

# Leukemia and Lymphoma Incidence in Rodents Exposed to Low-Frequency Magnetic Fields

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Boorman, G. A., Rafferty, C. N., Ward, J. M. and Sills, R. C. Leukemia and Lymphoma Incidence in Rodents Exposed to Low-Frequency Magnetic Fields. *Radiat. Res.* 153, 627-636 (2000).

A weak association between residential or occupational exposure to electric and magnetic fields (50/60 Hz fields) and an increased incidence of leukemia has been reported. Numerous animal studies have evaluated the potential association between magnetic-field exposure and leukemia. These include long-term (up to 2½ years) bioassays, initiation/promotion studies, investigations in transgenic models, and tumor growth studies. Exposure to 60 Hz circularly polarized magnetic fields of 1000 µT for 28 months did not affect lymphoma incidence in mice. The study included over 2000 C57BL/6J mice. In another study, 1000 B6C3F<sub>1</sub> mice exposed to 60 Hz magnetic fields up to 1000 µT for 2 years showed no increase in lymphomas. Approximately 400 transgenic Eµ-*Pim1* mice exposed to 50 Hz fields up to 1000 µT for up to 18 months had no increased incidence of leukemia. Similarly, *Trp53*<sup>-/-</sup> mice and *Pim1* transgenic mice exposed to 60 Hz magnetic fields for 23 weeks showed no increased incidence of lymphoma. Three studies in F344 rats exposed to 50 or 60 Hz magnetic fields up to 5 mT showed no increased incidence of leukemia. The combined animal bioassay results are nearly uniformly negative for magnetic-field exposures enhancing leukemia and weaken the possible epidemiological association between magnetic-field exposures and leukemia in humans as suggested by epidemiological data. © 2000 by Radiation Research Society

## INTRODUCTION

Historically, some epidemiological studies have suggested a possible association between exposure to 50/60 Hz electric and magnetic fields and increased incidence of childhood leukemia or adult lymphomas, while other studies fail to find this association (1). The recent epidemiological studies do not resolve the issue. An association between residential exposures and increased incidence of childhood leukemia was recently found in southern Ontario (2), while another study found a statistical increase in leukemia with 50 Hz magnetic-field

exposure in Germany (3). In contrast, other recent epidemiological studies have not supported 50/60 Hz magnetic-field exposure as a risk factor for leukemia (4-8). After more than 20 years of research and more than 40 epidemiological studies, it has been suggested that the epidemiological evidence falls far short of that needed to conclude that a causal relationship exists (9).

The average 24-h personal 60 Hz magnetic-field exposure for individuals in the U.S. has been estimated to be approximately 0.09 µT, while time-weighted occupational exposures in the highest exposure category are in the range of 0.1 to 4.0 µT (10). These magnetic-field intensities are several orders of magnitude lower than those used in most animal studies.

In general, there is a good correlation (84%) between agents known to cause cancer in humans and those causing cancer in rodents (11). Further, for many agents, the cancer affects the same organ in humans as it does in at least one of the animal species tested (11). Specifically for leukemia and lymphoma, 100% of the chemicals that cause hematopoietic tumors in humans cause cancer when tested in rats and mice. In 73% of the cases, chemical exposure results in leukemia or lymphoma in rodents (11).

The goal of this paper is to review animal studies for evidence that 50 or 60 Hz magnetic-field exposure could alter the incidence or onset of leukemia or lymphoma in rodents. We identified 15 animal studies (Tables 1 and 2) in which the potential effect of low-frequency magnetic-field exposure on leukemia and lymphoma in rodent models was evaluated (12-25). The studies included standard long-term animal bioassays, initiation/promotion studies, studies using transgenic mouse models, and leukemia progression studies. Over 5000 animals and approximately 12 different exposure conditions are included in these studies. Each study was evaluated for the quality (and description) of the magnetic-field exposure system, the documentation of the animal care procedures, and the consistency of the pathology evaluation. The studies varied widely in the number of animals per group, the length of the study, and the intensity of the magnetic-field exposures. The data were evaluated for the incidence of both neoplastic and preneoplastic lesions of the hematopoietic and lymphoid systems.

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TABLE 1  
Tests of Magnetic Fields in Mouse Leukemia Bioassays

