Assessing the Potential Carcinogenic Activity of Magnetic Fields Using Animal Models

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We update our 1997 publication by reviewing 29 new reports of tests of magnetic fields (MFs) in six different *in vivo* animal models of carcinogenesis: 2-year, lifetime, or multigeneration exposure studies in rats or mice; and promotion/progression models (rat mammary carcinoma, rat liver focus, mouse skin, several models of human leukemia/lymphoma in rats and mice, and brain cancer in rats). Individual experiments are evaluated using a set of data quality criteria, and summary judgments are made across multiple experiments by applying a criterion of rough reproducibility. The potential for carcinogenicity of MFs is discussed in light of the significant body of carcinogenesis data from animal bioassays that now exists. Excluding abstracts, approximately 80% of the 41 completed studies identified in this and our previous review roughly satisfy data quality criteria. Among these studies, the criterion for independent reproducibility is not satisfied for any positive results but is satisfied for negative results in chronic bioassays in rats and mice and for negative results in both promotion and co-promotion assays using the SENCAR mouse skin model. Results of independent replication studies using the rat mammary carcinoma model were conflicting. We conclude that long-term exposure to continuous 50- or 60-Hz MFs in the range of 0.002–5 mT is unlikely to result in carcinogenesis in rats or mice. Though results of most promotion/progression assays are negative, a weak promoting effect of MFs under certain exposure conditions cannot be ruled out based on available data. *Key words*: animal models, carcinogenesis, EMF, electric fields, health effects, magnetic fields, toxicology. — *Environ Health Perspect* 108(suppl 1):79–100 (2000).
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Previously, we reviewed 36 publications that reported results of some 30 completed tumorigenicity tests of electric and magnetic fields (EMFs) in eight major animal model systems and 6 studies that were in progress (*1*). Since our review was published, the 6 in-progress studies have been completed, and some 20 new reports have been identified (Table 1). More than 60 reports describing completed studies are now available for review. The great majority of these studies test for potential tumorigenicity of 50- or 60-Hz sinusoidal magnetic fields (MFs) (delivered either continuously or intermittently). More than 90% of the exposure conditions examined in these studies involve MFs between 1 μT and 2 mT. Thus, an extensive database is now available from tests of 50- or 60-Hz MFs at flux densities in the range of and exceeding some environmental human exposures. In this review we update and extend our previous analysis. We employ a set of quality and comparability criteria to consider whether the results from these reports are sufficient to justify an overall conclusion as to the carcinogenic potential of EMFs in animal model systems. Assessments of the carcinogenic potential of environmental EMFs have also recently been conducted by the National Research Council (NRC) and the National Institute for Environmental Health Sciences (*2–6*).

Quality Assurance and Reproducibility/Comparability Criteria

Good laboratory practice (GLP) standards (*7*) address the complex quality assurance (Q/A) aspects of *in vivo* laboratory studies, particularly long-term chronic animal bioassays. GLP includes such aspects as standard laboratory operating procedures and protocols for test methods, facilities management and operating procedures, personnel qualifications, and data management and recordkeeping. It is not possible from examining most published reports to determine whether a particular study conforms to many of the quality standards specified by GLP. Therefore, we consider that studies that state they have been conducted according to GLP provide important Q/A information that cannot otherwise be determined. We have noted in the text and in Table 2 those studies that indicate they have been conducted according to GLP.

Each experiment was also evaluated against five additional data quality objectives: *a*) conformity of exposure conditions and biologic tests to accepted protocols for a particular assay; *b*) sufficiency of the experimental details reported relative to permitting an adequate characterization of exposure conditions and biologic results; *c*) inclusion of critical control experiments; *d*) internal reproducibility and/or dose–response character of results; and *e*) use of appropriate statistical methodology.

We have noted in the text and in Table 2 when any aspect of a study was conducted under blinded conditions. However, we have evaluated the significance of this Q/A feature on a case-by-case basis, since there is a difference of opinion among investigators as to the desirability of using a blinded approach, particularly for pathologic evaluations (*8,9*).

We have also noted in the text and in Table 2 when a study protocol included a positive control. The importance and feasibility of including positive controls varies for different assays. Specifically, the size and complexity of some protocols, particularly long-term chronic bioassays, preclude the practical addition of a positive control. A positive control, when feasible, is particularly important to include in an assay that is relatively nonstandardized or variable. We have commented in the text on those cases in which the addition or omission of a positive control contributed significantly to the evaluation of study results.

As we have previously discussed with reference to the genotoxicity literature (*10*), an important limitation in applying data quality criteria to experiments from the published literature is that experiments that do not meet these criteria because of a failure to include sufficient information may be quite adequate experimentally, but if this cannot be determined from the information provided in the publication, a conservative analysis must classify them as not meeting quality criteria. In our analysis we have attempted to at least partially take this potential problem into account by pointing out which experiments failed to meet data quality criteria solely because of incomplete information.

Multiple experiments satisfying data quality objectives in the same animal model system were cross compared to determine whether an overall positive or negative

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Table 1. Carcinogenesis bioassay reports reviewed.

Study (reference)	Tests aimed primarily at detecting initiators		Tests aimed primarily at detecting agents that affect postinitiation stages of carcinogenesis					
	2-year or lifetime	Multi-generation	Rat mammary	Mouse skin	Mouse lymphoma	Rat leukemia transplant	Lymphoma/leukemia-prone mouse strains	Rodent brain
Anderson et al. (*80*)						X		
Anderson et al. (*79*)						X		
Anderson et al. (*34*)			X					
Anisimov et al. (*29*)			X					
Babbitt et al. (*15*)	X				X			
Bellossi (*85*)							X	
Boorman et al. (*13*)	X							
Boorman et al. (*35*)			X					
Byus et al. (*57*)				X				
Ekström et al. (*30*)			X					
Fam and Mikhail (*17*)		X						
Harris et al. (*83*)							X	
Kharazi et al. [discussed by the RAPID Working Group (*3*)]								X
Kumlin et al. (*56*)				X				
Mandeville et al. (*14*)	X							
Mandeville et al. (*133*)								X
McCormick et al. (*12*)	X							
McCormick et al. (*77*)							X	
McLean et al. (*53*)				X				
Morris et al. (*82*)						X		
Mevissen et al. (*31*)			X					
Mevissen et al. (*32*)			X					
NTP (*11*)	X							
NTP (*33*)			X					
Sasser et al. (*81*)						X		
Sasser et al. (*52*)				X				
Shen et al. (*84*)					X			
Thun-Battersby et al. (*38*)			X					
Yasui et al. (*16*)	X							

conclusion was justified for a particular model system. For this second-level analysis we considered that a result was most likely under the conditions of assay if the result could be classified as roughly reproducible. [For an example of the use of this approach for genotoxicity data, see McCann et al. (*10*).] The criterion of rough reproducibility attempts to take into account the infrequency with which studies are precisely replicated in the open literature. We considered that two results were roughly comparable if exposure and assay conditions were similar enough to conclude that the condition of independent reproducibility would most likely be satisfied were such a test to be conducted for any of the studies satisfying the condition. Aspects considered in making a judgment that protocols were roughly similar included rodent strains employed, dosing amounts and schedules (e.g., dose of initiator in promotion studies), exposure and end point monitoring schedules, parameters monitored, and results in null and positive controls. Exposures were considered roughly similar if flux densities employed were within a factor of 5, if frequencies employed were either 50 or 60 Hz, and if waveforms delivered were similar in character (e.g., both continuous or both intermittent or pulsed in experiments compared).

Clearly, decisions as to whether a particular experiment adheres to data quality or independent reproducibility criteria are often not clear cut. Nor is there any clear-cut method for unequivocally making summary judgments concerning the positivity or negativity of an agent based on tumorigenicity data from multiple nonidentical assay systems and exposure conditions. Scientific judgment must be applied, which, inevitably is somewhat subjective.

Results

The types of bioassays used to test EMFs for carcinogenic potential fall roughly into two categories. These include long-term (2-year/lifetime or multigeneration) chronic exposure studies aimed primarily at determining whether EMF has activity as a complete carcinogen, and a variety of usually shorter-term bioassays aimed at determining whether EMFs have potential to modulate post-initiation stages of carcinogenesis. The 29 reports available for review since our previous publication (*1*) are listed in Table 1. These include 7 reports from 5 independent research groups describing results of single- or multigeneration chronic exposure studies, and 22 reports presenting results from 12 independent research groups conducting a variety of bioassays focused primarily on post-initiation stages of carcinogenesis.

Applying the data quality criteria specified above, we present an analysis of experiments presented in these 29 new reports. Results of these reports are summarized in Table 2. We also integrate these results with those from our previous review (*1*) and offer a summary judgment as to whether a conclusion as to the positivity or negativity of EMFs in each model system is justified.

Tests of MFs in 2-Year, Lifetime, or Multigeneration Exposure Studies

In our previous publication (*1*), we identified several 2-year or multigeneration chronic exposure studies that were either in progress or incompletely reported and therefore not available for adequate review [see McCann et al. (*1*) for references and discussion]. The three studies reported as in progress have now been completed (*11–15*). Studies that were complete at the time of our earlier review but that could not be evaluated because they were available only in preliminary or abstract form have now appeared in more complete form (*16,17*). We briefly review and assess results reported in these seven new reports.

The studies conducted by the National Toxicology Program (NTP) using F344 rats

Table 2. Tests of magnetic fields in carcinogenesis bioassays.

Rodent strain	Initiator/(promoter)	EMF exposure[a]	Comments on quality criteria	Results reported by author	Reference
		Tests aimed primarily at detecting initiators			
F344/N rats and B6C3F$_1$ mice (male and female, 100 per sex group)		60-Hz, 2 μT, 0.2 mT, or 1 mT (18.5 hr/d, 7 d/wk for 106 wk); or 60-Hz, 1 mT (intermittent: 1 hr on/1 hr off, 18.5 hr/d, 7 d/wk, 106 wk)	GLP; independent audits of pathology data, specimens, and tables	Equivocal evidence of carcinogenic activity[b] in male rats based on increased incidence of thyroid gland C-cell neoplasms in male rats exposed to 2 μT and 0.2 mT MFs ($p < 0.01$)	(*11–13*)
F344/DuCrj rats (male and female, 48 per sex group)		50-Hz, 0.5 mT, 5 mT 22.6 hr/d for 2 yr	Histopathologic analysis limited to tissues exhibiting macroscopic signs of disease	Negative. A statistically significant ($p < 0.05$) increase in fibroma of the subcutis in male rats was considered not biologically significant when compared to historical controls	(*16*)
F344 rats (female, 50 per group)		60-Hz, 2 μT, 20 μT, 200 μT, or 2 mT (20 hr/d, 2 yr beginning 2 d before birth)	Independent analyses to monitor animal health, and Q/A audits of the exposure systems and pathology data and diagnoses; both the exposure and the histopathologic analyses were conducted under blinded conditions	Negative	(*14*)
C57Bl/6 mice (females, 380 per MF-exposed group)		60-Hz, 1.41 mT, circularly polarized, 18.5 hr/d. Exposure began at 4 wk and ended at natural death (~ 29 mo)	GLP; internal and external peer reviews of the histopathologic diagnoses; the exposure and histopathologic analyses were conducted under blinded conditions	Negative for lymphoid cell neoplasms	(*15*)
CFW mice (male and female). Numbers of animals exposed to the MF = 3 (1st gen.); 44 (2nd gen.); 92 (3rd gen.)		60-Hz, 25 mT (23 hr/d)	Unusual experimental design; limited information provided on some critical aspects of the experimental protocol and pathologic analysis	Positive. Statistically significant increase in lymphoma incidence in third-gen. animals exposed to the MF compared to unexposed controls	(*17*)
		Tests aimed primarily at detecting agents that affect postinitiation stages of carcinogenesis			
Rat mammary gland					
Outbred rats (females, ~ 40–50 per group)	MNU (50 mg/kg, i.v., 1×/wk for 3 wk)	50-Hz, ~ 20 μT ac or dc; 3 hr/d for 15 mo; MF exposure began 2 d after the first injection	Insufficient information on the design of the exposure system and the rat strain employed	Positive. Increased incidence of adenocarcinoma in animals exposed (under 24-hr light conditions) to MNU and ac fields compared to rats exposed to MNU alone ($p < 0.05$); decreased latency in rats exposed (under 12 hr light/12 hr dark) to MNU and ac fields compared to rats exposed to MNU alone ($p < 0.05$); and decreased latency in rats exposed (under 24-hr light condition) to MNU and dc fields compared to rats exposed to MNU alone ($p < 0.05$)	(*29*)
Sprague-Dawley rats (females, 99 per group)	DMBA (5 mg/rat, i.g., 1×/wk for 4 wk)	50-Hz, 100 μT, 24 hr/d, 7 d/wk for 91 d	No histopathologic analysis; all phases of the study conducted under blinded conditions; exposure parameters validated by independent audit; exposure system patterned on an NTP-recommended protocol	Positive. Increased incidence of palpable mammary tumors in rats exposed to the MF compared to sham-exposed animals. At necropsy, increased incidence of macroscopically visible tumors (83% vs 62% at 91 d, $p < 0.05$)	(*32*)
Sprague-Dawley rats (females, 99 per group)	DMBA (10 mg/rat, i.g., 1×)	50-Hz, 100 μT, 24 hr/d, 7 d/wk for 27 wk	All phases of the study conducted under blinded conditions; exposure parameters independently validated at regular intervals	Positive. Increased incidence of palpable mammary tumors in MF-exposed rats compared to sham-exposed controls at wk 13, 14, 15, 17, and 18 ($p < 0.05$). At necropsy, increased incidence of macroscopically visible histologically verified tumors ($p < 0.05$)	(*38*)
Sprague-Dawley rats (females, 99 per group)	DMBA (5 mg/rat, i.g., 1×/wk for 4 wk)	50-Hz, 10 μT, 24 hr/d, 7 d/wk for 91 d	Partial histopathologic analysis; exposure and biochemical measurements conducted under blinded conditions.	Negative	(*31*)
Sprague-Dawley rats (females, 60 per group)	DMBA (7 mg/rat, i.g., 1×)	50-Hz, 0.25 and 0.5 mT, 15 sec on/15 sec off, 19–21 hr/ d for 21 wk beginning 1 wk followiing DMBA	Use of a rat substrain with a high propensity to develop mammary tumors spontaneously; no vehicle control group; malignant status of tumors not confirmed histologically	Negative	(*30*)

