. Engl. J. Med.*, **307**, 249 (1982).
8) Grayson, J. K. Radiation exposure, socioeconomic status, and brain tumor risk in the US Air Force: a nested case-control study. *Am. J. Epidemiol.*, **143**, 480–486 (1996).
9) Milham, S., Jr. Silent keys: leukaemia mortality in amateur radio operators. *Lancet*, **i**, 812 (1985).
10) Szmigielski, S. Cancer morbidity in subjects occupationally exposed to high frequency (radiofrequency and microwave) electromagnetic radiation. *Sci. Total Environ.*, **180**, 9–17 (1996).
11) Hocking, B., Gordon, I. R., Grain, H. L. and Hatfield, G. E. Cancer incidence and mortality and proximity to TV towers. *Med. J. Aust.*, **165**, 601–605 (1996).
12) Dolk, H., Shaddick, G., Walls, P., Grundy, C., Thakrar, B., Kleinschmidt, I. and Elliott, P. Cancer incidence near radio and television transmitters in Great Britain. I. *Am. J. Epidemiol.*, **145**, 1–9 (1997).
13) Dolk, H., Elliott, P., Shaddick, G., Walls, P. and Thakrar, B. Cancer incidence near radio and television transmitters in Great Britain. II. *Am. J. Epidemiol.*, **145**, 10–17 (1997).
14) Weintraub, M. I. Glioblastoma multiforme and the cellular telephone scare. *J. Neurosurg.*, **80**, 169–170 (1994).
15) Adey, W. R., Byus, C. V., Cain, C. W., Haggren, W., Higgins, R. J., Jones, R. A., Kean, C. J., Kuster, N., MacMurray, A., Phillips, J. L., Stagg, R. B. and Zimmerman, G. Brain tumor incidence in rats chronically exposed to digital cellular telephone fields in an initiation-promotion model. *18th Annual Meeting, Bioelectromagnetics Society*, 27 (1996).
16) Imaida, K., Taki, M., Yamaguchi, T., Ito, T., Watanabe, S., Wake, K., Aimoto, A., Kamimura, Y., Ito, N. and Shirai, T. Lack of promoting effects of the electromagnetic near-field used for cellular phones (929.2 MHz) on rat liver carcinogenesis in a medium-term liver bioassay. *Carcinogenesis*, **19**, 311–314 (1998).
17) Ito, N., Tsuda, H., Tatematsu, M., Inoue, T., Tagawa, Y., Aoki, T., Uwagawa, S., Kagawa, M., Ogiso, T., Masui, T., Imaida, K., Fukushima, S. and Asamoto, M. Enhancing effect of various hepatocarcinogens on induction of preneoplastic glutathione S-transferase placental form positive foci in rat — an approach for a new medium-term bioassay system. *Carcinogenesis*, **9**, 387–394 (1988).
18) Ito, N., Imaida, K., Hasegawa, R. and Tsuda, H. Rapid bioassay methods for carcinogens and modifiers of hepatocarcinogenesis. *In* "Critical Reviews in Toxicology," vol. 19, ed. R. Õ. McClellan, pp. 385–415 (1989). CRC Press Inc., Florida.
19) Hagiwara, A., Tanaka, H., Imaida, K., Tamano, S., Fukushima, S. and Ito, N. Correlation between medium-term multi-organ carcinogenesis bioassay data and long-term observation results in rats. *Jpn. J. Cancer Res.*, **84**, 237–245 (1993).
20) Ito, N., Hasegawa, R., Imaida, K., Hirose, M. and Shirai, T. Medium-term liver and multi-organ carcinogenesis bioassays for carcinogens and chemopreventive agents. *Exp. Toxicol. Pathol.*, **48**, 113–119 (1996).
21) Ito, N., Shirai, T. and Hasegawa, R. Medium-term bioassays for carcinogens. *In* "Mechanisms of Carcinogenesis in Risk Assessment," vol. 116, ed. H. Vainio, P. Magee, D. McGregor and A. J. McMichael, pp. 353–388 (1992). IARC Scientific Publications, Lyon.
22) Shirai, T. A medium-term rat liver bioassay as a rapid *in vivo* test for carcinogenic potential: a historical review of model development and summary of results from 291 tests. *Toxicol. Pathol.*, **25**, 453–460 (1997).