Test system	Rodent strain	Initiator/ (Promoter)	Magnetic-field exposure	Length	Number of animals	Author's conclusions	Strengths/ weaknesses	References
Promotion and chronic non-initiated	C57BL/6J, female	X irradiation, 0, 3.0, 4.0 and 5.1 Gy in 4 doses	1400 $\mu$ T circularly polarized (60 Hz), 18.5 h/day, 7 days/week	28 months	190 to 380/group, 2660 total	Negative	Good study with very large groups; multiple lymphoma types evaluated	(15)
Promotion	Swiss Webster, both sexes	DMBA injected at birth	1000 $\mu$ T (60 Hz), 3 h/day, 6 days/week	32 weeks	About 30/group, 408 total	Negative, but increased liver initiation	Good study, large groups; DMBA model; limited engineering information	(14)
Progression	DBA.2, female	$1 \times 10^7$ P388 leukemia cells	1.4, 200, and 500 $\mu$ T (60 Hz), 6 h/day, 5 days/week	16-31 days	10/group; 198 total	Negative	Adequate study with small groups; short latency	(12)
Multigeneration chronic non-initiated	CFW mice	None	25,000 $\mu$ T (60 Hz), 24 h/day, 7 days/week (details incomplete)	3 generations	1st generation—3/group, 2nd generation—22/group, 3rd generation—46/group, 142 total	Positive in all 3 generations	Inadequate study with fundamental deficiencies in controls, pathology and engineering	(13)
Promotion	CBA, female	X irradiation, 5.24 Gy in 4 doses (0.45 Gy/min)	15 $\mu$ T (20 kHz, pulsed, saw-tooth, vertical), 24 h/day	131 weeks	47-64/group, 227 total	Negative, but response may be saturated	Good study but VDT signals may not be relevant to ELF effects; lymphoma end point may be saturated	(66)
Multigeneration chronic non-initiated	AKR mice (leukemia prone)	None	6000- $\mu$ T "pulsed magnetic field" at 12 Hz and 460 Hz, 30 min, 2x/week	6 generations, duration	18-30/group, about 360 total	Negative	Inadequate study with fundamental deficiencies in controls, pathology and engineering	(69)
Transgenic chronic	<i>Pim1</i> , female	None	1, 100-, 1000- $\mu$ T continuous (50 Hz) and 1000- $\mu$ T intermittent (15 min, on/off cycle), (50 Hz), 20 h/day	78 weeks	100/group, 600 total	Negative for lymphoma	Good study with large groups; no histopathology on "healthy animals"; controls different from companion RF study (68)	(15)
Transgenic	<i>Pim1</i> , both sexes, and TSG-Trp53, both sexes	ENU ( <i>Pim1</i> only)	2, 200, 1000 $\mu$ T continuous (60 Hz), and 1000 $\mu$ T, intermittent ( <i>Pim1</i> ); 1000 $\mu$ T continuous (60 Hz) ( <i>Trp53</i> ), 18.5 h/day	23 weeks	30/group, 420 total	Negative	Good study but groups are small; predictive value of transgenic models not well understood; short study	(21)
Transgenic chronic	Eu- <i>Pim1</i> females	None	900 MHz with pulse repetition of 217 Hz, mean exposure 2.6 to 13 W/m <sup>2</sup>	18 months, survivors discarded at 18 months	100 control, 101 exposed, less than half examined pathologically	Significant increase in lymphoma in RF group	Lack of examination of animals at 18 months limits the value for late occurring lymphomas	(68)
Chronic non-initiated	B6C3F mice, both sexes	None	2, 200, 1000 $\mu$ T continuous (60 Hz) and 1000 $\mu$ T intermittent (1 h on/off cycle) (60 Hz), 18.5 h/day 7 days/week	106 weeks	100/group, 1000 total	Negative, decreased lymphoma, 1000- $\mu$ T intermittent females	Good study with large groups and multiple exposures	(17, 19)

RESULTS AND DISCUSSION

*Leukemia in Humans*

Cancer in different organs and tissues in both humans and animals may be caused by infectious agents, chemicals and

physical agents. Cancers that arise in the lymphoid tissues are referred to as lymphomas, while cancers that arise within the hematopoietic tissues of the bone marrow and secondarily enter the circulating blood are referred to as leukemias (26). Acute lymphoblastic leukemia (ALL) represents the most

TABLE 2  
Tests of Magnetic Fields in Rat Leukemia Bioassays

Test system	Rodent strain	Initiator/ (Promoter)	Magnetic- field exposure	Length	Number of animals	Authors' conclusions	Comments	Refer- ences <sup>1</sup>
Chronic noninitiated	F344 rats, both sexes	None	2, 200, 1000 $\mu$ T continuous, (60 Hz) and 1000 $\mu$ T intermittent (1 h on/off cy- cle) (60 Hz), 18.5 h/day	106 weeks	100/group, 1000 to- tal	Negative for leukemia/ lymphoma significant decrease in mononu- clear cell leukemia, 1000 $\mu$ T intermittent males	Good study with large groups and multiple exposure groups	(16, 19)
Chronic noninitiated	F344/N rats, fe- male	None	2, 20, 200, 2000 $\mu$ T (60 Hz), 20 h/day	2 years	50/group, 250 total	Negative	Good study with ade- quate group sizes	(18)
Chronic nonirradiated	F344 rats, both sexes	None	500, 5000 $\mu$ T (50 Hz) 22.6 h/day	2 years	48/group, 288 total	Negative	Good study with ade- quate group sizes	(20)
Progression	F344, male	$2.2 \times 10^7$ LGL leukemia cells	1000 $\mu$ T, 2 $\mu$ T (60 Hz), 20 h/day	18 weeks (22)	18/group, 72 total (22)	Negative	Good study with ade- quate group sizes; positive controls; limited in scope to progression	(22, 23)
Progression	F344, male	$2.2 \times 10^7$ and $2.2$ $\times 10^8$ LGL leu- kemia cells	1000- $\mu$ T continu- ous, 1000- $\mu$ T in- termittent (60 Hz), 3 min on/ off cycle, 20 h/ day	28 weeks	18/group, 144 total	Significant for intermit- tent fields for $2.2 \times$ $10^7$ injected LGL leu- kemia cells. Negative for other conditions	Good study with ade- quate group sizes; positive controls; limited in scope to progression	(24)

non form of childhood leukemia (27) and includes both B-cell and T-cell leukemias. In the U.S., the disease incidence peaks between 2 and 6 years of age, with leukemia being twice as common in Caucasians as African-Americans (27).

