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Exposure to 60 Hz magnetic fields and risk of lymphoma in PIM transgenic and TSG-*p*53 (*p*53 knockout) mice

David L.McCormick[4], Bernadette M.Ryan, John C.Findlay, James R.Gauger[1], Tim R.Johnson[1], Robert L.Morrissey[2] and Gary A.Boorman[3]

Life Sciences Department and [1]Electronics and Electromagnetics Section, IIT Research Institute, Chicago, IL 60616, [2]Pathology Associates International, Chicago, IL 60616 and [3]National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA

[4]To whom correspondence should be addressed
Email: dmccormick@iitri.com

The results of a number of epidemiology studies suggest that exposure to power frequency (50 and 60 Hz) magnetic fields may be a risk factor for hematopoietic neoplasia. To generate experimental data to test this hypothesis, the influence of magnetic field exposure on lymphoma induction was determined in two strains of mice that are genetically predisposed to the disease. PIM mice, which carry the *pim*-1 oncogene, are highly sensitive to lymphoma induction by *N*-ethyl-*N*-nitrosourea (ENU); ENU-treated PIM mice were studied as a 'high incidence' lymphoma model. TSG-*p*53 (*p*53 knockout) mice, in which the *p*53 tumor suppressor gene has been deleted from the germ line, develop lymphoma as an age-related change; hemizygous TSG-*p*53 mice were studied as a 'low incidence' lymphoma model. Beginning 1 day after a single i.p. injection of 25 mg ENU/kg body wt, groups of 30 PIM mice/sex were exposed for 18.5 h/day to pure, linearly polarized, transient-free 60 Hz magnetic fields at field strengths of 0 (sham control), 0.02, 2.0 or 10.0 Gauss (G). An additional group of 30 PIM mice/sex was exposed intermittently (1 h on, 1 h off) to 10.0 G fields. Groups of 30 TSG-*p*53 mice/sex were exposed continuously to magnetic field strengths of 0 (sham control) or 10.0 G; TSG-*p*53 mice received no ENU. Studies were terminated after 23 weeks of magnetic field exposure. Lymphoma incidence in male PIM mice exposed continuously to 10.0 G magnetic fields was significantly reduced from that seen in sex-matched sham controls; survival, lymphoma incidence and lymphoma latency in other groups of PIM mice did not differ from sham controls. Survival and lymphoma incidence in all groups of TSG-*p*53 mice was 7% or less, regardless of magnetic field exposure regimen. These data do not support the hypothesis that exposure to magnetic fields is a significant risk factor for lymphoid neoplasia in mice with a genetic predisposition to the disease.

Introduction

Magnetic fields generated by the production, transmission and use of electricity are ubiquitous in industrialized society. Although public concerns related to the possible health effects of power frequency (50 or 60 Hz) magnetic fields have generally focused on high-voltage overhead electrical transmission and distribution lines, extremely low-frequency (ELF) magnetic fields are also generated by office equipment such as video display terminals and laser printers, and a wide range of common household appliances, including vacuum cleaners, toasters, electric shavers, hair dryers and electric blankets (1). Because magnetic field intensity decreases with distance from the source, exposures resulting from close proximity to sources of relatively low intensity (e.g. household appliances) may exceed the magnitude of exposures associated with the presence of an overhead transmission line in the neighborhood (2).

Although considerable public concern has developed over the potential for carcinogenic effects of power frequency magnetic fields, there are no conclusive scientific data on which risk assessments can be based. The epidemiology literature in bio-electromagnetics reveals few clear trends that can be used to quantify the risks associated with human exposure to magnetic fields. The results of several epidemiology studies suggest that occupational or residential exposure to power frequency magnetic fields is associated with increased risks of leukemia in both children and adults (3–7), brain cancer (7–9), and breast cancer in women (10,11) and in men (12). Where statistically significant positive associations between magnetic field exposure and risk of malignancy have been reported, the increases in relative risk have been small (generally <2.0). However, in view of the ubiquitous nature of magnetic fields, even a small incremental increase in the risk of neoplasia resulting from exposure to ELF magnetic fields could pose a significant public health problem.