23) Watanabe, S., Taki, M. and Kamimura, Y. Power absorption of rats in 929-MHz near-field exposure system. *Second World Congress for Electricity and Magnetism in Medicine and Biology*, 274 (1997).
24) Watanabe, S. and Taki, M. Power absorption of rats in 1.439-GHz near-field exposure system. *The 20th Annual Meeting of The Bioelectromagnetics Society*, 35 (1998).
25) Vaughan, G. M. New sensitive serum melatonin radioimmunoassay employing the Kennaway G280 antibody: Syrian hamster morning adrenergic response. *J. Pineal Res.*, **15**, 88–103 (1993).
26) Rannug, A., Holmberg, B. and Mild, K.H. A rat liver foci promotion study with 50-Hz magnetic fields. *Environ. Res.*, **62**, 223–229 (1993).
27) Rannug, A., Holmberg, B., Ekstrom, T. and Mild, K. H. Rat liver foci study on coexposure with 50-Hz magnetic fields and known carcinogens. *Bioelectromagnetics*, **14**, 17–27 (1993).
28) Tamarkin, L., Cohen, M., Roselle, D., Richert, C., Lippman, M. and Chabner, B. Melatonin inhibition and pinealectomy enhancement of 7,12-dimethylbenz(a)-anthracene-induced mammary tumors in the rat. *Cancer Res.*, **41**, 4432–4436 (1981).
29) Kothari, A., Borges, A., Ingle, A. and Kothari, L. Combination of melatonin and tamoxifen as a chemoprophylaxis against N-nitroso-N-methylurea-induced rat mammary tumors. *Cancer Lett.*, **111**, 59–66 (1997).
30) Mevissen, M., Lerchl, A. and Loscher, W. Study on pineal function and DMBA-induced breast cancer formation in rats during exposure to a 100-mG, 50 Hz magnetic field. *J. Toxicol. Environ. Health*, **48**, 169–185 (1996).
31) Anisimov, V. N., Popovich, I. G. and Zabezhinski, M. A. Melatonin and colon carcinogenesis: I. Inhibitory effect of melatonin on development of intestinal tumors induced by 1,2-dimethylhydrazine in rats. *Carcinogenesis*, **18**, 1549–1553 (1997).
32) Cos, S. and Sánchez-Barceló, E. J. Differences between pulsatile or continuous exposure to melatonin on MCF-7 human breast cancer cell proliferation. *Cancer Lett.*, **85**, 105–109 (1994).
33) Cos, S. and Sánches-Barceló, E. J. Modulation of the length of the cell cycle of MCF-7 human breast cancer cells by melatonin. *Life Sci.*, **58**, 811–816 (1996).
34) Reiter, R. J., Anderson, L. E., Buschbom, R. L. and Wilson, B. W. Reduction of the nocturnal rise in pineal melatonin levels in rats exposed to 60-Hz electric fields *in utero* and

for 23 days after birth. *Life Sci.*, **42**, 2203–2206 (1988).
35) Reiter, R. J. Electromagnetic fields and melatonin production. *Biomed. Pharmacother.*, **47**, 439–444 (1993).
36) Rapacholi, M. H., Basten, A., Gebski, V., Noonan, D., Finnie, J. and Harris, A. W. Lymphomas in E*μ-pim1* transgenic mice exposed to pulsed 900 MHz electromagnetic fields. *Radiat. Res.*, **147**, 631–640 (1997).
37) Hasegawa, R. and Ito, N. Liver medium-term bioassay in rats for screening of carcinogens and modifying factors in hepatocarcinogenesis. *Food Chem. Toxicol.*, **30**, 979–992 (1992).
38) Ito, N., Hasegawa, R., Imaida, K., Hirose, M., Asamoto, M. and Shirai, T. Concepts in multistage carcinogenesis. *Crit. Rev. Oncol. Hematol.*, **21**, 105–133 (1995).
39) Ito, N., Hasegawa, R., Imaida, K., Hirose, M. and Shirai, T. Medium-term liver and multi-organ carcinogenesis bioassays for carcinogens and chemopreventive agents. *Exp. Toxicol. Pathol.*, **48**, 113–119 (1996).