For childhood leukemia, a number of genetic syndromes have been associated with increased risk, although they account for a small percentage of the cases (27). In acute childhood leukemia, chromosomal translocations are common, but there is considerable heterogeneity (28-30). Recently up to 85% of infant acute leukemias were found to have 11q23/MLL gene rearrangements (31), and it is possible that some infants are born with leukemia.

In adults, lymphomas and leukemias are more diverse and include Hodgkin's and non-Hodgkin's lymphomas, and acute and chronic leukemias of both lymphoid and myeloid origin (26). Large granular lymphocytic (LGL) leukemia is an uncommon T-cell variant in adults (32) characterized by proliferation of antigen-activated cytotoxic T cells (33).

Despite impressive advances in our understanding of the process of leukemogenesis, little is known about the etiology or risk factors for childhood or adult leukemia (34-36). Among environmental factors, prenatal exposure to X rays is the best-established risk factor for leukemia (27, 31). The increased risk of leukemia after treatment with alkylating agents is also established (26). Magnetic-field (50/60 Hz) exposure is proposed as a risk factor (5, 37). Other potential risk factors include benzene (adult but not childhood leukemia),

birth weight, prior history of fetal loss in the mother, pesticide exposure, and viral and other infections. The role of infectious agents, including the Epstein-Barr virus, in the eti-

ology of leukemia is an area of ongoing research (38). A recent report suggests that children who change residences more frequently are at greater risk of developing leukemia, and the author speculated that this is consistent with an infectious etiology (7). For the vast majority of leukemias, neither the risk factor nor the mechanism is well known.

#### Animal Models of Leukemia

Animal models have a long history of predicting known human carcinogens (39). For many chemicals that cause cancer in humans, there is a target organ in common between humans and at least one animal species (11). The reported associations between magnetic-field exposure and childhood (40-42) and adult leukemias (43-45) have led to the conduct of a significant number of rodent studies. Since leukemia appears to be the only cancer end point potentially associated with magnetic-field exposure (1), it appeared worthwhile to review the animal literature for evidence of enhanced leukemia with exposure to magnetic fields.

In a review of the known human carcinogens (46), it was found that benzene, azathioprine, myleran, chlorambucil, cyclophosphamide, diethylstilbestrol and melphalan have caused leukemia or lymphoma in mice. Of the carcinogens causing leukemia in humans, benzene, vinyl chloride, azathioprine, myleran, chlorambucil, methyl-CCNU, cyclophosphamide and melphalan also cause leukemia/lymphoma or other rodent tumors. Various types of radiation cause leukemia/lymphoma in both humans and mice.

In mice, lymphomas and leukemias are usually considered

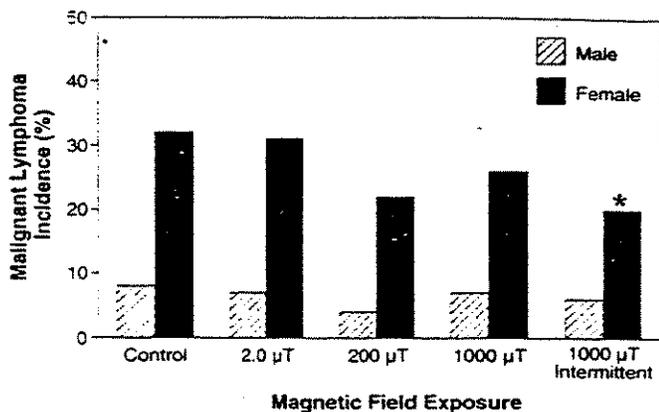


FIG. 1. Incidence of malignant lymphoma in B6C3F<sub>1</sub> mice exposed to sham fields or 60 Hz magnetic fields for 18.5 h/day for up to 2 years. Diagnoses confirmed histologically, 100 animals/exposure or control group. There was a significant decrease (\*) in lymphomas in female mice exposed to 1000-μT intermittent (1 h on/1 h off) fields when compared to controls (17, 19).

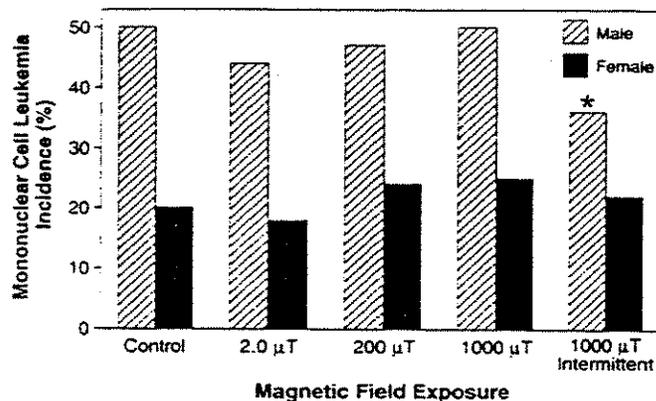


FIG. 2. Incidence of mononuclear cell leukemia in F344/N rats exposed to sham fields or 60 Hz magnetic fields for 18.5 h/day for up to 2 years. Diagnoses confirmed histologically, 100 animals/exposure or control group. There was a significant decrease (\*) in mononuclear cell leukemia in male rats exposed to 1000-μT intermittent (1 h on/1 h off) fields when compared to controls (16, 19).

together in evaluating a response to a chemical (47). Leukemias in mice often show a similar distribution and pattern to analogous diseases in humans. In young mice, lymphomas often arise in the thymus (usually of T-lymphocyte origin), while later in life, they arise in the spleen and lymph nodes (usually of B-cell origin). The mouse gene *Tcl1* is analogous to the breakpoint gene *TCL1* found in human T-cell proliferations and chronic lymphocytic leukemias (48). Mice used to study genetic instability in radiation-induced leukemias show genetic instability similar to *de novo* multistage carcinogenesis (49). Mouse leukemia models have been used in drug development to evaluate various chemotherapeutic regimens prior to their use in humans (50).