It is important to note, however, that other occupational and residential epidemiology studies have reported no association between magnetic field exposure and cancer risk (13–16); these studies have often been conducted using populations and disease endpoints that are similar to those in which positive associations have been reported elsewhere. The reasons underlying the discordance in the results of magnetic field epidemiology studies are unclear. In this regard, however, reviews of the magnetic field epidemiology literature have identified a number of important methodological issues, including the adequacy of exposure assessment, that may be at least partially responsible for the conflicting data (17,18).

An alternate explanation for the conflicting results of epidemiology studies concerning magnetic fields and cancer is that magnetic field exposure has little or no influence on cancer risk in the general population, but may enhance the risk of neoplasia in sensitive subpopulations. The sensitivity of a subpopulation to magnetic field effects could result from genetic predisposition to a disease endpoint and/or previous or concurrent exposure to other agents that increase risk. Should this hypothesis be true, differential representation of sensitive subpopulations could explain the apparently contradictory epidemiology findings.

Because epidemiology data do not now support conclusive assessments of the possible risks of neoplasia associated with exposure to magnetic fields, well-controled animal studies may

Abbreviations: ELF, extremely low frequency; ENU, *N*-ethyl-*N*-nitrosurea.

prove crucial to the identification of its potential hazard to humans. There is general consensus in the scientific community that ELF magnetic fields are not genotoxic (19,20). As such, evaluations of the influence of magnetic fields on the induction of organ-specific neoplasia have focused on tumor promotion and progression. *In vivo* studies conducted in mouse skin and the rat mammary gland suggest that magnetic fields may promote tumor development in those tissues (21–23); however, independent confirmation of these results has not yet been presented.

Although epidemiological data have identified the hematopoietic system as a possible target for magnetic field action, the hypothesis that magnetic field exposure induces hematopoietic neoplasia has received little study in animal model systems. Similarly, the hypothesis that magnetic field effects are seen in primarily in individuals with a genetic or other predisposition to hematopoietic neoplasia has not been evaluated experimentally. The present report summarizes the results of studies in which the influence of 60 Hz magnetic fields on lymphoma induction was evaluated in two strains of mice that are genetically predisposed to the disease.

Materials and methods

Animals and animal husbandry

Studies were conducted using two transgenic model systems with different incidences and kinetics of lymphoma induction. Using this approach, the possible activity of magnetic fields as a promoter of lymphoma induction was assessed in both 'high incidence' and 'low incidence' models. The 'high incidence' model provides the opportunity to evaluate promotional activity in a model system in which neoplastic development is a rapidly occurring, active process. The 'low incidence' lymphoma model system permits the evaluation of biological activity in a model in which sham controls are at the threshold of neoplasia. This dual approach was used in order to increase the sensitivity of the overall experimental design, thereby maximizing the probability of detecting a positive effect.

PIM transgenic mouse (high incidence animal model system). PIM transgenic mice carry the *pim*-1 oncogene, a murine oncogene identified as a common site of viral integration in lymphomas induced by Moloney murine leukemia virus. PIM mice develop lymphoblastic lymphomas rapidly after a single dose of the carcinogenic nitrosamide, *N*-ethyl-*N*-nitrosourea (ENU; 24–27) and were studied as a 'high incidence' model system. The kinetics and natural history of lymphomagenesis in the PIM model system have been characterized extensively in our laboratory, and this model has been used to evaluate the activity of chemopreventive drugs as inhibitors of lymphoma induction (27). The histopathology of induced lesions in the PIM model system has been reported (26,27).

PIM [(C57Bl/LiA×CBA×C57/Bl6)fBR-(TG)pim-1] mice (purchased from GenPharm International colonies maintained at Taconic Farms, Germantown, NY) received a single i.p. injection of 25 mg ENU (Ash-Stevens, Detroit, MI; in sterile saline, pH 5.0)/kg body wt. Beginning 1 day after ENU administration, groups of 30 PIM mice per sex were exposed to magnetic field strengths of 0 (sham control), 0.02, 2 or 10 Gauss (G). An additional group of 30 PIM mice/sex was exposed intermittently (1 h on, 1 h off) to 10 G fields. Magnetic field exposure was continued for 23 weeks.