(*Continued*)

Table 2. *Continued.*

Rodent strain	Initiator/(promoter)	EMF exposure[a]	Comments on quality criteria	Results reported by author	Reference
Sprague-Dawley rats (females, 100 per group)	DMBA (5 mg/rat, i.g., 1×/wk for 4 wk)	50-Hz, 0.1 mT or 0.5 mT; or 60-Hz, 0.1 mT for 18.5 hr/d, 7 d/wk for 13 wk	GLP; magnetic field characterizations independently verified; pathology slides, data records, and tables verified by independent evaluation and reviewed, under blinded conditions, by the NTP Pathology Working Group; complete study audit by an independent Q/A contractor	Negative, but high control incidences of mammary tumors precluded a determination of possible magnetic field effects	(*33,34*)
Sprague-Dawley rats (females, 100 per group)	DMBA (2 mg/rat, i.g., 1×/wk for 4 wk)	50-Hz, 0.1 mT or 0.5 mTfor 18.5 hr/d, 7 d/wk for 13 wk		Negative	(*33,34*)
Sprague-Dawley rats (females, 100 per group)	DMBA (10 mg/rat, i.g., 1×)	50-Hz, 0.1 mT or 0.5 mT; or 60-Hz, 0.1 mT for 18.5 hr/d, 7 d/wk for 26 wk		Negative	(*33,35*)
Mouse skin—promotion					
SENCAR mice (females, 56 per group; nontumor biomarkers for tumor promotion were examined in an additional 24 mice per group)	DMBA (10 nmol/mouse, topical)	60-Hz, 2 mT, 6 hr/d, 5 d/wk for 23 wk	GLP	Negative for skin tumors and nontumor biomarkers	(*54,55*)
Mouse skin—co-promotion					
SENCAR mice (females, 56 per group; nontumor biomarkers for tumor promotion were examined in an additional 24 mice per group)	DMBA (10 nmol/mouse, topical, 2 wk prior to TPA); +/– TPA (1.04, 2, or 4.2 µg/wk)	60-Hz, 2 mT, 6 hr/d, 5 d/wk for 23 wk	GLP	Negative for skin tumors and nontumor biomarkers	(*52,54,55*)
SENCAR mice (sex unspecified, 47–48 per group)	DMBA (10 nmol)/mouse, topical/(PMA, 0.3 µg/mouse/wk for 23 wk beginning 1 wk following DMBA)	60-Hz, 2 mT, 6 hr/d, 6 d/wk for 23 wk		Negative.	(*53*)
K2 mice (female transgenics over-expressing ODC and their nontransgenic littermates, 21–22 per group)	UV (200 J/m^2, 3×/wk) for 10.5 mo	50-Hz, continuous: 0.1 mT; intermittent: 1.3, 13, and 130 µT, each applied in succession for 20 min followed by a 2 hr pause. Both conditions applied 24 hr/d for 10.5 mo except for UV exposure time and cage and room cleaning (2 hr/wk)	Inadequate detail in data presentation	Positive. Statistically significant ($p < 0.015$) increase in rate of onset of macroscopically detectable tumors in both transgenic mice exposed to UV and MFs compared to UV controls	(*56*)
SENCAR mice (number per group not reported)	DMBA (10 nmol/mouse, topical)/(TPA (0.25 mg)/mouse, 2×/wk)[c]	60-Hz, continuous: 0.2 mT and 2 mT; intermittent (30 min on/30 min off): 2 mT. Both conditions applied 7 hr/d, 7 d/wk for 43 wk	Insufficient information provided for analysis	Positive. 0.2 mT, continuous: 20% increase in tumor incidence at 43 wk; 22% increase in total tumors/papillomas and tumors/papillomas per animal at 43 wk. 2 mT, intermittent: small increase in tumors/papillomas per animal between 10–20 wk. Authors do not indicate whether results were statistically significant	(*57*)
Mouse lymphoma					
C57Bl/6 mice (females, 190–380 per group)	Ionizing radiation (cobalt 60): 3.0 Gy, 4.0 Gy, or 5.1 Gy, delivered as fractionated doses at 4 weekly intervals beginning at 4 wk	60-Hz, 1.41 mT, circularly polarized, 18.5 hr/d. Exposure began at 4 wk and ended at 29 mo	GLP; internal and external peer reviews of the histopathologic diagnoses; exposure and histopathologic analyses conducted under blinded conditions	Negative for a variety of lymphoid/leukemia neoplasms.	(*15*)

(*Continued*)

Table 2. *Continued.*

Rodent strain	Initiator/(promoter)	EMF exposure[a]	Comments on quality criteria	Results reported by author	Reference
Swiss-Webster mice (male and female, 75-89 per sex group)	DMBA (35 µg/ mouse, 1×, s.c. at birth)	50-Hz, 1 mT (3 hr/d, 6 d/wk for 16 wk beginning at 14 d of age	Incomplete data presentation	Statistically significant ($p < 0.01$) increase in metastatic infiltration by lymphoma cells into liver in the MF-exposed group compared to sham-exposed controls. No statistically significant differences between MF-exposed and sham-exposed groups in thymic lymphoma incidence at 32 wk	(*84*)
Rat leukemia transplant					
F344 Fischer rats (males, 126/group)	LGL leukemia cells (2.2×10^7/rat, i.p.) injected on the first d of MF exposure	60-Hz, 1 mT, 20 hr/d, 7 d/wk for 18 wk	GLP; progress of experiments periodically reviewed by an independent auditor; positive control group receiving 5 Gy whole body irradiation included	Negative. Disease parameters (body weight, splenomegaly) monitored for 18 wk. Hematologic, morphologic, and and histopathologic parameters monitored for 10–11 wk by repeated bleeding (18 animals per group) and serial sacrifice (108 animals per group)	(*80–82*)
F344 Fischer rats (males, 18/group)	LGL leukemia cells (2.2×10^7 or 2.2×10^6 cells/rat, i.p.) injected on the first d of MF exposure	60-Hz, 1 mT, continuous or intermittent (3 min on/off), 20 hr/d, 7 d/wk for 22 wk	GLP; characteristics of magnetic field exposure validated by the National Institute of Standards and Technology	In the group exposed to intermittent fields, enhancement of the onset of leukemia in the group injected with 2.2×10^7 cells only ($p < 0.01$). Hematologic parameters monitored for 14 wk wk (2.2×10^7 injected cell groups) or 16 wk (2.2×10^6 injected cell groups)	(*79*)
Lymphoma/leukemia-prone mouse strains—transgenic systems					
TSG-*p53* mice (hemizygous for the *p53* null-allele) (males and females, 30/sex group)		60-Hz, 1 mT, 18.5 hr/d for 23 wk	GLP	Negative	(*77*)
Eµ-*pim*-1 mice (males and females, 30/sex group)	ENU (25 mg/kg, 1×, i.p.) one d prior to MF exposure	60-Hz, 2 µT, 200 µT, 1 mT (continuous, 18.5 hr/d for 23 wk); or 60-Hz, 1 mT (intermittent, 1hr on/1 hr off, 18.5 hr/d for 23 wk)		Negative. Lymphoma incidence in males exposed to 1 mT continuous fields significantly reduced ($p < 0.05$) compared to controls	(*77*)
Eµ-*pim*-1 mice (females, ~ 100/ group)		50-Hz, 1 µT, 100 µT, or 1 mT (continuous, 20 hr/d) up to 18 mo; and 50-Hz, 1 mT (pulsed, 15 min on/off)	Necropsies performed only on animals exhibiting clinical signs of disease; incomplete analysis due to autolysis or other causes; exposure and pathology conducted under blinded conditions; histopathology independently evaluated; positive control (ENU) included	Negative. Statistically significant increase in a lethal nontumor end point: a transgene-dependent renal glomerular disease in 1 mT (continuous) MF-exposed group compared to sham-exposed controls	(*83*)
Lymphoma/leukemia-prone mouse strains—leukemia-prone mice					
AKR mice		12-Hz, 6 µT; or 460-Hz, pulsed. Both exposures for 30 min, 2×/wk for 5 generations	Incomplete characterization of exposure and other aspects of study protocol; high spontaneous incidence of leukemia in control	Negative for leukemia	(*85*)
Rat brain					
F344/N (females, 50/group)	ENU (5 mg/kg i.v. on d 18 of gestation)	60-Hz, 2 µT, 20 µT, 200 µT, or 2 mT for 16 mo beginning 48 hr after ENU treatment	GLP; variability in tumor indidence among control groups; exposure, clinical observations, and pathologic evaluations conducted under blinded conditions; exposure system and pathology evaluations validated by independent audit; pathology slides reviewed under blinded conditions; positive control (TPA) included	Negative	(*133*)
C57Bl/6 mice (females, 190-380 per group)	Ionizing radiation (cobalt 60): 3.0 Gy, 4.0 Gy, or 5.1 Gy, delivered as fractionated doses at 4 weekly intervals beginning at 4 wk	60-Hz, 1.41 mT, circularly polarized, 18 hr/d. Exposure began at 4 wk and ended at 29 mo	GLP; internal and external peer reviews of the histopathologic diagnoses; exposure and histopathologic analyses conducted under blinded conditions	Negative	Babbitt et al. (see discussion of the RAPID Working Group (*3*)

Abbreviations: d, day; ENU, *N*-ethyl-*N*-nitrosourea; gen., generation; J, joule; mo, month; PMA, phorbol 12-myristate 13-acetate; TPA, 12-*O*-tetradecanoylphorbol-13-acetate wk, weeks; yr, year; ~, approximately. [a]ac fields are sinusoidal unless otherwise noted. [b]An evidence category used by the NTP. Equivocal evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be exposure related (*11*). [c]This very high dose of TPA is most likely a typographical error in Byus et al. (*57*).

and $B6C3F_1$ mice set the standard for long-term chronic exposure bioassays (*18*). These assays are designed primarily to determine whether an agent can act as a complete carcinogen, but since a variety of neoplasms develop spontaneously in the rodent strains used, agents that affect promotion or progression may also be detected. In the NTP protocol, relatively large numbers of animals of both sexes (usually 50 animals per sex exposure group) are exposed chronically to a test agent and are monitored over a 2-year period for survival, body weight, and clinical signs of disease. At death or termination of the experiment, animals are evaluated by complete necropsy and histopathologic examination.

In the NTP MF exposure study (*11–13,19*), larger-than-standard–size groups (100 animals per sex exposure group) of rats and mice were employed in an effort to increase the sensitivity of the assay for the detection of possibly weak MF effects. As shown in Table 2, F344/N rats and $B6C3F_1$ mice of both sexes were exposed (18.5 hr/day, 7 days/week) to continuous 60-Hz MFs of 2 μT, 0.2 mT, or 1 mT, or to intermittent 60-Hz, 1-mT fields (1 hr on/1 hr off). Exposure began when the animals were 6–7 weeks old. The experiment also included sham-exposed controls (100 animals per group) for each species and sex.

This study was conducted in accordance with GLP, and in addition, independent audits of pathology data, specimens, and tables were conducted (*11–13*). A preliminary 8-week toxicity study was also conducted using the same set of exposures as employed in the 2-year chronic bioassay to determine a baseline for standard toxicologic parameters (*20*). Though statistically significant increases in liver weight and liver-to-body weight ratios in female rats of all exposure groups were noted, the study did not identify any significant toxic effects. Investigators noted that increased liver weight is a common finding in animals exposed to xenobiotics. Liver weight and liver-to-body weight ratios were not included in reports of the carcinogenesis study (*11–13*).

Analysis of the carcinogenesis bioassay results conducted by NTP (*11–13*) includes a comprehensive histopathologic evaluation and statistical analyses primarily to determine whether MF exposure resulted in statistically and biologically significant effects on tumor incidence. A limitation of the NTP protocol is that it does not include a serial sacrifice component and thus does not permit analysis of tumor latency, which, along with tumor incidence, can be an indicator that an agent can affect neoplastic development.

Five evidence categories of carcinogenic activity are employed by the NTP to summarize the strength of the evidence observed in each experiment [e.g., see the description of these categories in NTP (*11*)]. The selection-of-evidence category is based primarily on histopathologic and statistical considerations, though in difficult cases other factors may play a part. Such factors include bioassay conditions such as Q/A issues and evidence external to the bioassay such as structure–activity correlations or results of genetic toxicology tests.

Statistical analyses were conducted by the NTP study investigators to test for differences between control and MF-exposed groups in mortality and tumor incidence across a large number of tumor types. For the most part, significant differences were not observed. The few differences that were noted were: *a*) early mortality ($p < 0.05$) of the 1-mT–exposed group of male mice; *b*) increased incidences of thyroid gland C-cell adenomas in the 2-μT– and 0.2-mT–exposed groups of male rats ($p < 0.05$), C-cell carcinomas in the 2-μT–exposed group of male rats, and combined C-cell adenomas and carcinomas in both the 2-μT– and 0.2-mT–exposed groups of male rats ($p < 0.01$); and *c*) decreased incidences of mononuclear cell leukemia in male rats ($p < 0.05$) and several tumor types in mice ($p < 0.01$). The decreases in tumor incidences were considered by investigators unlikely to be related to MF exposure [see Boorman et al. (*13*) and McCormick et al. (*12*) for discussion].

Investigators concluded that the increased incidences of thyroid gland C-cell neoplasms in male rats constituted *equivocal evidence of carcinogenic activity*, based on the evidence categories applied by the NTP (*11,13*). As noted by investigators, however, the statistically significant increases observed were consistent with the frequency of false positives expected to occur by chance because of the large number of tumor types over which statistical tests were performed. Thus, the increase in thyroid gland C-cell neoplasms quite possibly reflects random variability in tumor distribution rather than indicating a biologic effect of MFs.

Investigators indicate that the statistically significant early mortality noted in male mice exposed to 1 mT continuous fields did not appear to be accounted for by any clinical toxicity or specific tumor types (*11,12*), but the difference is not further discussed.