Large granular lymphocytic leukemia is the most common leukemia in the F344 rat (51, 52). In contrast to leukemia, lymphomas are very rare in the F344 rat. The LGL leukemia in the F344 rat has similarities to the human chronic lymphocytic leukemia of T-cell origin. Large granular lymphocytic leukemia may have some similarities to the disease found in the F344 rat (51). However, the rat has not been as widely used in leukemia research, in part because the disease in the mouse appears more analogous to the disease in humans.

Most carcinogenic agents can be characterized as either genotoxic or nongenotoxic. Genotoxic agents (or their metabolites) cause direct DNA damage such as mutations or DNA adducts, while nongenotoxic agents affect the process of carcinogenesis through receptor-mediated mechanisms, by modulation of growth factors, and by other means. Nongenotoxic agents include drugs, hormones and agents that may also promote the process of carcinogenesis, in some cases by sustained cell proliferation. The limited data indicating that magnetic-field exposure may alter the cancer process are more suggestive of a nongenotoxic than a genotoxic mechanism (53-55). It is hypothesized that if magnetic-field exposures alter the cancer process, it is more likely to occur through a promotional mechanism.

#### Long-Term Rodent Models with Magnetic-Field Exposures

In four studies, rats and/or mice were exposed to magnetic fields for periods varying from 24 to 28 months (Tables 1 and 2). Groups of 100 male and female B6C3F<sub>1</sub> mice and groups of 100 male and female F344/N rats were exposed to 0, 2-, 200- or 1000-μT continuous or to 1000-μT intermittent 60 Hz magnetic fields for up to 2 years (16, 17, 19). Complete pathology examinations with audits of pathology specimens and an independent peer review of pathology diagnoses were performed. In mice, there was no increase in leukemia/lymphoma, and a significant decrease in lymphomas in female mice in the 1000-μT intermittent group was observed (Fig. 1). Increased hyperplasia of the lymphoid tissues was not found with magnetic-field exposure. In rats, there was no increase in mononuclear cell leukemia in any group (Fig. 2). The only significant leukemia finding was a decreased incidence of mononuclear cell leukemia in male rats exposed to 1000-μT intermittent fields. There was no evidence of increased incidence of preneoplastic lesions of the lymphoid tissues in the exposed groups in rats.

In a second study, groups of 50 female F344 rats were exposed to 0, 2-, 20-, 200- or 2000-μT magnetic fields at 60 Hz from day 20 of gestation to 2 years of age (18). This study was done in a blind fashion and included complete pathology evaluation with independent peer review of the pathology diagnoses. The incidence of leukemia was similar between exposed and control groups (Fig. 3).

In a third study, groups of 48 F344 rats were exposed to 0, 500- or 5000-μT magnetic fields at 50 Hz (20). The engineering was well documented, which is critical at the high exposure intensities above 2000 μT that were used. There was no difference in leukemia incidence among groups, with the highest incidence observed in the control groups for both genders (Fig. 4).

A fourth study, designed to evaluate the potential promotional effect of magnetic-field exposure after exposure to ion-

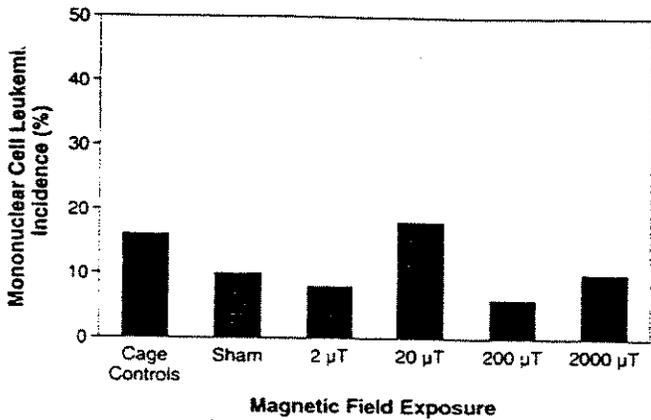


FIG. 3. Incidence of mononuclear cell leukemia in female F344/N rats exposed from day 20 of gestation to sham fields or 60 Hz magnetic fields for 20 h/day for up to 2 years. Diagnoses confirmed histologically, 50 animals/exposure or control group. There was no significant effect of magnetic-field exposure on incidence of mononuclear cell leukemia (18).