TSG-p53 (p53 knockout) mouse (low incidence animal model system). TSG-*p*53 mice, in which the *p*53 tumor suppressor gene has been deleted from the germ line, develop neoplasms spontaneously as an age-related change. Both nullizygous (lacking both copies of the *p*53 gene) and hemizygous (lacking one copy of the *p*53 gene) mice are sensitive to neoplastic development in the hematopoietic system, bone and several other target tissues (28). In hemizygous *p*53 mice <1 year of age, the primary site of neoplastic development is the hematopoietic system (28). Hemizygous *p*53 mice were used as a 'low incidence' lymphoma model system. The 23-week study duration was selected such that the incidence of lymphoma in sham control mice would be at or near zero in both sexes.

Age-matched hemizygous TSG-*p*53 [C57Bl/6TacfBR-(KO)p53] mice were purchased from GenPharm International colonies maintained at Taconic Farms. Mice were randomized into groups of 30 per sex, and were exposed continuously to magnetic field strengths of 0 or 10 G; TSG-*p*53 mice received no ENU.

Animal husbandry. After receipt from the supplier, mice of both strains were held in quarantine for a period of 10–14 days prior to the initiation of magnetic field exposures. Environmental conditions in all animal holding areas were maintained within the ranges of 72 ± 3°F and 50 ± 15% relative humidity; a minimum of 10 air changes/h was supplied to all animal rooms. Throughout the quarantine and exposure periods, mice were housed on hardwood bedding (Beta-Chips; Northeastern Products, Warrensburg, NY) in polycarbonate shoebox cages, according to National Toxicology Program specifications. Animals were allowed free access to NIH-07 diet (Zeigler Brothers, Gardners, PA) and City of Chicago drinking water (provided by automatic watering system) throughout all studies. Animals were observed twice daily for mortality or evidence of moribundity, and were weighed weekly.

Magnetic field exposure and monitoring

Magnetic field exposure. Mice in groups designated for continuous exposure were exposed to linearly polarized 60 Hz magnetic fields for 18.5 h/day for 23 weeks; mice in the 10 G intermittent exposure group were exposed using a regimen of 1 h on/1 h off during the 18.5 h daily exposure period. A 4 h morning shutdown and a 1.5 h afternoon shutdown were scheduled daily to permit animal observation and husbandry operations without personnel exposure to experimentally generated magnetic fields. Magnetic field frequency content was nearly pure 60 Hz (<3% total harmonic distortion), and fields were ramped on and off over 7–9 cycles to prevent high frequency transients. Spatial homogeneity of experimental magnetic fields was ±10% or better throughout the animal exposure volume, and temporal homogeneity was ±4% or better in all groups during the studies; a regular schedule of cage rotation within cage racks and exposure bays was performed to control for possible positional effects. Ambient magnetic fields to which sham control mice were exposed were <1 mG at all times. Associated electric fields in the animal holding areas were <100 V/m.

Magnetic field and environmental monitoring. Magnetic field strength and waveform were monitored continuously in all animal rooms throughout the study period. Ambient magnetic fields were monitored continuously in the quarantine room and the room housing sham controls, and were also monitored during periods of module shutdown in room housing groups receiving magnetic field exposure. Temperature, humidity, air flow, lighting, noise and vibration were monitored continuously in all animal exposure rooms. No temperature, humidity, vibrational or auditory cues associated with generation of experimental magnetic fields were present in animal exposure rooms. Static (DC) magnetic fields were mapped throughout the animal facility prior to the initiation of studies.

Post-mortem analyses

Necropsy and histopathology. Studies were terminated after 23 weeks of magnetic field or sham exposure. All animals, whether dying intercurrently or surviving until the terminal necropsy, received a limited gross necropsy focusing on target tissues for neoplastic development in the PIM model system (27). Primary sites of disease involvement [spleen, thymus and lymph node (mandibular)] and tumor infiltration/metastasis (liver, kidney and lung) were harvested from all animals, fixed in neutral buffered formalin, processed by routine histologic methods and evaluated by light microscopy.