Yasui et al. (*16*) exposed groups of 48 male and female F344/DuCrj rats beginning at 5 weeks of age to sham, or 50-Hz, 0.5-mT and 5-mT fields for 22.6 hr/day for 2 years (Table 2). Body weight and mortality were monitored throughout the experiment. Neoplastic end points were tumor incidence across a number of tumor types at terminal sacrifice, hematopoietic effects determined by examination of peripheral blood smears from tail bleeding at 52 and 78 weeks, and the age-specific prevalence of several tumor types detectable by palpation or moribund appearance prior to mortality.

Investigators reported that there were no statistically significant differences between exposed and sham-exposed groups that were considered to be of biologic significance. The incidence of one tumor type, fibroma of subcutaneous (s.c.) tissue, was elevated in male rats exposed to 5 mT MFs ($p < 0.05$), but the increase was considered by investigators not to be biologically meaningful, as it was within the historical control range previously observed in their laboratory for this tumor type. With the qualification that the histopathologic analysis was apparently only carried out on tissues that exhibited macroscopic signs of disease, this study appears to satisfy quality criteria.

The Yasui et al. study (*16*) is the only long-term chronic exposure study available other than the NTP study discussed above (*11,13*) that examined F344 male rats. It is therefore of interest to compare the two studies, as both tested overlapping ranges of MF intensities. Selected parameter values from the two studies are summarized in Table 3. As shown, at the termination of both studies, mean body weights were similar. Survival percentages are somewhat higher for all groups in the Yasui et al. study. This overall difference in mortality could be due to dietary differences or to the fact that different substrains of F344 rats were used in the two studies (F344/N rats in the NTP study and F344/DuCrj rats in the Yasui et al. study). Also, as shown in Table 3, whereas the overall percent of neoplasms and the percent of benign neoplasms were similar in the two studies, the incidence of malignant neoplasms in the Yasui et al. study was less than half that observed in the NTP study. This disparity could also be due to substrain differences and possibly also to the more limited histopathologic analysis conducted by Yasui et al., as indicated above. Note also that neither the increased incidence of fibroma of s.c. tissue reported by Yasui et al. (*16*) nor the increased incidence of thyroid C-cell adenoma and carcinoma reported by the NTP (*11,13*) were observed in the other study. Thus, these two studies provide independent evidence that strongly suggests that MFs under the conditions tested do not affect tumor incidence in male F344 rats.

Mandeville et al. (*14*) exposed groups of 50 female F344 rats beginning 2 days prior to birth to 60-Hz sham (< 0.02 μT), 2-μT, 20-μT, 200-μT, and 2-mT fields for 20 hr each day for 2 years (Table 2). In addition to sham-exposed controls, controls housed in a different room from exposed and sham-exposed groups were included. Body weight

Table 3. Values of selected parameters from two 2-year cancer bioassays of effects of magnetic field exposures in male F344 rats.[a]

Parameters	Yasui et al. (*16*)			NTP (*11,13*)				
	Sham	0.5 mT	5 mT	Sham	2 μT	0.2 mT	1 mT (cont.)	1 mT (int.)
Mean body weights at 104–105 weeks (g)	440–450[b]	440–450[b]	440–450[b]	484	467	473	478	476
Survival at 2 years (%)	~ 73[c]	~ 82[c]	~ 78[c]	57	46	47	48	59
Overall tumor incidence								
% of animals with neoplasms	100	100	100	100	98	98	100	98
% of animals with benign neoplasms	100	100	98	99	97	97	98	94
% of animals with malignant neoplasms	33	29	23	65	59	61	65	58
Specific tumor types (%)								
Fibroma of s.c. tissue	4	10	19[d]	12	8	9	13	12
Thyroid C-cell adenoma and carcinoma	17	21	13	16	31[e]	30[e]	25	22

Abbreviations: cont., continuous; int., intermittent. [a]Studies were conducted by the NTP (*11,13*) and Yasui et al. (*16*). [b]Estimated from Figure 1 in Yasui et al. (*16*). [c]Estimated from Figure 2 in Yasui et al. (*16*). [d]$p < 0.05$. [e]$p < 0.01$.

and survival were monitored throughout the study and full necropsies and histopathologic evaluations of all tissues were performed on all animals under study. Neoplastic parameters reported are tumor incidence at the end of the study and cumulative tumor incidence during the course of the study. A number of statistical tests were performed to compare tumor incidence in exposed and control groups (both sham-exposed controls and room controls) and to determine whether a trend in incidence over the different dose groups could be discerned. Investigators reported no statistically significant effects of MF exposure on survival or tumor incidence.

With one qualification (discussed below), this study appears to conform to quality criteria. Both the exposure and the histopathologic analyses were performed under blinded conditions. The study was also subjected to a Q/A procedure performed by an independent pathology laboratory during the course of the experiment and the pathology results were reviewed (also under blinded conditions) by a panel that included independent pathologists (*14*). It should be noted, however, that survival of the sham-exposed controls and survival of two of the MF exposure groups were significantly lower than that of the room control group (32–38% vs 60%). In the NTP study (*11*), the survival of female F344 rats at 104 weeks was 61–69% over all groups, similar to survival of room controls in the Mandeville et al. (*14*) study. Thus, a caveat to the conclusion that the Mandeville et al. (*14*) study satisfies quality control criteria must be some concern that either uncontrolled or confounding factors may have produced early mortality in the sham-exposed controls and in two of the MF-exposed groups. Curiously, this difference did not appear to affect the terminal tumor incidence rates, which were similar in all groups. This discrepancy in mortality rates was not addressed by Mandeville et al. (*14*) or the EMF Research and Public Information Dissemination Program (RAPID) Working group (*3–5*).

Since the F344 rats employed in the Mandeville et al. (*14*) study are the same strain and substrain of animal utilized by the NTP in their EMF study discussed above (*11*) and were obtained from an NTP facility, and the MF exposure ranges in both studies overlap, the two studies provide independently replicated evidence that MFs under the conditions tested do not affect tumor incidence or mortality rates in female F344 rats.

The mouse lymphoma study of Babbit et al. (*15*) is unique because of its size (2,660 female C57Bl/6 mice), its use of a lifetime model employing both uninitiated and ionizing-radiation–initiated animals, and its completeness with respect to a detailed histopathologic analysis of tissues relevant to lymphoma/leukemia end points. Tumors observed in these tissues were enumerated and classified according to the Pattengale system (*21*). This system identifies five classes of lymphoid neoplasms (follicular center cell, plasma cell, immunoblastic, small lymphocytic, lymphoblastic) on the basis of morphologic and immunologic criteria (*21*). The analysis of Babbitt et al. (*15*) included these five classes as well as related tumor types.

The Babbitt et al. (*15*) study conforms to quality control criteria. The study conformed to GLP and both the exposure and pathology phases of the study were conducted under blinded conditions. The pathology phase of the study was also subjected to extensive internal and external peer review. The Babbitt et al. (*15*) study thus provides a statistically sensitive, high quality assay of both the initiating and promoting potential of MFs with respect to thymic lymphoblastic lymphomas, which occur in relatively young animals, as well as a variety of other lymphoid neoplasms that occur in aged mice. Here we discuss the portion of the study aimed at detecting effects of MF exposure on otherwise uninitiated animals, and in subsequent sections we discuss the tests for possible effects of MF exposure on animals pre-exposed to ionizing radiation.

Babbitt et al. (*15*) exposed 380 female C57Bl/6 mice to 60-Hz, 1.41-mT (circularly polarized) MFs 18.5 hr/day from 4 weeks of age to natural death (median age at death of room controls was 29 months). Controls included 190 sham-exposed mice and a group of 380 unexposed mice housed in a separate room. Body weight, mortality, and clinical signs were monitored throughout the study. At death or terminal sacrifice all animals were necropsied and a complete histopathology report was generated on the tissues examined.

Detailed tumor incidence and mortality data are provided for total lymphoid neoplasms and for the subtypes mentioned above. No indication of a statistically significant increase in tumor incidence was noted for any lymphoid tumor end point. Investigators note, however, that visual inspection of hazard plots (the percent of animals dying with lymphoma present at various time points during the course of the study) for several of the end points tabulated (total lymphomas, B-cell lymphomas, histiocytic sarcomas, and all hematopoetic neoplasms) suggests these tumors appeared earlier in the MF-exposed animals. The differences noted, however, are not statistically significant.

Fam and Mikhail (*17*) have reported results of a three-generation MF exposure study several times in abstract form [see McCann et al. (*1*) for list of references] and most recently in peer-reviewed format. The study employed CFW male and female mice and 23 hr/day exposure to high-intensity MFs of 60 Hz, 25 mT. The first generation consisted of 1 male and 2 female mice for each of the exposure and control groups (i.e., a total of 6 mice). These animals were continuously exposed to the MF during mating, gestation, and birth of the second-generation of animals. To derive the third generation, 4 males and 8 females were chosen from the second-generation MF-exposed group and 2 males and 4 females from the second-generation control group. Then, as before, these animals were continuously exposed to the MF during mating, gestation, and birth of the third generation. The total numbers of mice in the MF-exposed group evaluated in each generation were 1 male and 2 females in the first generation, 16 males and 28 females in the second

generation, and 44 males and 48 females in the third generation. The total numbers in the control group were, respectively, one male and two females, 12 males and 8 females, and 16 males and 25 females.

After sacrifice, all animals were autopsied and tissue sections were taken from a number of organs to determine the presence of lymphoid neoplasms. The presence of nonlymphoid tumors was not recorded. Results are reported in tabular form for second and third generation animals. A nonstatistically significant increase in early and advanced lymphoma was observed in the second generation animals, and a highly statistically significant ($p < 0.001$) result was observed in the third generation.

This report is unique in that the intensity of MF exposure far exceeds that employed in any of the other available long-term chronic studies. The next highest intensity employed was 5-fold less, 5 mT, in the Yasui et al. (*16*) study discussed above. In addition, the positive result reported by Fam and Mikhail (*17*) is highly statistically significant. However, there are a number of aspects of this study that are either unclear or do not meet quality control criteria, which brings into question the validity of the findings. A number of concerns are discussed in the report of the RAPID Working Group (*3*). For example, the multigeneration protocol is particularly unusual in its use of single progenitors, limited information is provided on critical aspects of the experimental protocol (particularly the protocol for animal sacrifice), several of the pathology figures presented in the article as representative of mouse leukemia infiltrates appeared instead to be age-related lymphocytic infiltrates, and control mice were not sham-exposed but were exposed to 500 mG of 60-Hz stray MFs.

In summary, the study of Fam and Mikhail (*17*) is inadequately presented and does not conform to quality control criteria. Although it would not be appropriate to completely discount the study, it also would be inappropriate to consider it further without significant clarification and follow-up from the investigators.

Summary. Four of the five long-term chronic exposure studies reviewed above provide convincing evidence that fields of intensities ranging from 2 μT to 5 mT do not result in an increase in tumor incidence in male or female F344 rats or B6C3F$_1$ mice or in female C57Bl/6 mice. With the exception of specific caveats noted in the discussion above, these studies were of high quality and three (*11–15*) were conducted according to GLP. In addition, exposure ranges tested in particular studies overlapped those of at least one of the other studies, providing some evidence of reproducibility for the negative results. As discussed above, there is insufficient evidence at this time either to completely discount or to accept as valid the strongly positive but clearly flawed study of Fam and Mikhail (*17*).

Tests of Magnetic Fields in Assays Designed to Detect Effects on Post-initiation Stages of Carcinogenesis

Tests of magnetic fields using the rat mammary carcinoma model. Though a variety of animal models of breast cancer are available (*22*), the most commonly used model continues to be the 7,12-dimethylbenz[*a*]anthracene (DMBA) promotion model in rats developed more than 30 years ago [for recent review see Russo and Russo (*23,24*)]. In our previous report (*1*), we reviewed eight published reports of completed studies and one in progress report. The completed studies included positive results reported by Löscher and colleagues [Löscher et al. (*25*), Baum et al. (*26*), Mevissen et al. (*27*), and Beniashvili et al. (*28*)]. We concluded that these positive studies suggested the possibility of a promoting effect of MF exposure at the flux densities tested (20 μT–100 μT). We cautioned, however, that despite statistical significance, results were not highly statistically significant, that there was considerable variability in tumor incidence rates among unexposed groups, and that the sensitivity of the DMBA/mammary system to modulation by many dietary and other endogenous factors implied that caution should be applied in evaluating the results (*1*).

Seven new reports are now available for analysis (*29–35*). The conditions under which these newly available experiments were conducted and the results obtained are in Table 2. For details and discussion of earlier experiments, see our previous review (*1*). Each new experiment is discussed below.

The new study of Beniashvili and colleagues (*29*) includes some variation in lighting conditions not present in their earlier report but appears to include conditions that approximately replicate those in the group's earlier positive report (*28*). In particular, as shown in Table 2, groups of approximately 40–50 outbred female rats (strain unspecified) were injected with the initiator *N*-methyl-*N*-nitrosourea ([MNU] 50 mg/kg, intravenous [i.v.], 1×/week for 3 weeks). MF exposure (50 Hz, ~20 μT, ac or dc, 3 hr/day) was initiated 2 days after the first MNU injection and continued for 15 months. The first appearance of mammary tumors was determined by weekly palpation, and mammary adenocarcinoma incidence was confirmed histologically.

This study (*29*) satisfies most but not all quality control criteria. The biologic aspects of the protocol appear to conform to prior experience with MNU induction of mammary tumors in rats, most critical controls are included, and appropriate statistical methodology is employed. Though a dose–response curve is not reported, the appearance of palpable mammary tumors over time is recorded and the same MF exposure conditions were previously employed in similar experiments using different lighting regimes (*28*), thus roughly approximating replication conditions. The report, however, does not provide sufficient experimental details concerning the design of the exposure system and the rat strain employed. In addition, a sham-exposed control group was not included.

In the group's earlier report (*28*), MNU apparently was administered only once; the mammary tumor incidence reported in MNU-treated rats was 59%, with a mean latency period of 74 days. In the more recent report, these values are 32% and 166 days. Thus, tumor incidence appears to be lower and the latency period considerably longer in the more recent report despite using 3 times the amount of MNU used in the earlier study. The significance of this apparent inconsistency is uncertain. The discrepancy could be due to an error of omission in the protocol description in the group's first report. In the published literature there is considerable variability in the i.v. dose of MNU required to elicit comparable mammary tumor incidence in the same rat strains [e.g., see Rose and Mountjoy (*36*) and VanderPloeg et al. (*37*)], so the apparent variability in sensitivity to MNU in the two reports (*28,29*) from the Beniashvili group may not necessarily be of concern with respect to study quality.