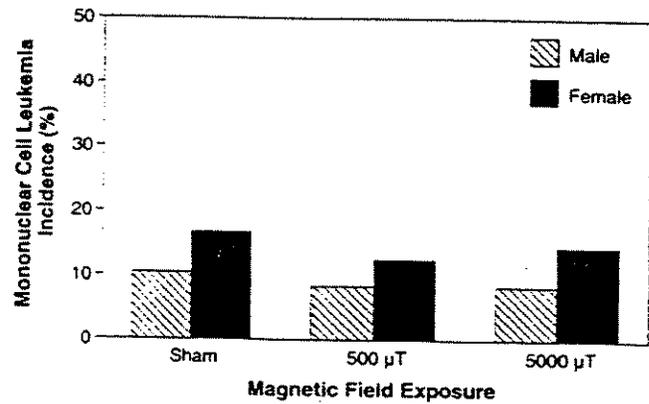


FIG. 4. Incidence of mononuclear cell leukemia in F344 rats exposed to sham fields or 50 Hz magnetic fields for 21 h/day (monthly average) for up to 2 years. Diagnoses confirmed histologically, 48 animals/exposure or control group. There was no significant effect of magnetic-field exposure on incidence of mononuclear cell leukemia (20).

izing radiation, also included three groups of mice not receiving an initiating dose of ionizing radiation (25). C57BL/6J mice develop lymphomas with aging (or after exposure to ionizing radiation), and lymphomas were the focus of the study. A group of 190 female mice (sham controls), a group of 190 female mice (room controls), and a group of 380 mice (used to 60 Hz 1,400- $\mu$ T circularly polarized magnetic fields) were followed for 28 months. The large number of mice (940 total) makes this study relatively sensitive to detecting a potential effect of magnetic-field exposure on leukemia (25). The lymphomas were classified as to cell of origin (56, 57). The majority were B-cell lymphomas, and there was no effect of magnetic-field exposure (Table 3). Histiocytic sarcomas were the second most frequent tumor diagnosed. Lymphoblastic lymphoma and lymphocytic lymphoma, which may be of either B- or T-cell origin, occurred at an incidence of 2% or less (Table 3). A small percentage of lymphomas were not classifiable as to cellular origin, and only four granulocytic leukemias were found. No effects of magnetic-field exposure on either total lymphomas or any lymphoma subtype were observed.

In a small study, groups of 8 to 15 male and female CFW mice were exposed to 60 Hz magnetic fields at 25,000- $\mu$ T field intensity, which can create both heat and vibration (13). The authors did not adequately explain how these potential confounders were addressed. A magnetic-field effect was reported in the second generation of the exposed female mice; however, the age of the exposed and control animals differed. The control females were 49 to 102 days old, while the exposed females were up to 418 days old (13). In second-generation males (controls, 51 to 103 days old, exposed, 55 to 103 days old), leukemia was not found in either exposed or control groups. The third generation involved larger groups of animals (16 to 25 for controls; 44 to 48 for exposed groups), but age-related risk was not given. The criteria for selecting pups for studies of subsequent generations were not

given. Some of the figures in the article were more suggestive of hyperplasia than neoplasia. The controls and exposed animals were housed in different areas that may not have been comparable. These factors make the reported effects difficult to interpret.

#### Magnetic-Field Exposures after Initiation by a Physical or Chemical Agent

A large initiation/promotion study used ionizing radiation in fractionated doses to evaluate the potential effect of magnetic fields on radiation-induced cancer (25). The study with 2660 female C57BL/6J mice evaluated 60 Hz circularly polarized magnetic fields at 1400- $\mu$ T field intensity. The C57BL/6J mice were initiated by exposure to 0, 3.0, 4.0 or 5.1 Gy ionizing radiation in four fractions at about 4 weeks of age followed by either sham or 60 Hz magnetic-field exposure for 18.5 h per day. The animals were allowed to live

TABLE 3  
Effect of 60 Hz Magnetic Fields on Leukemia in Female C57BL/6J Mice

Diagnosis	Room controls	Sham	
	(n = 380)	controls (n = 190)	1,400- $\mu$ T MF (n = 380)
Lymphoblastic lymphoma*	5 (1.3%)	1 (0.5%)	1 (0.3%)
Lymphocytic lymphoma*	5 (1.3%)	2 (1.1%)	7 (2.0%)
B-cell lymphoma*	110 (29%)	57 (30%)	119 (31%)
Lymphoma, NOS†	9 (2.4%)	6 (3%)	13 (3.4%)
Lymphomas, combined	129 (34%)	66 (35%)	140 (37%)
Granulocytic leukemia	2 (0.5%)	0 (—)	2 (0.5%)
Histiocytic sarcoma	109 (29%)	42 (22%)	90 (24%)

Note. For complete details, see ref. (25).

\* MF = 60 Hz circularly polarized magnetic fields.

† Both B- and T-cell origin.

‡ Number of affected mice (%).

§ Includes follicular center cell, plasma cell and immunoblastic lymphomas.

¶ NOS = not otherwise specified.

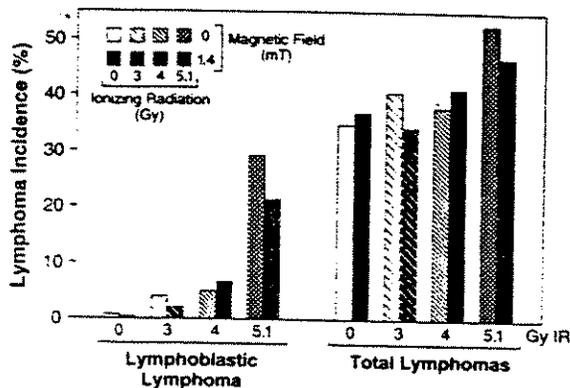


FIG. 5. Incidence of lymphoblastic lymphoma or total lymphomas in female C57BL/6J mice exposed beginning at 4 weeks of age to four weekly fractionated doses of ionizing radiation (0, 3, 4, 5.1 Gy) followed by exposure to sham fields or 60 Hz circularly polarized magnetic fields for 18 h/day for up to 28 months. Diagnoses confirmed histologically. 190 mice/control group with 380 mice/magnetic-field exposure group. The lymphoblastic lymphomas were almost entirely of thymic origin and increased with increasing dose of ionizing radiation. There was no significant effect of magnetic-field exposure on incidence of lymphoblastic lymphoma or total lymphoma (25).

discrepancies resolved by an independent review panel, lending credibility to the diagnostic classification. The strength of the study is the large group size (this part of the study involved over 1700 mice). A limitation of the study design is the use of one field intensity. No effect of magnetic-field exposure on the incidence of total lymphomas or on lymphoma subtypes was found (Fig. 5, Table 4). This finding is important since this mouse model has been widely used to study the process of leukemogenesis, which in the mouse has many similarities to the disease in humans (58-60).