Statistical analysis. Differences in survival curves were compared by life table analysis and the logrank test (29). Differences in terminal survival and incidences of neoplasia were compared by Fisher's exact test. Group mean body weights were compared within a strain and sex by analysis of variance, with *post hoc* comparisons performed using Dunnett's test. A significance level of $P < 0.05$ was used for all comparisons.

Results

PIM mouse model

Survival. Similar patterns of tumor-related mortality were seen in all groups of PIM animals in the study; survival curves for groups of male and female PIM mice are presented in Figures 1 and 2, respectively. Patterns of tumor-related mortality in the sham control group were consistent with those observed in previous studies conducted in this laboratory with the PIM model system (27). As seen in our previous studies, essentially all intercurrent mortality observed in PIM mice was related to the development of lymphoid malignancy.

Incidence of lymphoma. In male PIM mice, the mortality-adjusted incidence of malignant lymphoma in the sham control group was 49%; this incidence was compared with mortality-

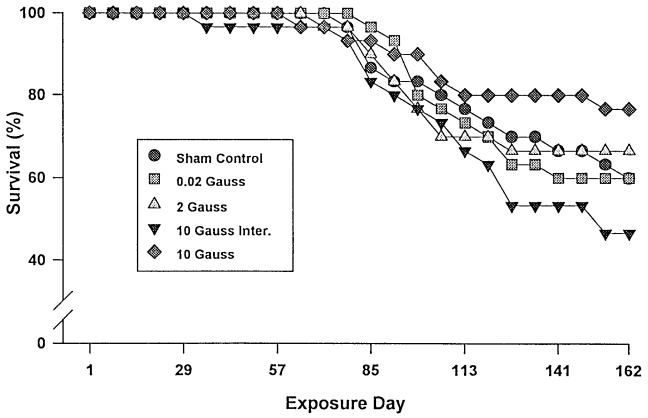

Fig. 1. Survival in male PIM mice exposed to 60 Hz magnetic fields. At study termination, survival in male mice exposed continuously to 10 G magnetic fields was significantly increased from sham controls.

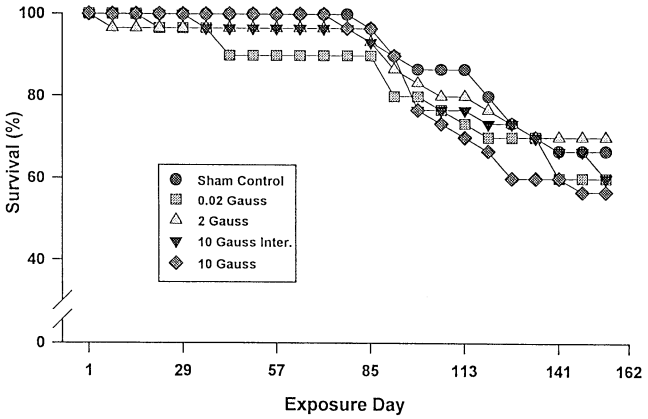

Fig. 2. Survival in female PIM mice exposed to 60 Hz magnetic fields. No statistically significant differences from control were seen in any group exposed to magnetic fields.

Table I. Influence of 60 Hz magnetic fields on lymphoma induction in PIM transgenic mice

Field strength (G)	Terminal body weight (g; mean ± SD)	Survival (%)	Lymphoma incidence (%)
Males			
0 (sham control)	41.5 ± 6.0	60	49
0.02	39.9 ± 5.8	60	47
2	41.5 ± 5.4	67	43
10	43.0 ± 6.0	77	23*
10 (intermittent)	40.1 ± 5.4	47	57
Females			
0 (sham control)	34.0 ± 4.1	67	47
0.02	31.8 ± 4.8	60	45
2	31.8 ± 4.3	70	45
10	32.0 ± 3.2	57	47
10 (intermittent)	32.2 ± 3.0	60	53

*$P = 0.041$ versus sham control via Fisher's exact test; $P = 0.054$ versus sham control via life table method.

adjusted lymphoma incidences of 47% in the 20 mG group, 43% in the 2 G group, 23% in the 10 G continuous group and 57% in the 10 G intermittent group (Table I). In comparison with the 49% incidence of lymphoma in male PIM sham controls, only the 23% incidence of lymphoma seen in male mice in the 10 G continuous group was significantly different ($P = 0.041$ by Fisher's Exact test). However, this reduction