The primary value of the Anisimov et al. (*29*) report with respect to this review is the extent to which it may be considered a replication of the positive results reported previously by the same group (*28*). The condition using a 12-hr light/12-hr dark illumination schedule and a 3-hr daily MF exposure in the more recent study (*29*) roughly duplicates conditions reported previously (*28*). Differences are the apparent discrepancy in the reported number of MNU treatments discussed above and some difference in the duration of the experiments [24 months (*28*) compared to 15 months (*29*)]. Previously, the group reported a statistically significant ($p < 0.05$) increase in tumor incidence in groups exposed to MNU and to either ac or dc fields compared to the group exposed only to MNU. In the current report (*29*), though there are increases in the incidence of mammary adenocarcinomas in both the ac and dc groups compared to the group exposed only to MNU, the increases are not statistically significant. Significant increases were only observed in the MF-exposed groups when the experiment was conducted under 24-hr lighting conditions. In the group's earlier report (*28*), apparently

significant decreases in the mean latency period were also reported for the two MF-exposed groups pretreated with MNU compared to the group exposed only to MNU. In the current report (*29*), the MNU-treated ac-exposed group exhibits a significantly shorter latency ($p < 0.05$) than the MNU-only group, thus reproducing the earlier result. However, the dc-exposed group does not show any decrease in latency. Thus, the results presented in these two reports differ in some respects. The most recent study does, however, support the group's previous findings with respect to an apparent enhancement effect of ac fields on the rate of development of MNU-induced mammary adenocarcinoma.

The Löscher group recently presented the results of two studies (*32,38*) intended in part to test the reproducibility of their earlier findings (*25,26*) that continuous exposure of female Sprague-Dawley rats to 50-Hz, 100-μT MFs for 13 weeks results in *a*) a significant increase in tumor growth as determined by palpation (*25*); *b*) a significant increase in tumor volume determined at autopsy (*26*); and, *c*) a statistically significant increase in the incidence of adenocarcinomas (*26*).

In the first of these two studies (*32*), investigators report a statistically significant ($p < 0.05$) increase in mammary tumor incidence in MF-treated rats compared to sham-exposed DMBA-treated controls as determined by palpation from 9 weeks through the termination of the study at 13 weeks. A significant increase ($p < 0.05$) in tumor incidence was also reported based on the incidence of macroscopically visible tumors determined at autopsy. This experiment appears to be thoroughly described and meets quality control criteria except for the omission of a histopathologic analysis. All phases of the study were conducted under blinded conditions, exposure parameters were validated by independent audit, and the exposure system was patterned on an NTP-recommended protocol.

In the second study, Thun-Battersby et al. (*38*) exposed 99 female rats to sham or 50-Hz, 100-μT MFs 24 hr/day, 7 days/week for 27 weeks. A single dose of DMBA (10 mg/rat, intragastric [i.g.]) was administered after 1 week of exposure to the MF. The number, volume, and location of mammary tumors were monitored by palpation for 27 weeks. At necropsy, macroscopically visible tumors were confirmed histologically, and neoplastic lesions were classified. The study conforms to quality control criteria. In addition, all aspects of the study were conducted under blinded conditions, and, as in the previous study, exposure parameters were independently monitored at regular intervals.

The results reported by Thun-Battersby et al. (*38*) again confirm the group's earlier observations (*25,32*) of a statistically significant ($p < 0.05$) increase in the incidence of palpable mammary tumors in MF-exposed rats at 13 weeks compared to sham-exposed controls. The earlier report of an increase in tumor volume on necropsy at 13 weeks (*26*) is also approximately replicated (results were statistically significant at 12 weeks [$p < 0.05$]), although Thun-Battersby et al. (*38*) determined tumor volume during this time period by palpation, since their experiment was not terminated until 27 weeks. Finally, the statistically significant increase in adenocarcinomas at 13 weeks reported by Baum et al. (*26*) was not observed at 27 weeks by Thun-Battersby et al., though this more recent report did observe a nonstatistically significant increase in the incidence of adenocarcinomas at 27 weeks.

The Löscher group (*31*), using the same experimental protocol employed in their earlier studies (*25,27*), report that continuous exposure of female Sprague-Dawley rats (99 per group) for 91 days to 50-Hz, 10-μT MFs does not result in a statistically significant increase in the incidence of mammary tumors when the MF-treated group is compared to DMBA sham-exposed controls. The exposure phase of this study and biochemical measurements (e.g., melatonin) were conducted under blinded conditions, and the study satisfies quality control criteria except that a histopathologic analysis was performed on only some tumors.

Interpretation of the combined results now available from the Löscher group is complex. The most completely reported positive experimental results prior to the reports discussed above (*32,38*) are from two studies (*25–27*). The first of these studies (*25,26*) employed 100-μT MF exposures and reported tumor incidence (proportion of animals with tumors) on the basis of results of weekly palpation (*25*) or histopathologic examination (*26*). These two analyses indicated that a statistically significant ($p < 0.05$) difference in tumor incidence between MF-exposed and sham-exposed DMBA-treated rats was observed at 13 weeks based on results of palpation (*25*), but that a significant difference was not observed when incidence was calculated based on numbers of tumors observed in a histopathologic examination of animals from the same study examined at 13 weeks (*26*). Instead, Baum et al. (*26*) observed: *a*) a statistically significant increase in median tumor volume between MF-exposed and sham-exposed animals, suggesting an effect of MF exposure on tumor growth but not on overall tumor incidence; and *b*) a significant increase in the incidence of animals with histologically confirmed adenocarcinomas, suggesting an effect of MF exposure on tumor progression. The second study (*27*) employed 50-μT MF exposures and also reported statistically significant increases in tumor incidence based on palpation during the course of the 13-week study and macroscopically visible tumors at autopsy.

The recent studies of Mevissen et al. (*32*) and Thun-Battersby et al. (*38*) discussed above are partially consistent with the results of these two earlier studies. First, a statistically significant increase in tumor incidence at 13 weeks on the basis of palpation and the number of animals with macroscopic tumors observed at autopsy (also at 13 weeks) was reported in the replication study (*32*); this is roughly consistent with the original observation of Löscher et al. (*25*) and Mevissen et al. (*27*). However, statistically significant differences in tumor volume between MF-exposed and sham-exposed animals based on measurements at autopsy at 13 weeks were not observed in the replication study (*32*), in contrast to the report of Baum et al. (*26*) [Mevissen et al. (*32*) did not determine the incidence of adenocarcinomas histologically].

In the more recent 27-week study of Thun-Battersby et al. (*38*), the palpation result at 13 weeks is again confirmed. However, as this experiment was not terminated until 27 weeks, autopsy and histopathology results cannot be directly compared with earlier 13-week experiments. Thun-Battersby et al. (*38*) did, however, estimate tumor volume during the course of their experiment by palpation, and report a statistically significant ($p < 0.05$) increase in tumor volume in MF-exposed rats compared to sham-exposed controls at 12 weeks. Thus, while the recent reports of Mevissen et al. (*32*) and Thun-Battersby et al. (*38*) do not strictly replicate all of the group's original findings, they do roughly replicate the observations based on palpation.

Ekström et al. (*30*) used female Sprague-Dawley rats (60 per group) to test for a possible enhancing effect on the rate of development of mammary tumors induced by DMBA (7 mg/rat, i.g.) from chronic exposure (21 weeks) to 50-Hz intermittent (15 sec on/15 sec off) MFs (250 μT and 500 μT). No statistically significant differences in latency, tumor incidence, tumors per tumor-bearing animal, or total tumor weight were observed in either of the MF-exposed groups compared to the DMBA control.

This study does not conform to all quality control criteria and thus is difficult to interpret or compare to other studies using the DMBA–mammary tumor model. As discussed by investigators, a Sprague-Dawley rat substrain with a high propensity to develop mammary tumors spontaneously in the absence of DMBA was used. Since a vehicle control group was not included in the study, it is not clear to what extent tumors observed were spontaneous or DMBA induced. In

addition, the malignant status of tumors observed was not confirmed histologically.

Recently, the NTP completed studies (*33–35*) to independently test the reproducibility of the positive results reported by the Löscher group discussed above. Three experiments were conducted. The experimental conditions of each of these experiments are summarized in Table 2. Two 13-week studies and one 26-week study were conducted involving chronic exposures to 50- or 60-Hz MFs of 0.1 mT and 0.5 mT. All three studies are thoroughly documented and satisfy quality control criteria. Experiments were conducted according to GLP; the MF characterizations were independently verified; pathology slides, data records, and tables were verified by independent audit and reviewed under blinded conditions by the NTP Pathology Working Group. On completion of the study, a comprehensive retrospective study audit was conducted by an independent Q/A contractor.

In the first 13-week study, very high incidences (93%) of mammary tumors in the DMBA-treated control rats prevented determination of possible effects of MF exposure on tumor incidence at 13 weeks. In the second 13-week study, the dosing of DMBA was decreased so that tumor incidence in DMBA-treated sham-exposed controls was more consistent with results reported by the Löscher group (43% in the NTP study compared to 34–62% in the positive studies of the Löscher group).

The results of the second 13-week study (*33,34*) did not demonstrate any increase in tumor incidence in either MF-exposed group (50 Hz, 0.1 mT and 0.5 mT) compared to sham-exposed controls determined either by palpation over the course of the 13 weeks, macroscopically at necropsy, or histologically. The mean area per carcinoma determined at necropsy was slightly larger (8–16%) in both MF-exposed groups compared to the DMBA-treated sham-exposed controls. This small increase was not statistically significant.

The 26-week study (*33,35*) was conducted using a single dose of DMBA (10 mg/rat) prior to MF exposure in contrast to the fractionated dose protocol used previously. This exposure protocol resulted in a tumor incidence (as determined by palpation) at 13 weeks of approximately 65% and at 26 weeks of 100%. This experiment was appropriate for examining possible effects of MF exposure on tumor latency and on growth rate but was not appropriate for comparing tumor incidence at 26 weeks because of high tumor rates in the DMBA-treated sham-exposed controls. The weekly palpation data do not demonstrate any apparent increase in the rate of tumor growth in the MF-treated animals over the course of the experiment. In fact, fewer tumors and fewer tumors per rat were observed in all exposed groups compared to controls. The mean area per carcinoma, however, determined at necropsy suggests a slightly larger though not statistically significant tumor volume (9–24% greater than controls) in all three MF-exposed groups compared to the DMBA-treated sham-exposed controls.

Results of the second 13-week study and the 26-week study are validly comparable with the positive results reported by the Löscher group. Positive results reported by the Löscher group were the following:

- in animals exposed to 100 μT MFs, a statistically significant increase in tumor incidence persisting throughout 13- and 27-week protocols determined by palpation;
- a statistically significant increase in tumor incidence at the termination of either 13- or 27-week experiments as determined by macroscopically visible tumors at autopsy;
- a statistically significant increase in the incidence of adenocarcinomas at the termination of the 13-week experiment; and
- a statistically significant increase in tumor volume at the termination of the 13-week experiment of Baum et al. (*26*), an observation not found in one replication by the same group (*32*) but approximately replicated in a second study (*38*).

The first three points are clearly contradicted by the NTP study, whereas the final point is not clearly contradicted.

Tests of magnetic fields using the mouse skin model. Although the use of transgenic models of epidermal carcinogenesis in mice is increasing [e.g., Holden et al. (*39*); recent reviews by Brown et al. (*40*) and Arbeit (*41*)], the two-stage DMBA/12-*O*-tetradecanoylphorbol-13-acetate (TPA) model in SENCAR mice is still in wide use [reviewed by DiGiovanni (*42*); discussed in our previous review (*1*)]. For more recent research attempting to elucidate the complex factors involved in the development of neoplasia in this model, see Shibata et al. (*43*) and Kiguchi et al. (*44*) on the involvement of transforming growth factor-α (TGF-α); Rundhaug et al. (*45*) on the time-course of changes in expression of TGF-α, epidermal growth factor, and other protein factors; Larcher et al. (*46*) on the possible involvement of H-*ras* in the control of angiogenesis; and Battalora et al. (*47*) on the possible role of Ca^{+2} in promotion.

In our previous report (*1*) we reviewed 6 published reports of tests of MFs in the DMBA mouse skin model and four abstracts providing preliminary data [see McCann et al. (*1*) for references]. These 10 reports included several peer-reviewed studies that reported suggestive (*48,49*) or positive (*50*) effects of MF exposure, and one abstract that also reported positive results (*51*). We concluded that results of promotion experiments in the mouse skin system were substantially negative, but that there was some suggestion of late effects associated with MF exposure in co-promotion assays.

Since our earlier review (*1*), completed reports (*52–55*) are now available for three of the four abstracts, one new study has appeared (*56*), and another abstract from the Byus group is available (*57*). All but one (*54,55*) of these new studies examined only the co-promotion potential of MFs. The study of DiGiovanni et al. (*54,55*) primarily examined co-promotion but included an experiment on promotion (Table 2). The promotion experiment, using the SENCAR mouse, employed DMBA (2.56 μg) as initiator and chronic exposure (6 hr/day, 5 days/week) to 60-Hz, 2-mT continuous fields. Results were negative, confirming previous similar reports (*58,59*).