A second initiation/promotion study used dimethylbenz(a)anthracene (DMBA) to induce thymic lymphoma in Swiss Webster mice (14). The mice were injected with DMBA at birth and at 14 days of age were exposed to 50 Hz 1000- $\mu$ T fields for 16 weeks (14). There were 155 sham-exposed and 165 magnetic-field-exposed mice. The overall incidence of lymphoma was similar between groups (Table 5). The group size (over 150 mice per group) is a study strength, but the sensitivity of this model for detecting a promoter is not well known, and the short time (16 weeks) may not be adequate to detect a promoting effect of magnetic fields.

until moribund or until 29 months old, at which time the remaining animals were sacrificed. Major lymphoid tissues and organs, usually affected by lymphoma, were examined for the presence of leukemia/lymphoma. The leukemia was classified into morphological types (57) that represent the cell of origin [i.e. T cells, B cells, histiocytes (histiocytic sarcoma) or myelogenous (granulocytic leukemia)]. The pathology diagnoses were reviewed by a second and third pathologist with

*Magnetic-Field Exposures Using Transgenic Mouse Models*

There is currently considerable interest in tumor-predisposed transgenic mouse models for identification of potential environmental hazards. However, the utility of such models to detect chemical carcinogens is still open to debate (61, 62). Certain strains of transgenic mice have been shown to develop

TABLE 4  
 Effect of 60 Hz Magnetic Fields on Leukemia in Irradiated Female C57BL/6J Mice

Diagnosis	3.0 Gy		4.0 Gy		5.1 Gy	
	Control n = 190	MF <sup>a</sup> n = 380	n = 190	MF n = 380	Control n = 190	MF n = 380
Lymphoblastic lymphoma <sup>a</sup>	7 (3.7%)	7 (1.8%)	9 (4.7%)	24 (6.3%)	55 (28.9%)	80 (21.1%)
Lymphocytic lymphoma <sup>a</sup>	5 (2.6%)	11 (3.0%)	7 (3.7%)	12 (3.2%)	4 (2.1%)	8 (2.1%)
B-cell lymphoma <sup>a</sup>	59 (31.1%)	101 (26.6%)	54 (28.4%)	108 (28.4%)	38 (20.0%)	77 (20.3%)
Lymphoma, NOS <sup>b</sup>	6 (3.2%)	11 (2.9%)	2 (1.1%)	12 (3.2%)	3 (1.6%)	12 (3.2%)
Lymphomas, all	77 (40.5%)	130 (34.2%)	72 (37.9%)	156 (41.1%)	100 (52.6%)	177 (46.6%)
Granulocytic leukemia	3 (1.6%)	0	0	0	1 (0.5%)	1 (0.3%)
Histiocytic sarcoma	36 (18.9%)	74 (19.5%)	36 (18.9%)	73 (19.2%)	28 (14.7%)	52 (13.7%)

Note. For complete details, see ref. (25).

<sup>a</sup>MF = 60 Hz circularly polarized magnetic fields.

<sup>b</sup>In irradiated mice, occurred almost exclusively in the thymus and thus probably of T-cell origin.

<sup>c</sup>Number of affected mice (%).

<sup>d</sup>Both B- and T-cell origin.

<sup>e</sup>Includes follicular center cell, plasma cell and immunoblastic lymphomas.

<sup>f</sup>NOS = not otherwise specified.

**TABLE 5**  
**Lymphoma/Leukemia in DMBA/Magnetic-Field-Exposed Mice<sup>a</sup>**

Diagnosis	Sham controls		MF <sup>b</sup> -exposed	
	Males <i>n</i> = 80	Females <i>n</i> = 75	Males <i>n</i> = 89	Females <i>n</i> = 76
Thymic lymphoma	18 22.5%	28 37.3%	24 27.0%	26 34.2%
Granulocytic leukemia	1 1.3%	3 4.0%	3 3.4%	2 2.6%

Note. Data from Shen *et al.* (14).

<sup>a</sup> 35 µg DMBA injected subcutaneously within 24 h of birth.

<sup>b</sup> 50 Hz 1000-µT fields for 16 weeks or sham exposure beginning at 2 weeks of age.

cancer when exposed to X rays (63) and ultraviolet radiation (64).