Table II. Influence of 60 Hz magnetic fields on lymphoma induction in *p*53 knockout mice

Field strength (G)	Terminal body weight (g; mean ± SD)	Survival (%)	Lymphoma incidence (%)
Males			
0 (sham control)	43.5 ± 5.3	100	3
10	43.0 ± 5.8	97	0
Females			
0 (sham control)	30.0 ± 3.7	97	3
10	31.4 ± 6.3	100	7

in lymphoma incidence was not significant at the 5% level when analysed by the life table method ($P = 0.054$). Lymphoma incidence in other groups of male PIM mice did not differ from sham control by any statistical test used.

Histopathological evaluation of tissues from female PIM mice also failed to demonstrate any increased risk of lymphoma associated with exposure to magnetic fields. In comparison with a mortality-adjusted incidence of lymphoma of 47% in female mice in the sham control group, lymphoma incidences in female PIM mice exposed to magnetic fields were 45% in the 20 mG group, 45% in the 2 G group, 47% in the 10 G continuous exposure group and 53% in the 10 G intermittent exposure group (Table I). None of these differences from sham control was significant at the 5% level.

Other neoplastic lesions. Other than lymphoma, only one malignant lesion (a hepatocellular carcinoma with lung metastases in a sham control) was diagnosed in male PIM mice. Similarly, only one non-hematopoietic lesion (a histiocytic sarcoma in a mouse in the 10 G continuous exposure group) was diagnosed in female PIM mice. Both lesions are considered to be incidental findings.

Body weight and clinical toxicity. Exposure to 60 Hz magnetic fields had no effect on mean body weight and induced no clinical evidence of toxicity in any exposure group at any time. At the termination of the study, group mean body weights in male PIM mice exposed to magnetic fields ranged from 96.1 to 103.6% of sham control (Table I). Mean body weights in female PIM mice at the end of the study ranged from 93.5 to 94.7% of sham control values ($P > 0.05$ for all comparisons).

Clinical observations in PIM mice were generally associated with the development of malignant lymphoma. Consistent with the results of our previous studies (27), tumor-related mortality in PIM mice treated with ENU was commonly preceded by labored breathing and loss of body weight during the final 1–2 weeks of life. The observed breathing abnormalities may be associated with increasing burden of infiltrative malignancy in the lungs of PIM mice, a common finding in all experimental groups. Other clinical observations (ruffled fur, thin appearance), are also considered to be associated with neoplastic development, but were not associated with magnetic field exposure.

TSG-p53 mouse model

Survival. Exposure to 10 G magnetic fields had no effect on survival in either sex of TSG-*p*53 mice (Table II). Survival was 97% in both control and 10 G groups in both sexes.

Incidence of lymphoma. The incidence of malignant lymphoma was 7% or less in all experimental groups of TSG-*p*53 mice (Table II). In male TSG-*p*53 mice, lymphoma was diagnosed in 1/30 sham controls; in comparison, the incidence of

lymphoma in male TSG-*p*53 mice exposed to 10 G magnetic fields was 0/30. The incidence of malignant lymphoma in female TSG-*p*53 mice was 1/30 and 2/30 in groups receiving sham control and 10 G exposures, respectively. Neither of the differences between the sham control and 10 G groups was statistically significant.

Other neoplastic lesions. Other than lymphoma, only one malignant lesion was diagnosed in a TSG-*p*53 mouse. One male TSG-*p*53 mouse from the 10 G continuous group demonstrated a hepatocellular carcinoma; this lesion is considered to be an incidental finding.

Body weight and clinical toxicity. Mean body weights in male and female TSG-*p*53 mice exposed to 10 G fields were 98.9 and 104.7% of sham control, respectively ($P > 0.05$ for both comparisons; Table II). Exposure to 10 G magnetic fields induced no clinical evidence of toxicity in any TSG-*p*53 mouse at any time in the study.