Sasser et al. (*52*) and DiGiovanni and colleagues (*54,55*) recently published the detailed results of their study, which we previously discussed based on preliminary reports [see McCann et al. (*1*) for references and discussion]. The Sasser and DiGiovanni study (*52,54,55*) was well controlled and was also conducted according to GLP. The study employed SENCAR mice in the DMBA/TPA two-stage model and found no co-promotional effects from exposure of mice (56 animals per group) to 60-Hz, 2-mT MFs (6 hr/day, 5 days/week) at any time up to 23 weeks across three TPA doses (1.04 μg/week, 2 μg/week, and 4.2 μg/week). Though several aspects of the Sasser/DiGiovanni protocol (*52,54,55*) are not identical to the earlier positive experiment of Stuchly et al. (*50*) [see McCann et al. (*1*) for our earlier review of the Stuchly et al. study], the two experiments are comparable. As discussed by investigators, differences include the use of a diet lower in fat content by Sasser et al. (*52*) (4.5% compared to 11%), which is expected to result in a somewhat lower incidence of skin tumors in TPA-treated controls. This decreased sensitivity may be partly responsible for the large difference in tumor incidence rates in TPA-treated controls at comparable time periods in the two studies. Thus, the percentage of sham-exposed mice with tumors at 16 weeks among animals treated with 1 μg TPA weekly in the Stuchly et al. (*50*) experiment was about 90%, whereas in the experiment of Sasser et al. (*52*) the comparable percentage in sham-exposed controls treated with 1.04 μg/wk was about 20%. On the basis of pilot studies, Sasser et al. (*52*) and DiGiovanni et al. (*54*) thus selected significantly higher weekly doses of TPA than those used by Stuchly et al. (*50*) to achieve tumor incidence rates in TPA-treated controls in the same

response range as those in the positive study and to accommodate a sensitive statistical analysis. Thus, despite some differences between the two studies, the negative experiment of Sasser et al. (*52*) and DiGiovanni et al. (*54*) may be said to approximately replicate conditions of the earlier positive experiment of Stuchly et al. (*50*).

The apparently positive results reported by Stuchly et al. in 1992 (*50*) must be viewed within the context of the entire body of work presented by the Stuchly and McLean groups. In our previous review (*1*), we evaluated reports from these groups available at that time (*49,50,58–60*). McLean et al. (*60*), in abstract form, reported that the initial observation of transient co-promotional effects reported by Stuchly et al. (*50*) was not reproduced in two subsequent experiments. Since our review, more detailed results of these replication experiments have been published (*53*). These more detailed results appear to satisfy quality control criteria and provide data that confirm the absence of an increase in tumor incidence in MF-exposed mice at 23 weeks. Although limited data are provided in this new report of results at the more crucial earlier time period, McLean et al. (*53*) indicate in their discussion that the apparent transient effect on promotion from weeks 12 to 18 observed by Stuchly et al. (*50*) may have been due to inherent variability in the response of the SENCAR mouse in the two-stage assay.

Kumlin et al. (*56*) employed a transgenic hybrid strain of mice overexpressing ornithine decarboxylase (ODC), and nontransgenic littermates. Mice had coat colors varying from white to dark brown and their ages at the initiation of the study varied from 6 to 9 months. Investigators attempted to minimize possible effects of these variations by using similar age and color distributions in each experimental group. Chronic exposure to ultraviolet (UV) light (200 J/m^2, 3×/week for 10.5 months) was employed to induce skin tumor development. Possible co-initiation and co-promotion were examined both in transgenics and nontransgenic littermates by exposing UV-treated mice to either MFs or to sham fields. MFs were applied 24 hr/day for 10.5 months and were either continuous (50 Hz, 0.1 mT) or intermittent (50 Hz, 1.3, 13, and 130 μT, each applied in succession for 20 min followed by a 2-hr pause).

Investigators report that macroscopic skin tumors appeared earlier (measured by tumor incidence and numbers of tumors per animal) in both transgenic and nontransgenic mice exposed to both UV and either continuous or intermittent MFs compared to the corresponding groups exposed only to UV. These results were statistically significant only for the transgenic group ($p < 0.015$). Investigators also report an apparent increase in the incidence of skin tumors greater than 8 mm in diameter in MF- + UV-exposed animals at the termination of the study (46 weeks) but do not indicate whether this result was statistically significant.

This study employed a relatively new skin tumor model system developed in the investigator's laboratory (*61*) and it is thus not directly comparable to other skin tumor studies testing MFs, all of which used younger and different strains of mice (most often SENCAR) in the DMBA/TPA skin tumor model. With the exception of the inadequate detail in data presentation discussed below, leading to difficulties in interpreting the results, the study conforms to most quality control criteria and could be of interest.

The study is difficult to evaluate for several reasons. First, the key results (tumor incidence as a function of time) are presented only as values summed over the continuously and intermittently exposed groups. Second, investigators failed to provide data on numbers of animals with multiple lesions. Third, a positive control was not included; this would have been helpful to assist in validating the new assay. Finally, a puzzling feature of the study, as discussed by investigators, is the apparent lack of any increase over UV-exposed controls in the terminal incidence of histologically verified papillomas or squamous cell carcinomas in MF- + UV-exposed transgenic or nontransgenic animals compared to the 2- to 3-fold increase in epidermal cysts in the MF- + UV-exposed transgenics (*56*).

In abstract form, Byus and Ma (*57*) reported the results of studies to replicate and extend earlier experiments that were also published in abstract form (*51*). These studies examined the possible co-promoting effects of 60-Hz MFs in the SENCAR two-stage mouse model. Details of the experimental protocol and MF exposures are in Table 2. We discussed the earlier studies from this group previously (*1*). To our knowledge neither of these studies has been published in a more detailed format. Because of the limited information presented, and inconsistencies possibly due to typographic errors in the abstracts, it is not possible to evaluate these studies.

Summary. Results of tests for possible promoting or co-promoting effects of MFs are now available from five independent research groups. All but one of the co-promotion studies employed the DMBA model in SENCAR mice. Among studies using the SENCAR mouse model, the promotion studies (*48,59*) discussed in our previous review (*1*) as well as the more recent study of DiGiovanni et al. (*54*) are substantially negative, although Rannug et al. (*48*) reported a marginally statistically significant dose trend for intermittent exposure groups. To our knowledge, there has been no attempt to replicate these suggestive findings. However, recently the Rannug et al. (*48*) work was reviewed by the RAPID Working Group (*3*), which pointed out several limitations in the study such as the lack of control over switching transients and also the questionable appropriateness of lumping results from different exposure levels.

All co-promotion studies were conducted using long-term exposure to 60-Hz, 2 mT fields. Results of these studies are predominantly negative. Experiments from two research groups (*52,53*) strongly suggest that 60-Hz, 2 mT MFs do not co-promote development of skin tumors in SENCAR mice in the DMBA/TPA two-stage model at any time up to 23 weeks after the initiation of exposure. These negative studies contradict the transient co-promotion effect at week 18 initially reported by Stuchly et al. (*50*). One positive result ($p < 0.03$) that we discussed previously (*1*) has not yet been tested by replication. In this experiment, an increase in progression to malignancy was observed in SENCAR mice exposed to 60-Hz, 2 mT MFs for 52 weeks in a DMBA/TPA two-stage co-promotion assay in which TPA was applied for the first 23 weeks of the experiment (*49*).

Test of magnetic fields using animal models of leukemia and lymphoma. A number of murine models of lymphoma/leukemia are available. For recent reviews, see Uckun (*62*) and Pattengale (*21,63*). Though many factors, such as the complex role played by viruses in murine neoplasia, complicate the determination of the relevancy of these models to human cancer, some lymphoma/leukemias in mice have similarities to the diverse collection of neoplasms grouped under this general heading in humans (*21,64,65*). Table 4 illustrates a number of correlates between murine and human forms of lymphoma/leukemias in six relevancy categories: pathologic presentation (e.g., frequency of occurrence, severity, time course, metastatic characteristics); immunohistochemistry; mechanisms (e.g., physiologic, cellular, or molecular changes associated with neoplasia); cytogenetic changes associated with lymphomagenesis or leukemogenesis; oncogene involvement; and agents or conditions that modulate induction, promotion, or progression.

Several models of lymphoma/leukemia in mice have been suggested as possibly relevant to human B-CLL (*66–70*). One of the models described below that has been used to test EMF, the large granular lymphocyte (LGL) rat leukemia transplant model, has been proposed as an appropriate model for human T-CLL (*71*). The pathologic characterizations of the common forms of leukemia in children, acute lymphocytic leukemia, and

Table 4. The human relevance of murine leukemia/lymphoma models.

Relevancy category	Example	Reference
Pathologic presentation (e.g., frequency of occurrence, severity, time course, metastatic characteristics)	Almost all types of human lymphomas have also been observed in mice	(*21*);
	The distribution of lymphoma tumor types is roughly similar in humans and mice	(*147–149*);
	There are age similarities between murine lymphoblastic T-cell lymphoma/leukemia and the analogous childhood and young adult T-cell neoplasms in humans	(*21*)
Immunohistochemistry	The B/T ratios of lymphomas in human adults and older mice are similar (3–4:1)	(*21*)
Mechanisms (e.g., physiologic, cellular, or molecular changes associated with neoplasia)	Interleukin-6 is involved in the pathogenesis of murine plasmacytoma and human multiple myeloma	(*63*)
	Similar tumor antigen markers have been observed in both humans and mice	(*91*)
	Both malignant CD5 B cells in NZB mice and human B-CLL cells express interleukin-10 mRNA	cited in (*150*)
Cytogenetic changes associated with lymphomagenesis	Similar cytogenetic changes have been observed in certain lymphomas in humans and mice:	
	in radiation-induced thymic lymphomas in C57BL/6 or SCID mice and in human populations at high risk for lymphoma	(*87,88*)
	in mouse plasmacytomas and human Burkitt's lymphoma	(*21*)
	in follicular center cell lymphomas in SJL mice and in human germinal center lymphomas	(*148*)
	in CD5 B-cell chronic lymphocytic leukemia in NZB mice and in human B-CLL	(*70*)
Oncogene involvement	Although oncogene involvement is known to be important in lymphomagenesis in both mice and humans, relationships between specific oncogenes and pathogenic outcomes are not necessarily the same in both species	
	Among the human lymphomas, only Burkitt's is known to involve *c-myc*, whereas in mice *c-myc* has been associated with plasmacytomas	(*21,149*)
	Other examples where the same oncogene leads to different neoplasms in mice and humans	(*151*)
Agents or conditions that modulate induction, promotion, or progression	An increased risk of lymphoma/leukemia is associated with radiation exposure and certain chemicals, especially immunosuppressive cancer chemotherapeutic agents in both humans and mice	(*3,74,152*)
	A majority of approximately 10 carcinogens tested in long-term rodent bioassays that were associated with an increased incidence of lymphoma or leukemia in humans also induced related neoplasms in rats or mice.	(*153*)

acute myeloid leukemia, are quite different from that of CLL. The growth of both these childhood leukemias can be studied in immune-deficient mice by transplantation (*72,73*). It has also been suggested by Pattengale (*21*) that there are similarities between early-appearing murine lymphoblastic T-cell lymphomas and analogous childhood leukemia/lymphomas. These T-cell neoplasms are a primary end point in the Kaplan split-dose ionizing radiation model in mice (*74*), which has been used to test EMF (*15,75*). Results of these experiments are discussed below. Some soft tissue tumors and lymphomas that occur in *p53*-deficient mice are also similar to some tumors of childhood (*76*). A model using transgenic mice heterozygous for the *p53* null allele has recently been used to test EMF (*77*); results are described below.

It should be noted that whereas the responsiveness of models involving the mouse mammary gland and mouse skin to a wide variety of promoters is well established [see McCann et al. (*1*) for discussion and examples], this is not the case for the lymphoma/leukemia promotion/progression models. This lack of validation represents a serious limitation in interpreting the significance of results obtained from tests of EMF in these systems, especially the significance of negative findings. To the extent that the capability of individual systems used to test for possible effects of EMF have been demonstrated to detect agents affecting promotion or later stages of carcinogenesis, this is indicated below in the discussion of each system.

Among the reports involving leukemia or lymphoma end points included in our previous review (*1*), only two studies were available as completed reports in peer-reviewed journals (*75,78*). As both of these studies were criticized on issues involving methodology or sensitivity [see McCann et al. (*1*) for discussion], the negative results reported cannot be considered reliable. The remainder of the studies reviewed could not be fully assessed, as they were either in progress or reported only in abstract form [see McCann et al. (*1*) for references].

Since our earlier review (*1*), a considerable amount of new information has become available. First, the studies that were in progress at the time of our earlier review have been completed. These studies include *a*) an assay involving the split-dose ionizing radiation model in mice (*15*) that has been completed but not yet published in journal format; *b*) a large, multi-experiment LGL rat leukemia transplant assay (*79,80*), portions of which have appeared in journal format (*81,82*); and *c*) a transgenic assay in Eμ-*pim*-1 mice (*83*). Second, a negative lymphoma promotion study in *pim*-1 mice and mice heterozygous for *p53*, which at the time of our earlier review was available only in abstract form, has now been published in more complete form (*77*). Third, two studies we have not previously reviewed, one using a DMBA promotion assay in mice (*84*) and another examining effects of MF exposure on a strain of leukemia-prone mice (*85*) have been identified.

Below, we discuss the eight reports summarizing the results of these prevously unreviewed studies (*15,79–85*).

All assays reviewed are designed primarily to detect effects of EMF exposure on post-initiation stages of carcinogenesis. Some assays use initiating agents prior to EMF exposure such as ionizing radiation or *N*-ethyl-*N*-nitrosourea (ENU). Other assays such as the rat leukemia transplant model use neoplastic cell lines (cells that are already initiated) and measure the rate of neoplastic development in cell transplant recipients. Others use rodent strains with enhanced sensitivity for the spontaneous development of certain neoplasms, such as mice heterozygous for *p53*. We discuss each of these three general types of assays separately.

LYMPHOMA IN MICE PRE-EXPOSED TO INITIATING AGENTS. Exposure of C57Bl mice to fractionated doses of ionizing radiation results primarily in the induction of thymic lymphomas, most of which are lymphoblastic lymphomas. These tumors represent neoplasms of immature thymocytes at various stages of T-cell development (*21,86*). As indicated above, it has been suggested that there may be some similarities between early-appearing murine lymphoblastic T-cell lymphomas, the primary end point in this model system, and the analogous childhood and young adult T-cell neoplasms in humans (*21*).

As we previously discussed (*1*), the mechanism of lymphomagenesis induced by

split-doses of ionizing radiation in mice is incompletely understood. Recent research continues to explore the involvement of genetic changes (*87–89*), oncogenes (*90*), epigenetic factors (*86*), immunologic defenses (*91*), and the RadLV virus (*92*) in a complex process that appears to include a variety of cell types comprised of thymic and pre-thymic cells as well as other bone-marrow derived cells (*93–95*). With only one exception of which we are aware [the study by Chen and Berenblum on urethane (*96*)], this system has not been used previously to study effects of promoters on tumor development.