*Pim1* mice are highly sensitive to ethyl nitrosourea (ENU) and have a high incidence of lymphoma within 4 to 5 months after ENU treatment. Without ENU treatment, lymphomas generally develop after 12 months in *Pim1* mice. The activity of the *Pim1* oncogene is associated with the development of murine lymphoma; the human *PIM1* oncogene has yet to be implicated in human leukemia/lymphoma (21, 65). The *Trp53*<sup>-/-</sup> mouse is considered a good leukemia model because

transitions and mutations in *TP53* are common genetic alterations in human malignancies (21). The *Trp53*<sup>-/-</sup> mouse has a very low incidence of lymphoma in 4 to 5 months, with nearly all tumors occurring after 12 months of age. Three studies evaluated the potential of magnetic fields to alter leukemia rates in *Pim1* and *Trp53*<sup>-/-</sup> transgenic mice.

In the largest transgenic mouse study, groups of approximately 100 Eµ-*Pim1* transgenic mice were exposed to 50 Hz fields at 0, 1-, 100- and 1000-µT continuous and 1000-µT intermittent exposure (15 min on/15 min off) for up to 18 months (15). Animals dying during the study were examined histopathologically for the presence of leukemia. At 18 months, the study was terminated and the remaining animals were discarded without examination. This study did not show an association between magnetic-field exposure and the incidence of leukemia (Table 6). The large and multiple exposure groups are a study strength, while the lack of histopathological examination of the mice at the end of the study is a weakness of the study design.

In another study, groups of 30 male and female *Pim1* transgenic mice were given a single dose of ENU followed by exposure to 60 Hz fields at 2-, 200- and 1000-µT continuous and 1000-µT intermittent exposures (1 h on/1 h off) for 23 weeks (21). An increase in lymphoma incidence was not found in the exposed mice (Table 7), although male mice exposed to 1000-µT intermittent magnetic fields had significantly fewer lymphomas (*P* < 0.05). The study did not show an association between magnetic-field exposure and the incidence of leukemia (21). A weakness of this study is the small number of animals.

Groups of 30 male and female *Trp53*<sup>-/-</sup> mice were ex-

**TABLE 6**  
**Lymphoma in Eµ-*Pim1* Transgenic Mice Exposed to 50 Hz Magnetic Fields**

Exposure (µT)	<i>n</i>	Lympho-blastic	Nonlym-phoblastic	Total
Control	111	6	26	32 (28.8%) <sup>a</sup>
1	105	5	26	31 (29.5%)
100	103	8	19	27 (26.2%)
1000	105	9	23	32 (30.5%)
1000 (I) <sup>b</sup>	104	7	29	36 (34.6%)

Note. Data from Harris *et al.* (15).

<sup>a</sup> Number of affected mice (%).

<sup>b</sup> Fifteen minutes on/15 min off.

posed to 0 or 1000-µT 60 Hz magnetic fields for 23 weeks (21). The lymphoma incidence was 3% in the control males compared to 0% in the magnetic-field-exposed animals. In females, the lymphoma incidence was 3% in controls compared to 7% in the magnetic-field-exposed animals. Neither the decreased incidence in males nor the increased incidence in females was statistically significant. There are small numbers of animals in this study and the sensitivity of the *Trp53*<sup>-/-</sup> transgenic mouse model to detect leukemogenesis has not been well studied.

#### Magnetic-Field Exposures Using Transplanted Tumor Models

Magnetic fields may also affect the growth of cancer after it has developed. Three studies evaluated tumor growth in rodents injected with leukemia cells and then exposed to magnetic fields.

Groups of 18 male F344 rats were injected with fresh mononuclear leukemia cells (10<sup>7</sup> cells) and exposed to sham fields (<0.1 µT), ambient fields (approximately 2 µT), 60 Hz fields at 1000-µT field intensity, or whole-body irradiation (positive control) (22, 23). This study evaluated the growth of leukemia by serial sacrifice and repeated bleeding for up to 10 weeks by taking multiple blood samples and performing hematological examinations. Consistent significant differences were not found between the magnetic-field- and sham-exposed animals. The authors concluded that 1000-µT magnetic fields did not alter the clinical progression of mononuclear cell leukemia in the Fischer rat (22, 23).

**TABLE 7**  
**Effect of 60 Hz Magnetic Fields on Lymphoma Induction in *Pim1* Mice**

Exposure (µT)	Males <i>n</i> = 30	Females <i>n</i> = 30
Sham control	15 (49%)	14 (47%)
2	14 (47%)	13 (45%)
200	13 (43%)	13 (45%)
1000 (continuous)	7 (23%) <sup>a</sup>	14 (47%)
1000 (intermittent)	17 (57%)	16 (53%)

Note. Data from McCormick *et al.* (21).

<sup>a</sup> *P* < 0.05 compared to controls, Student's *t* test.

In a second study, groups of 18 rats were exposed to 1000- $\mu$ T magnetic fields with either continuous or intermittent (off/on at 3-min intervals) exposures for 20 h per day, 7 days per week or sham fields (24). Exposure to 5 Gy of ionizing radiation was used as a positive control. All rats were injected intraperitoneally with either  $2.2 \times 10^7$  or  $2.2 \times 10^6$  mononuclear cell leukemia cells at the initiation of the magnetic-field or sham exposure. Rats from each treatment group were bled and evaluated five to eight times during a 14- (2.2  $\times$  10<sup>7</sup>) or 16-week (2.2  $\times$  10<sup>6</sup>) exposure period. Significant differences in the body weight or red blood cell indices (number of red blood cells, hemoglobin, hematocrit) for either the continuous or the intermittent magnetic-field exposure groups receiving either  $2.2 \times 10^6$  or  $2.2 \times 10^7$  cells were not found (24). Combining the sampling days and using an analysis of variance, significant effects were found on red and white blood cell indices for the intermittent exposure group receiving  $2.2 \times 10^7$  cells. Groups receiving continuous magnetic-field exposure with either  $2.2 \times 10^6$  or  $2.2 \times 10^7$  cells did not show an effect using analysis of variance. Groups of rats receiving intermittent exposure and  $2.2 \times 10^6$  cells did not show an effect with analysis of variance (24). Animals exposed to whole-body irradiation (positive control) did show more rapid growth of leukemia as measured by white blood cell and red blood cell indices. These are relatively large studies but the sensitivity to detect subtle effects, as might be predicted with magnetic-field exposures, is not known.