Discussion

The results of the present studies demonstrate no increased risk of lymphoma in either PIM or TSG-*p*53 (*p*53 knockout mice) exposed to 60 Hz magnetic fields. When compared with strain- and sex-matched controls, neither PIM nor TSG-*p*53 mice exposed to magnetic field strengths of up to 10 G for 23 weeks demonstrated increases in tumor-related mortality, increases in lymphoma incidence or decreases in lymphoma latency. With one exception, patterns of animal survival, tumor-related mortality and body weight were comparable in sham controls and all magnetic field exposure groups, within a sex and strain. As such, these data do not support the hypothesis that exposure to 60 Hz magnetic fields is a significant risk factor for hematopoietic neoplasia in rodents with a genetic predisposition to disease.

The only statistically significant difference between sham controls and groups exposed to magnetic fields in either mouse strain was a decrease in lymphoma incidence in male PIM mice exposed continuously to 10 G magnetic fields. Although the biological significance of this reduction in lymphoma incidence is not clear, this finding reinforces the observation from other experimental groups that magnetic field exposure does not stimulate the development of lymphoid neoplasia in either PIM or TSG-*p*53 mice.

PIM and TSG-*p*53 mice demonstrate different genetic lesions that predispose them to lymphoma. The activity of the pim-1 oncogene appears to be limited to the etiology of murine lymphoma; by contrast, deletions and mutations in *p*53 are common genetic alterations in human malignancies. Furthermore, lymphoma incidence and the temporal patterns of disease development in the ENU-treated PIM mouse and the hemizygous TSG-*p*53 mouse are quite different. In the PIM model system, the overall incidence of lymphoma in ENU-treated mice was 45.3% (135 diagnosed cases in 298 animals at risk). By contrast, the overall incidence of malignant lymphoma in heterozygous TSG-*p*53 mice was only 3.3% (four diagnosed cases in 120 animals at risk). Magnetic field exposure did not increase the incidence or decrease the latency of lymphoma in either mouse strain. The lack of enhancement of lymphoma induction by magnetic fields in two mouse strains with different genetic lesions and vastly different underlying incidences of disease strengthens the conclusion that exposure to 60 Hz magnetic fields is not a major risk factor for hematopoietic neoplasia in mice.

The lack of stimulation of lymphoma induction in PIM mice by power frequency (60 Hz) magnetic fields appears to differ from the effects of radiofrequency (r.f.) magnetic fields in this mouse strain. Repacholi *et al*. have recently reported that PIM mice exposed to r.f. (pulse modulated 900 MHz) magnetic fields for up to 18 months developed more lymphomas than did sham controls (30); in the Repacholi study, PIM mice received no carcinogen. In comparing the results of our study with the data presented by Repacholi *et al*., it is important to note that the energy deposited in tissues by r.f. fields greatly exceeds that deposited by 60 Hz fields; this energy deposition may result both in tissue heating and in athermal effects that could influence genetic integrity and thereby influence neoplastic development. In this regard, two groups have reported the induction of DNA damage by *in vivo* (31) or *in vitro* (32) exposure to r.f. (2450 MHz microwave) fields. In contrast, there is no body of evidence demonstrating that such effects are induced by exposure to power frequency magnetic fields (19,20).

The results of the present study demonstrate that the development of hematopoietic neoplasia in PIM and hemizygous TSG-*p*53 mice is not accelerated or increased by exposure to pure, transient-free, linearly polarized 60 Hz magnetic fields. The 60 Hz sine wave is the fundamental component of magnetic fields generated in association with the production, transmission, and use of electricity in the USA. As such, the present data do not demonstrate significant oncogenic or tumor-promoting activity of the major component of magnetic fields to which humans are exposed in the USA. An important limitation to these data, however, is the known presence of harmonics, high frequency transients and other electromagnetic components in environmental magnetic fields; the design of the present studies does not address the possible biological activity of these magnetic field exposure parameters. As a result, the possibility remains that exposure to other magnetic field metrics (magnetic field transients associated with 60 Hz fields, higher order harmonics, waveforms other than pure sine waves, etc.) may be risk factors for neoplastic development in the hematopoietic system or other target tissues. However, within the limitations of our experimental design, the results of these studies suggest that the quantitatively largest component of environmental magnetic fields in the USA is unlikely to be an important risk factor for hematopoietic neoplasia in genetically susceptible subpopulations.

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