As shown in Table 2, Babbitt et al. (*15*) exposed groups of 190–380 female C57Bl/6 mice to four weekly doses of gamma irradiation totaling 3.0 gray (Gy), 4.0 Gy, or 5.1 Gy beginning at 4 weeks of age. MF exposure was initiated simultaneous with the first gamma irradiation treatment. For each radiation dose, groups of mice were either sham-exposed (190 mice) or exposed to 60-Hz, 1.41-mT (circularly polarized) MFs (380 mice). Exposure was for 18.5 hr/day and continued up to 29 months. In addition to MF sham-exposed controls (190 per group) at each of the three radiation doses, the experiment also included an unirradiated sham-exposed control group (190 mice), an unirradiated MF-exposed group (380 mice), and a group of 380 mice housed in a separate room that were unexposed to either gamma radiation or MFs.

In an earlier section, "Tests of Magnetic Fields in 2-Year, Lifetime, or Multigeneration Exposure Studies," we discussed results of this study obtained for animals unirradiated with ionizing radiation and exposed or unexposed to the MF. In that section we also discussed the quality assurance aspects of this study. Here we address results obtained for the irradiated groups. As for the unirradiated groups, body weight, mortality, and clinical signs were monitored throughout the study. At death or terminal sacrifice all animals were necropsied and a complete histopathology analysis was conducted including classification of lymphoid cell neoplasms as discussed above. A number of statistical comparisons were made between groups exposed to both ionizing radiation and the MF and each corresponding ionizing radiation control group. Comparisons were made for total lymphoid neoplasms and for each individual lymphoid tumor type. No statistically significant differences were observed with respect to the MF.

The sensitivity of the study is relatively high because of its quality and use of large numbers of animals in each test group. Although only one MF exposure level was employed, the use of test groups exposed to three different levels of gamma irradiation provides some internal measure of consistency as well as the possibility of discerning a radiation dose–response trend.

Analysis of this study is complicated to some extent by the lack of prior history with the system with respect to the effectiveness of known promoters and also by the fact that in animals exposed to gamma irradiation, the time course of lymphoma induction is complex. The primary effect of split-dose irradiation in the Kaplan model is to increase the incidence of early (up to about 300 days) lymphomas. Thus, experiments using the Kaplan model are usually terminated at approximately 1 year. However, Babbitt et al. (*15*) extended their experiment for the lifetime of the animals (approximately 2.5 years). Thus, in control groups exposed to different levels of ionizing radiation, a relatively early increase was observed in the percentage of mice dying with lymphoma present, and in aged mice a second wave of increase in lymphomas was observed. Possible effects of MF exposure on the rate of development of radiation-induced lymphomas were determined at various time points after initiation of exposure, up to 2.5 years. Since there was not a provision for serial sacrifice in this study, tumor incidence could not be determined precisely prior to terminal sacrifice. However, since, as indicated by investigators, lymphoblastic lymphoma was very likely the cause of death for animals dying during the first year of the study with this tumor present, the incidence value employed (death with lymphoma present) is most likely a valid reflection of lymphoma incidence.

When death with lymphoma present was compared for MF-exposed animals and corresponding radiation controls using only data obtained during the first year of the experiment, no statistically significant effects of MF exposure were apparent. Thus, the percent of animals dying with lymphoma present were, for the 0-, 3.0-, 4.0-, and 5.1-Gy exposed groups respectively; 0, 0.53, 5.3, and 25% for the controls; and 0, 1.1, 6.1, and 19% for the MF-exposed groups. Statistically significant effects of MF exposure of gamma-irradiated groups were also not observed at time periods longer than 300 days, up to 2.5 years. This was true for all lymphomas combined and for the subtypes examined, which were lymphoblastic, lymphocytic, and combined B-cell lymphomas. Also, no significant effects were seen for histiocytic sarcoma.

Shen et al. (*84*) exposed groups of male or female Swiss-Webster mice (75–89 per sex group) to 50-Hz, 1-mT MFs (3 hr/day, 6 days/week for 16 weeks beginning at 14 days of age) after a single treatment with DMBA (35 μg/mouse, sc) shortly after birth. At 32 weeks of age, the experiment was terminated and all animals were subjected to histopathologic examination. Neoplastic end points examined were premalignant, early, or advanced thymic lymphoma reported as tumor incidence and metastatic infiltration in the liver and spleen of mice with advanced lymphoma, which were also reported as incidence values.

The Shen et al. (*84*) report roughly satisfies data quality criteria, with some reservations. The specific model system employed has, to our knowledge, not been used previously, but data on group survival and tumor incidence in negative controls (two sham-exposure groups, one with and one without DMBA treatment) suggest that there was no excessive toxicity and that tumor incidences were within a range permitting valid comparisons.

With respect to the major end point, tumor incidence, the investigators report no significant effect. However, the results were less clear for some secondary end points. The investigators report that, for the most severe category of metastatic infiltration in liver, when data for males and females were pooled, comparison of incidence in MF-exposed and sham-exposed animals resulted in a statistically significant increase ($p < 0.01$ as determined by χ^2 two-way contingency table analysis) in the MF-exposed animals. Infiltration data for individual sexes are not reported. Using the data presented in the paper, we determined that the difference in infiltration incidence between MF-exposed and sham-exposed animals classified as "moderately infiltrated" was also statistically significant ($p < 0.02$) but in the opposite direction (i.e., the pooled group exposed to the MF exhibited less infiltration than sham-exposed controls). This analysis suggests that there was a relatively high degree of variability among the various groups and that the positive results reported by the investigators may not be biologically significant.

The issue of reproducibility was not directly addressed in the study. Lymphoma incidence was enumerated separately in male and female groups, but since significant differences in sensitivity to lymphomagenesis are known to exist between male and female mice [see for example, NTP (*11*), McCormick et al. (*12*), and Boorman et al. (*13*)], the use of different sex groups cannot serve as a rough internal check on consistency. Further, interpretation of the metastatic infiltration results is complicated by the fact that data from males and females were pooled rather than reported separately.

We previously indicated (*1*) the negative experiment of Svedenstål and Holmberg (*75*) did not satisfy several quality control criteria and is difficult to evaluate. Despite the fact that the studies of Shen et al. (*84*) and Babbitt et al. (*15*) employed similar MF exposures (50-Hz, 1 mT and 60-Hz,

1.41 mT, respectively) and include some information on metastatic infiltration in liver, it is difficult to compare the two studies, as different strains of mice, different initiators, and different protocol schedules were employed. Of possible interest, however, is the observation that an examination of the histopathology report in Babbitt et al. (*15*) does not suggest any increase in lymphocytic infiltration in the livers of aged mice exposed to the MF compared to sham-exposed controls; this contrasts with the effect reported by Shen et al. (*84*) for relatively young animals.

LEUKEMIA TRANSPLANT MODELS. LGL leukemia, also termed mononuclear cell leukemia, occurs spontaneously and at relatively high and variable frequencies in aged male F344 Fischer rats. A transplant model employing passaged LGL cells has been well described. For recent reviews, see Sasser et al. (*81*) and McCann et al. (*1*).

Although a number of chemicals have been associated with significant decreases in the spontaneous incidence of LGL leukemia in aged Fischer rats (*97,98*) and with decreases in the rate of onset of leukemia in transplant recipients in the LGL transplant model (*99*), the ability of this system to detect leukemogens or co-leukemogens is less certain. In our previous review (*1*) we discussed experiments of Dieter and colleagues (*100*) and suggested that their report of enhancement effects may not be definitive. More recently, Anderson et al. (*101*) examined trichlorophenol, one of the agents Dieter et al. reported as enhancing the disease process, as well as the known leukemogens benzene and ionizing radiation (5 Gy) for their ability to enhance the progression of LGL leukemia in transplant recipients. Daily administration of trichlorophenol had no effect on disease progression; benzene appeared to delay the onset of leukemia by about 6 weeks; and ionizing radiation resulted in small but statistically significant increases in some disease parameters. These results suggest that the ability of the LGL transplant system to detect any given co-leukemogenic agent is uncertain. Therefore, while the experiments of Anderson, Sasser, and colleagues (*79–82,101*) appear to be well done, the significance of the results with respect to whether MFs have any leukemogenic potential is uncertain. Below, we review the experiments conducted by this group.

In our previous review (*1*) we included preliminary negative results from this group, which were available in abstract form (*102,103*). As discussed above, since our review was published these experiments have been completed. Some of the results have been published in peer-reviewed format (*81,82*), and the complete study results are available in report form (*79,80,101*). These experiments were all conducted according to GLP, and their progress was periodically reviewed by an independent auditor. Engineering aspects of the study were also independently reviewed by the National Institute of Standards and Technology.

As shown in Table 2, two experiments were conducted. The first experiment (*80–82*) involving a total of 504 animals included chronic 18-week exposure to continuous, linearly polarized MFs (60 Hz, 1 mT). This experiment involved four treatment groups including the MF-exposed animals, a sham-exposed control group, ambient controls, and a positive control group that received 5-Gy whole-body irradiation. At the initiation of MF or sham field exposure, all animals received an inoculum of 2.2×10^7 cells intraperitoneally (i.p.). The progression of leukemia in transplant recipients was monitored by palpation of the spleen and by repeated bleeding of 18 animals in each group at weeks 0, 2, 4, 5, 6, 7, 8, and 10 following injection and the initiation of exposure. Hematologic parameters monitored included numbers of red and white blood cells, numbers of LGL cells, and hemoglobin concentration. These 18 animals per MF treatment group were also followed to their spontaneous deaths, which allowed evaluation of mortality (*81*). Additionally, serial sacrifice was performed on 108 additional animals in each of the four groups at weeks 5, 6, 7, 8, 9, and 11 (18 animals in each group were sacrificed at each time point) for additional morphologic, hematologic, and histopathologic evaluation (*82*). Investigators report that significant or consistent differences between exposed and control groups were not observed in any experimental parameter, whereas consistent statistically significant differences were observed for the positive control group in most experimental parameters.

In a second experiment (*79*) involving a total of 144 animals, two additional variables were examined (Table 2): the inoculum size (2.2×10^7 vs 2.2×10^6 cells per rat, i.p.); and chronic exposure (20 hr/day, 7 days/week for 22 weeks) to a continuous (linearly polarized) or intermittent (3 min on/off) MF (60 Hz, 1 mT). This experiment also included ambient and positive controls as in the experiments discussed above. Sham-exposed controls were not included in this study based on historical MF studies that demonstrated no significant difference between sham and ambient control groups. All animals were bled weekly: rats injected with 2.2×10^7 cells were bled from weeks 5 to 12, and animals injected with 2.2×10^6 cells were bled from weeks 6 to 16. Additionally, body weight and splenomegaly were monitored throughout the study and spleen weights were determined at necropsy.

The experiment employing conditions of a cell inoculum of 2.2×10^7 and exposure to continuous fields represents a replication of the first experiment discussed above (*80–82*). As in the first study, no significant differences were noted between ambient and MF-exposed groups in any neoplastic parameter.

A comparison of results in these two experiments employing inocula of 2.2×10^7 does, however, indicate other differences that illustrate the interexperimental variability of this system. First, the rate of disease development appears to be similar as measured by the time of onset of palpable splenomegaly (approximately 7 weeks in both sets of experiments) but appears to be quite different as measured by mortality. For the positive controls, 50% survival occurred at approximately 15 weeks in the first experiment (*80–82*) and at approximately 23 weeks in the second experiment (*79*). Second, the first experiment (*80–82*) demonstrated a significantly more rapid decline in survival of the positive controls compared to all other experimental groups, whereas the replication experiment (*79*) did not indicate any significant enhancement in the mortality rate of the positive controls over those of the other experimental groups. In contrast, the hematologic parameters measured in both sets of experiments demonstrate observable effects of the radiation exposure in the positive controls compared to the other experimental groups.

For the groups exposed to intermittent MFs (1 mT off/on at 3-min intervals) that received 2.2×10^7 cell inocula, statistically significant differences between the MF-exposed group and ambient controls were observed in virtually all hematologic parameters monitored (number of red blood cells, hemoglobin concentration, packed cell volume, nucleated red blood cells, white blood cells, LGL cells, and lymphocytes). The direction of the difference was consistent, suggesting an earlier onset of disease in the MF-exposed group. Similar effects were not observed in the group receiving the smaller inoculum.

Interpretation of this result is complex. First, group sizes were modest (18 animals per group), suggesting the possibility of variability in the outcome. Second, as the investigators point out, the lack of consistency in results between the two experiments involving different inocula could be an argument for the absence of a real effect. However, reduced sensitivity to MF effects due to slower progression of the disease in animals receiving the smaller inoculum cannot be ruled out. Third, the differences observed were statistically significant only if the data were combined over the time course of the disease progression. However, relatively small and inconsistent differences in disease parameters were observed in this system for

irradiation, a known potent leukemogen. Thus, if MFs were a leukemogen or co-leukemogen of weak to moderate potency, the results observed would not be unexpected.

In summary, the results of this study do not rule out the possibility that chronic exposure of rats inoculated with 2.2×10^7 LGL cells to a 60-Hz, 1 mT intermittent (3 sec on/off) field may result in enhancement of LGL leukemia growth in transplant recipients. The factors suggesting that the intermittent MF may have some enhancing effect are first, the high quality of the study, particularly with respect to inclusion of appropriate controls and a relatively large number of monitored disease parameters, as well as a detailed presentation of results; second, the consistency of the direction of the effect; and third, the fact that a large number of hematologic parameters demonstrated an apparent enhancement effect. This third factor must, however, be tempered with the caveat that biologic variation in one hematologic parameter might be expected to affect other parameters as well.