In a third study, groups of 10 female DBA/2 mice were implanted with P388 leukemia cells and exposed to 60 Hz fields at 1.4, 200 and 500  $\mu$ T within 2 to 3 h after implantation and then for 6 h per day until the animals died (12). There was no effect of magnetic fields on disease progression; however, all mice died within 3 weeks, limiting the opportunity to demonstrate an effect.

#### *Magnetic-Field Exposures Other than 50 or 60 Hz Sinusoidal Fields*

Groups of 47 to 64 CBA mice were initially exposed to 5.24 Gy X rays and then subjected over their lifetime to either 200 kHz saw-tooth 15- $\mu$ T magnetic fields or no magnetic fields (66). In parallel studies, groups of mice were either exposed to saw-tooth 15- $\mu$ T fields over their lifetime (without ionizing radiation) or sham-exposed. No statistically significant differences between the magnetic-field-exposed animals and their corresponding controls were found (66). In a follow-up study, it was reported that CBA mice continuously exposed or sham-exposed to 50 Hz magnetic fields for 54 h showed no difference in cell proliferation in the various organs examined (67).

Groups of 100 to 101 transgenic E $\mu$ -*Pim1* mice were exposed to pulsed 900 MHz electromagnetic fields for 18 months (68). The exposed group (43/101) had a significantly increased ( $P > 0.01$ ) incidence of lymphoma compared to control mice (22/100) (68). The authors conclude that 900

MHz field exposure may have an effect on the incidence of leukemia (68).

Groups of leukemia-prone AKR mice were exposed to 6-mT "pulsed magnetic fields" at repetition frequencies of either 12 Hz or 460 Hz for 30 min two times per week, and the mice were followed for five generations (69). Weights of the spleens and thymus at postmortem were used to judge the presence of lymphoma. No difference in leukemia or survival curves over five generations was found (69). However, the lack of histopathology and the sparse description of the magnetic-field exposures make this study difficult to evaluate.

#### SUMMARY AND CONCLUSIONS

Four long-term magnetic-field studies with exposures for 2 years or more (16-18, 20) were reviewed. The four studies included exposures beginning prior to or after birth, field intensities up to 5000  $\mu$ T, both linear or circularly polarized fields, and over 3000 animals (F344 rats, B6C3F<sub>1</sub> and C57BL/6J mice). There were 9 control and 25 exposed groups. There was no increase in the incidence of lymphoma or leukemia in any exposed group compared to controls, and two exposed groups had significant reductions in leukemia/lymphoma incidence compared to controls.

Two studies evaluated the potential of magnetic fields to promote leukemia induced by physical or chemical agents. In one study, female mice were exposed to ionizing radiation followed by exposure to magnetic fields for their lifetime, while in a second study, DMBA was used to induce thymic leukemia in male and female mice. Neither study showed an effect of magnetic-field exposure on the promotion of leukemia.

Three studies evaluated the potential of magnetic fields to alter leukemia in *Trp53*<sup>-/-</sup> and *Pim1* transgenic mice. The studies varied from 23 weeks to 18 months of magnetic-field exposure. One study used *Pim1* mice that had been initiated with ENU to induce leukemia (21). Magnetic-field exposure did not increase leukemia incidence in these models; one exposed group had significantly fewer lymphomas.

Three studies involved an evaluation of tumor growth in rodents that were injected with leukemia cells and then exposed to magnetic fields. These studies failed to demonstrate an effect of magnetic fields on tumor growth.

Several studies involved higher-frequency fields. One study showed an increase in leukemia in mice exposed to pulsed magnetic fields at 900 MHz (68), whereas all other studies were negative for an effect on leukemia incidence.

When considered in totality, the animal studies provide an adequate and sufficient evaluation of 50 and 60 Hz magnetic-field exposures. The animal data are cohesive, consistent and uniformly negative for showing any increased incidence of leukemia in a variety of rodent models after magnetic-field exposure. It is noteworthy that in several instances, the exposed groups had significantly reduced leukemia incidence compared to the controls. The potential association between 50/60 Hz magnetic-field exposure and increased rates of leu-

s suggested by some epidemiological studies (1, 2) is weakened by the lack of an effect in animal studies. Without further understanding of possible mechanisms through which magnetic fields may exert an effect on biological systems, it is unlikely that additional animal studies will resolve the discrepancies in epidemiological findings.

*Note added in proof:* A major UK case-control childhood cancer study found no evidence that exposure to magnetic fields associated with the electricity supply increases the risks for childhood leukemia or any other childhood cancer (*Lancet* 354, 1925-1931, 1999).

#### ACKNOWLEDGMENTS

The authors thank Drs. Gordon Flake, Mary Wolfe and Barb Davis for the careful review of the manuscript and for their helpful suggestions.

Received: July 14, 1999; accepted: October 20, 1999

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