TESTS IN LYMPHOMA/LEUKEMIA-PRONE MOUSE STRAINS. *Transgenic models.* A large and increasing number of transgenic mouse models are now available for the study of oncogenesis. For general reviews see Seldin (*104*) and Adams and Cory (*105*). Several transgenic models, including a *p53*^{def} system (discussed below), are currently undergoing multilaboratory validation as alternative carcinogen testing methods (*106,107*). Two transgenic mouse systems have been used to test for possible effects of EMF on carcinogenesis. These are model systems involving the oncogenes *pim*-1 and *p53.f*

For recent reviews of the function and regulation of *pim*-1, see Hoover et al. (*108*), Jonkers and Berns (*109*), and Berns et al. (*110*). In the transgenic models involving the *pim* oncogene that have been used to test for possible effects of EMF (*77,83*), *pim*-1 is linked to the immunoglobulin heavy chain enhancer (Eμ). This linkage mimics the chromosomal translocation associated with lymphoid tumors and promotes transgene expression in both T and B cells (*105,111*). Eμ–*pim*-1 mice exhibit a 5–10% spontaneous incidence of T-cell lymphomas that appear early in life (at approximately 7 months of age) (*90*). After 10 months of age, nonlymphoblastic lymphomas predominate (*83,112*). These mice are susceptible to point-mutation–inducing genotoxic carcinogens such as ENU (*113,114*) and to other genotoxic carcinogens including X-irradiation (*90*), benzo[*a*]pyrene (*115*), and the heterocyclic amine 2-amino-1-methyl-6-phenylimidazo-[4,5-*b*]pyridine (*116*). Most lymphomas induced in this system by ENU are lymphoblastic lymphomas (*117*). Nongenotoxic lymphomagenic agents tested in the system, such as benzene (118) and TPA (*115*), have been negative. Eμ–*pim*-1 mice have also been used to test for possible effects of microwave frequency electromagnetic fields (*112*).

The Eμ–*pim*-1 system employing ENU as inducer has been demonstrated to detect inhibitory effects of one of two agents tested that are known to have a broad spectrum of chemopreventive activity in other animal model systems (*119*). To our knowledge, the system employing ENU has not been used to test for promoters or other agents that enhance the post-initiation stages of carcinogenesis.

The function and regulation of *p53* have been comprehensively reviewed (*120–124*). For discussion of the use of *p53* transgenic models in the study of multistep lymphomagenesis, see Seldin (*104*). Mice homozygous for the *p53* null allele (knockout mice that lack the p*53* protein entirely) are highly susceptible to T-cell lymphoma. However, in these homozygous knockout mice, spontaneous tumors develop so rapidly that the detection of co-carcinogenic or late-stage effects of test agents is not feasible (*104*). The *p53* system *p53*^{def}, which has been used to test for possible carcinogenic enhancement effects of EMF (*77*), uses mice heterozygous for the *p53* null allele (*p53*$^{+/-}$). Malignant lymphomas also occur spontaneously in heterozygotes. In animals less than one year of age, few tumors are observed, but among these, tumors of the hematopoietic system predominate (*77*). Over a longer time period, osteosarcomas and soft-tissue sarcomas develop spontaneously, and these tumors are similar to those commonly observed in children (*76*).

In the *p53*^{def} system, since tumors do not usually develop until the mice reach one year of age, detection of effects of treatment with potential co-carcinogens is feasible (*76*).In fact, several known carcinogens such as dimethylnitrosamine (*76,125*), ionizing radiation (*126*), *p*-cresidine, and 4-vinyl-1-cyclohexene diepoxide (*127*) have been observed to accelerate development of various neoplasms in this model. A 50-chemical multilaboratory study is currently in progress to further validate the sensitivity and specificity of the *p53*^{def} test system (*106*). It has been suggested that the *p53*^{def} system may provide some advantage for detection of carcinogenic potential relevant to human risk by its apparent insensitivity to rat or mouse strain-specific carcinogens (*128,129*).

A possible limitation for detection of potential co-carcinogenic effects of EMF is that the *p53*^{def} system has failed to respond to the nonmutagenic carcinogens tested so far (*127,129*). In fact, recently it was suggested that the *p53*^{def} system be used solely for testing for the potential carcinogenicity of agents with evidence of genotoxic potential (*130*). This caveat is of particular relevance to the interpretation of results obtained in tests of EMF, which are generally considered to lack genotoxic potential [recently reviewed by McCann et al. (*10*)].

Tests of EMF Using the *pim*-1 and *p53*^{def} Systems. At the time of our previous review (*1*), negative results of tests of MFs in the *p53*^{def} and *pim*-1 systems by McCormick and colleagues had been reported in abstract form (*131*). More completely described results of these experiments are now available (*77*).

In this report (*77*), experiments using the *p53*^{def} system involved exposure (18.5 hr/day for 23 weeks) of male and female mice (30 per sex group) to 60-Hz, 1-mT continuous, linearly polarized, transient-free MFs. The experiment was terminated at the end of the exposure period. Mortality, lymphoma incidence, and the incidence of other neoplastic lesions (determined by partial necropsy) were reported. All aspects of the protocol are thoroughly described and the study conforms to data quality criteria.

Over the 23-week period of the experiment, statistically significant changes in mortality or tumor incidence were not observed in animals exposed to the MF compared to sham-exposed controls. Investigators conclude that these data do not support the hypothesis that MFs are a significant risk factor for hematopoietic neoplasia.

Experiments were also conducted concurrently using the Eμ–*pim*-1 system with ENU (25 mg/kg, 1×, i.p.) as inducer 1 day prior to MF exposure. These experiments also involved 23-week exposures (18.5 hr/day) of male and female mice (30 per sex group), and were also terminated at 23 weeks. However, in the experiments using the Eμ–*pim*-1 system, a broader range of MF intensities were examined. These included continuous (60-Hz, 2 μT, 0.2 mT, and 1 mT linearly polarized, transient free) as well as intermittent (60-Hz, 1 mT, 1 hr on/off) fields. This experiment was similar to that described above for the *p53*^{def} system. Virtually all neoplastic lesions identified were lymphomas. Investigators report that lymphoma incidence in male mice exposed to continuous 1 mT fields was signficantly ($p < 0.05$) reduced from that in sex-matched sham-exposed controls, and that significant differences were not observed in any other parameter.

Harris et al. (*83*) exposed groups of female mice (approx. 100/group) to 50-Hz MFs for 20 hr/day up to 18 months. MFs were either continuous (1 μT, 100 μT, and 1 mT) or pulsed (1 mT, 15 min on/off). Controls included wild-type and Eμ–*pim*-1 sham-exposed controls and a positive control group of Eμ–*pim*-1 mice unexposed to the MF but treated with ENU (50 mg/kg, i.p.). A full necropsy was performed on all mice

indicating clinical signs of disease by 18 months after the initiation of exposure and a histopathologic analysis was conducted on a wide range of tissues. Immunofluorescence and immunohistochemical techniques were used to phenotype representative lymphomas. The incidence of lymphoblastic and non-lymphoblastic lymphomas was determined for those animals dying over the course of the experiment and the cumulative incidence of the different types of lymphomas identified by immunophenotyping on representative animals was also reported.

No statistically significant differences or suggestive trends were noted for any MF-exposed group in any parameter compared to Eμ–*pim*-1 sham-exposed controls. However, investigators reported a statistically significant ($p < 0.001$) increase in a lethal nontumor end point, a transgene-dependent renal glomerular disease, in the group of mice exposed to continuous 1 mT fields.

Except for the reservations discussed below, this experiment satisfies basic quality control criteria. In addition, both the exposure and pathology phases of the study were conducted under blinded conditions, and the histopathology results were independently evaluated. The significance of this study as an indication of lack of carcinogenic potential of EMF is uncertain for several reasons. First, investigators did not examine survivors not showing clinical signs of disease after 18 months of exposure for evidence of subclinical disease. This omission could have limited the sensitivity of the analysis for detection of a late enhancement effect. Second, as discussed above, to the extent that known non-genotoxic carcinogens have been tested in this system, they have been negative. Thus, it is possible that a nongenotoxic agent such as EMF (*10*) might not be detected. Third, investigators indicate that approximately 13% of the 293 animals in the study that died or exhibited clinical signs of disease within 18 months were undiagnosable because of autolysis or other causes. This animal loss may raise some general concerns about quality standards applied in the study. However, it may not otherwise bring into question the negative results reported, since investigators report that these undiagnosable animals were distributed roughly equally throughout the control and exposure groups. Even if it is assumed that neoplastic disease in these undiagnosable animals only occurred in one of the MF-exposed groups, the resulting increase in tumor incidence would not be large enough to alter the basic conclusion of the study.

The experiments employing the $p53^{def}$ and Eμ–*pim*-1 systems reviewed here are substantially negative. Although McCormick et al. (*77*) and Harris et al. (*83*) used the Eμ–*pim*-1 system and both employed similar frequencies and MF intensities, the two experiments are not comparable because all test groups employed by McCormick et al. (*77*) were pretreated with ENU, and Harris et al. (*83*) did not employ ENU in any groups exposed to MFs.

Leukemia-prone AKR mice. In an older study that we have not previously reviewed, Bellosi (*85*) exposed the leukemia-prone AKR strain of mice to MFs. The fields are described as pulsed, modulated at either 12 Hz or 460 Hz, and of 6 mT intensity. More precise characterization of the pulsed field is not provided. Exposure was for 30 min twice weekly and was continued for five generations. Group sizes were maintained at between 20 and 30 animals throughout the experiment. Procedures used to maintain group sizes across five generations are not specified. Control groups were most likely sham-exposed, but this is not precisely indicated in the report. Survival, spleen weight, and thymus weight were reported as averages for each generation group, presumably including results from both male and female animals. Investigators report no statistically significant differences between exposed and control groups in any of the three parameters. Interpretation of these results is complicated by the fact that different numbers of animals were used to determine survival on the one hand and spleen and thymus weights on the other; criteria used to select animals for determination of spleen and thymus weights are not specified.

The significance of the negative results of this study are questionable. In addition to the quality control concerns indicated above, the very high incidence of leukemia in the AKR strain of mice suggests that any enhancement effect of MF exposure on the neoplastic process, particularly a weak effect, might be difficult to discern.

Assays for promotion of brain cancer in rodents. At the time of our previous review (*1*), ongoing studies of possible effects of EMF exposure on promotion of brain cancer in rodents had not been completed (*132*). Reports of tests in two rodent systems are now available and are reviewed below. Mandeville and colleagues (*133*) test for possible promotion effects using the ENU transplacental model in rats. Babbitt and colleagues [discussed by the EMF RAPID Working Group (*3*)] test for promotion effects using the split-dose ionizing radiation model in mice.

THE ENU TRANSPLACENTAL MODEL. For reviews of the ENU transplacental model, see Peterson et al. (*134*), Berleur and Cordier (*135*), Inskip et al. (*136*), and Maekawa and Mitsumori (*137*), as well as our previous discussion (*1*). Two promoters known to enhance the development of neoplasia in other model systems, TPA and zinc acetate, have been reported to enhance the development of neurogenic tumors in the ENU transplacental model (*138,139*). These results have not been considered definitive, however, because of the small numbers of animals tested (*140*). Hexachlorophane, a potential promoter of brain cancer known to produce astrocyte hypertrophy in the brain (*140*), did not promote brain cancer in this model, nor did several other agents known to promote neoplasia in other model systems. These agents include phenobarbital (*141*), chronic stress (*142*), X-irradiation (*143*), and methylazoxymethanol (*144*). We are unaware of other promoters tested in the ENU transplacental model. This system has also recently been used to test for possible effects of microwave frequency electromagnetic fields (*145*).

Mandeville and colleagues (*133*) monitored for potential effects of chronic exposure to MFs (60-Hz, 2 μT, 20 μT, 200 μT, and 2 mT) on mortality and the development of neurogenic tumors in offspring of F344/N female rats initiated transplacentally with ENU. Specifically, pregnant rats were initiated with ENU (5 mg/kg, i.p., on day 18 of gestation) and continuous exposure to MFs begun 48 hr following treatment with ENU. Each experimental group was comprised of 50 female offspring. Control groups included a saline-injected group without ENU treatment or MF exposure, an ENU-treated control group without MF exposure, an ENU-treated control group sham-exposed to the MF, and an ENU-treated positive control group receiving TPA [10 μg/kg, i.p. (*139*)] on days 19–21 of gestation and every 15 days starting at day 14 after birth and throughout the study). Animals were monitored throughout the study for weight loss, mortality, and clinical signs of disease. A complete histopathologic examination of brain, cranial nerves, spinal cord tissues, and major organs was conducted on all animals. The experiment was terminated when surviving offspring reached 65 weeks of age. The only statistically significant differences observed were for total incidence of neurogenic tumors (including glial tumors of the central nervous system and Schwannomas of the peripheral nervous system) in the positive controls (ENU+TPA) compared to the group exposed to ENU only (i.e., no sham or MF exposure) ($p < 0.05$). No statistically significant differences were observed when tumor incidence in each MF-exposed group was compared to the ENU-treated sham-exposed control.

Aside from the variability in tumor incidence among control groups discussed below, this study satisfies quality control criteria. In addition, clinical observations and pathologic evaluations were conducted under

blinded conditions and according to GLP. The exposure system and pathology evaluations were validated by independent audit and the pathology slides were reviewed by a panel of pathologists.

The analysis of this study is complicated because the overall incidence of neurogenic tumors differed considerably between the unexposed ENU control and the sham-exposed ENU control (38 and 60%, respectively). This difference is statistically significant ($p < 0.05$) but most likely reflects inherent variability in the system rather than a biologic effect. Since all the experimental groups were concurrent, the difference between these two control groups also suggests that a statistical comparison in which the two ENU controls (unexposed and sham-exposed) are combined is well justified. In fact, a χ^2 two-way contingency table analysis indicates that the effect observed in the ENU+TPA control is not statistically significant ($p = 0.33$) when the comparison is made to the combined unexposed and sham-exposed ENU controls. It should also be noted that total neurogenic tumor incidence in the ENU + 20 μT-exposed group is almost identical to that of the ENU+TPA control (28/50 vs 29/50) and approaches significance ($p = 0.07$) when compared to the unexposed ENU control.

In summary, results of this study do not provide any evidence that MFs promote neurogenic tumors in the ENU transplacental system, although the assay has limited sensitivity due to the variability among control groups. The significance of the negative results of this study must also be taken in the context of the limited information available on the promotion of neurogenic tumors in this system.

THE SPLIT-DOSE IONIZING RADIATION MODEL. This model, as developed by Kaplan [e.g., see Kaplan and Brown (*74*)] and discussed previously (see the section "Lymphoma in mice pre-exposed to initiating agents"), is primarily used to study the development of T-cell lymphomas that do not involve neural tissues. To our knowledge this model has not previously been used to study the promotion of brain cancer. However, high doses of ionizing radiation are associated with brain cancer in children [reviewed by Inskip et al. (*136*)] and there is some evidence that ionizing radiation induces brain cancer in monkeys (*146*). It is therefore possible that the split-dose irradiation treatment used in the Kaplan model has some initiating potential for neurogenic tumors.

Babbitt and colleagues [see discussion by the EMF RAPID Working Group (*3*)] examined this possibility in conjunction with studies primarily aimed at using the split-dose ionizing radiation model to determine whether chronic exposure to 60-Hz, 1.4-mT circularly polarized MFs enhanced the development of leukemia/lymphoma in female C57Bl/6 mice (190–380 per group) (*15*) (see discussion above in "Lymphoma in mice pre-exposed to initiating agents").

Three brain tissue sections—from the frontal cortex and basal ganglia, the parietal cortex and thalamus, and the cerebellum and pons—were included in the histopathologic analysis conducted on each animal necropsied for the leukemia/lymphoma study. Very few primary brain tumors were identified (a total of seven in all treatment and control groups), and these appeared to be randomly distributed among control and treatment groups. Thus, the doses of ionizing radiation used did not appear to induce brain neoplasms, nor was there evidence of any neoplastic neurogenic effects in any groups also exposed to MFs.

The study was conducted according to GLP and satisfies all quality control criteria. In addition, the exposure and histopathologic analyses were conducted under blinded conditions, and the histopathologic analysis was subjected to internal and external peer reviews.

This study is primarily of interest as a test of the ability of MFs to induce (as opposed to promote) brain cancer, and that aspect was discussed in a previous section ("Tests of Magnetic Fields in 2-Year, Lifetime, or Multigeneration Exposure Studies"). Because in the experiments described in this section ionizing radiation did not induce brain tumors, the study cannot properly be considered a test of the potential of MFs to promote brain cancer.

Discussion

In this report we have updated and extended our previous review of tests of electric and magnetic fields in animal model systems designed to assay for potential carcinogenic activity. A total of 29 new reports were identified, bringing the total of completed reports now reviewed to more than 60. These reports encompass the work of some 20 independent research groups throughout the world. Roughly one-third of the studies in these reports employ 2-year/lifetime or multigeneration chronic exposure bioassays (14 reports from 5 independent research groups). The remainder of the studies use mostly shorter-term bioassays to determine whether EMF has the potential to modulate postinitiation stages of carcinogenesis. The primary assays for postinitiation activity used are the rat mammary carcinoma model (19 reports from 4 independent research groups), the mouse skin model (15 reports from 6 independent research groups), and several animal models of leukemia/lymphoma (15 reports from 5 independent research groups).

As shown in Table 5, for all but two of the six general model systems reviewed (lifetime or multigeneration exposure studies in rats or mice; rat mammary carcinoma model; rat liver focus assay; mouse skin model; models of human leukemia and lymphoma in rats or mice; and brain cancer promotion in rats), both positive and negative results have been reported.

We have previously discussed the difficulties involved in making summary judgments as to positivity or negativity across a number of EMF test results using the same or similar test system or across different test systems (*10*). As indicated in the section "Quality Assurance and Reproducibility/Comparability Criteria," we have relied on a combination of data quality and independent reproducibility criteria to assist in making summary judgments as to positivity or negativity in each model system.

The results of applying data quality and independent reproducibility criteria to assist in making summary judgments are indicated in Table 5. Application of data quality criteria results in several modifications of the data set. First, reports appearing only in abstract form or as in progress have been excluded from the analysis and do not appear in the table [see McCann et al. (*1*) and the body of this report for excluded reports]. Second, studies not conforming to data quality criteria or characterized by factors potentially invalidating study results are also excluded from the primary analysis but are included in parentheses in the table for information. Reports corresponding to these studies are indicated in footnote "b". Finally, studies not meeting quality criteria solely because of limited information presented in reviewed reports are included with studies meeting all quality criteria and appear in the table in boldface type. Failure of these studies to fully meet quality criteria, however, is noted in the text.

As shown in Table 5, application of data quality criteria does not have a significant impact on the distribution of positive and negative results for any model system. Thus, both positive and negative results are still reported for all but two of the model systems reviewed, even after applying quality control criteria. It should be noted, however, that studies employing the rigorous GLP standard were uniformly negative except for the equivocal finding using the LGL rat leukemia model.

Applying independent reproducibility criteria to each model system has a much more dramatic impact on the dataset. As recently pointed out by the NRC (*6*), there unfortunately have been very few attempts to construct precisely replicated independent data sets for EMF tests in any system. We have relied previously on a criterion of rough reproducibility to assist in making summary

Table 5. Combined summary of review results from McCann et al. (*1*) and from the current review.[a]

Animal model system	Total number of completed studies reviewed[b]	Number of studies reporting statistically significant positive results	Criterion for rough reproducibility satisfied? (Y,N,I)[c]	Number of studies reporting uniformly negative results	Criterion for rough reproducibility satisfied? (Y, N, I)[c]
Lifetime or multigeneration exposure studies in rats or mice	**4** (1)	**1** (1)	N	**3**	Y
Rat mammary carcinoma model	**10** (2)[d]	**6** (0)	N, I	**5** (1)	N, I[e]
Rat liver focus assay	**2**	**0**	–	**2**	N
Mouse skin model					
Promotion	**4** (1)[f]	**0** (1)	–	**4**	Y
Co-promotion	**6**	**3**	N	**3**	Y
Models of human leukemia and lymphoma in rats or mice	**7** (3)	**2**	N	**5** (3)	N,I[g]
Brain cancer promotion in rats	**1**	**0**	–	**1**	–

[a]The table includes results of tests using ac fields only. [b]Study refers to a set of experiments conducted concurrently. Thus, a study may include one or more exposure or protocol conditions. The counting method we have used is biased toward positive results in that if any of the experiments comprising a study are positive, we counted the study as positive. Since a study may be reported in more than one publication, the number of studies does not correspond to the number of reports reviewed. In progress studies and studies reported only in abstract form are not included in the table. Studies roughly satisfying data quality criteria are in boldface; studies not satisfying criteria are in parentheses. Studies not satisfying quality criteria solely because of lack of information in the report are included as roughly satisfying criteria. The reports describing studies included in the table are: lifetime or multigeneration exposure studies in rats or mice (*11–17*); rat mammary carcinoma model (*25–35,38,154–156*); rat liver focus assay (*157,158*); mouse skin model (*48–50,52–54,56,58,59,159*); models of human leukemia and lymphoma in rats or mice (*15,75,77–85*); brain cancer promotion in rats (*133*). Studies not roughly satisfying quality criteria are as follows. Lifetime or multigeneration studies: Fam and Mikhail (*17*); rat mammary carcinoma model: NTP—first 13-week study (*33,34*); Ekström et al. (*30*); mouse skin model: Rannug et al. (*48*); models of human leukemia in rats or mice: Svedenstål and Holmberg (*75*); Thomson et al. (*78*); Bellossi (*85*). [c]Y = Yes; N = No; I = criterion satisfied for intralaboratory replicability. [d]The NTP report (*33–35*) consists of three experiments, two of which were conducted concurrently (the first 13-week experiment and the 26-week experiment). We have therefore counted the NTP report as two studies. [e]Both the second 13-week study and the 26-week study conducted by the NTP (*33–35*) were negative. [f]The Rannug et al. (*48*) study consisted of concurrent experiments involving either continuous or intermittent exposures to MFs and, as indicated in footnote "b," would therefore normally be counted as a single study. However, because only experiments involving continuous exposures satisfied quality criteria, we have entered the results of Rannug et al. (*48*) as two studies. [g]The two experiments of Anderson, Sasser and colleagues involving a cell inoculum of 2.2×10^7 (*79–82*) satisfy the criterion for intralaboratory replicability.

judgments about the positivity or negativity of EMF test results in genotoxicity assay systems (*10*). Here we apply the rough reproducibility criterion to the available test results from animal model systems.

As shown in Table 5, among studies roughly satisfying quality criteria, the criterion for independent reproducibility is not satisfied for any positive results; it is satisfied, however, for negative results in lifetime exposure studies in rats and mice and for both promotion and co-promotion assays in the mouse skin model. The criterion for intralaboratory reproducibility is satisfied for both positive and negative results using the rat mammary carcinoma model (i.e., results of independent replications are contradictory) and for negative results in studies using the LGL rat leukemia model.

The reproducibility analysis is complex and critically important in making summary judgments among the results reviewed. Table 6 lists, for each model system reviewed, pairs of test results that were obtained independently by different laboratories or that were results of nonconcurrent intralaboratory replication studies. Each pair of studies listed conforms to the criterion of rough reproducibility (see "Quality Assurance and Reproducibility/Comparability Criteria"). The studies listed in Table 6 also all approximately satisfy basic quality criteria as discussed above (i.e., they appear in boldface in Table 5).

As shown, twelve pairs of studies satisfy rough reproducibility criteria. These include four pairs of lifetime or multigeneration exposure studies [(*11–13*) vs (*16*), (*11–13*) vs (*14*), (*11–13*) vs (*15*), and (*14*) vs (*16*)]; four pairs of studies using the rat mammary carcinoma promotion model [(*29*) vs (*28*), (*32,38*) vs (*25–27*), (*33–35*) vs (*25,26,32,38*), and (*33,34*) (the second 13-week study) vs (*33,35*) (the 26-week study)]; three pairs of studies using the mouse skin promotion/co-promotion model [(*54*) vs (*58,59*), (*50*) vs (*53*), (*52,54*) vs (*50,53*)]; and one pair employing a mouse leukemia transplant model [(*80–82*) vs (*79*)]. We discuss the results of these pairwise comparisons briefly below.

Lifetime or Multigeneration Exposure Studies

As shown in Table 6, aspects of the comprehensive 2-year chronic bioassay conducted by the NTP (*11–13*) overlap three independently conducted long-term chronic bioassays (*14–16*), and two of the latter three studies also have overlapping aspects (*14,16*). Four pairwise comparisons are indicated in Table 6: *a*) results obtained in male F344 rats at overlapping exposures spanning a range of 0.2–5 mT (continuous) [this comparison involves the NTP bioassay (*11–13*) and the study of Yasui et al. (*16*)]; *b*) results obtained in female F344 rats at overlapping exposures spanning a range of 0.002–2 mT (continuous) [this comparison involves the NTP bioassay (*11–13*) and the study of Mandeville et al. (14)]; *c*) results obtained in female C57Bl/6 mice at overlapping exposures spanning a range of 0.2–1.4 mT (continuous) [this comparison involves the NTP bioassay (*11–13*) and the study of Babbitt et al. (*15*)]; and *d*) results obtained in female F344 and F344/DuCrj rats at overlapping exposures spanning a range of 0.2–5 mT (continuous) [this comparison involves the studies of Mandeville et al. (*14*) and Yasui et al. (*16*)]. The results of these four comparisons provide independently replicated evidence that chronic exposure to MFs under the conditions of the assays does not result in any statistically significant increase in the incidence of: *a*) any tumor type in male (two independent assays) or female (three independent assays) rats; and *b*) lymphoid neoplasms in female mice.

Rat Mammary Carcinoma Model

For the rat mammary carcinoma promotion model, four pairwise comparisons are possible, involving three intralaboratory comparisons [(*29*) vs (*28*), (*32,38*) vs (*25–27*), and (*33,34*) (the second 13-week study) vs (*33,35*) (the 26-week study)], and one independent replication [(*33–35*) vs (*25,26,32,38*)]. Two of the three intralaboratory comparisons confirm positive tumor incidence results, although, as discussed in the text and indicated in Table 6, there were some differences between studies comprising both of these intralaboratory replication study pairs. The intralaboratory replications conducted by the NTP were both negative. The independent replication study of NTP resulted in negative results for tumor incidence, which contradicts the earlier positive reports from the Löscher group. The NTP 26-week study, however, found a small but not statistically significant increase in tumor volume in all three groups of MF-exposed animals, not clearly contradicting the earlier statistically significant finding at approximately 13 weeks reported by the Löscher group (*26,38*).

Table 6. Reproducibility of positive or negative results of carcinogenesis tests of EMFs in animal model systems.

Test system	Studies satisfying Q/A criteria that are sufficiently comparable for rough reproducibility analysis[a]	Overlapping exposure range compared	Overall judgment as to positivity or negativity	Comments
Lifetime or multigeneration exposure studies	NTP (*11–13*) vs Yasui et al. (*16*)	0.2–5 mT, continuous	Negative in male rats	Neither the increased incidence of fibroma of s.c. tissue reported by Yasui et al. nor the increased incidence of thyroid C-cell adenoma and carcinoma reported by the NTP were observed in the other study
	NTP (*11–13*) vs Mandeville et al. (*14*)	0.002–2 mT, continuous	Negative in female rats	
	NTP (*11–13*) vs Babbitt et al. (*15*)	0.2–1.4 mT, continuous	Negative for lymphoid neoplasms in female mice	
	Mandeville et al. (*14*) vs Yasui et al. (*16*)	0.2 mT–5 mT	Negative in female rats	
Rat mammary carcinoma model	Anisimov et al. (*29*) vs Beniashvili et al. (*28*) (intralaboratory comparison)	0.002 mT	Enhancement of the rate of development of MNU-induced mammary adenocarcinoma in female rats	
	Mevissen et al. (*32*) and Thun-Battersby et al. (*38*) vs Löscher et al. (*25*), Baum et al. (*26*), and Mevissen et al. (*27*) (intralaboratory comparison)	0.05–0.1 mT	Positive in female rats based on tumor incidence rates determined by palpation	Statistically significant differences in tumor volume reported by Baum et al. (*26*) were not observed in the replication study of Mevissen et al. (*32*) but were observed in the study of Thun-Battersby et al. (*38*)
	NTP (*33–35*) vs Mevissen et al. (*32*), Löscher et al. (*25*), Baum et al. (*26*), and Thun-Battersby et al. (*38*)	0.05–0.5 mT	Results contradictory for tumor incidence as measured by palpation, macroscopically visible tumors at autopsy, and adenocarcinomas	
	NTP (*33,34*) (second 13-wk study) vs NTP (*33,35*) (26-week study) (intralaboratory comparison)	0.1 mT or 0.5 mT	Negative	
Mouse skin model				
Promotion	DiGiovanni et al. (*54*) vs Stuchly et al. (*58*) and McLean et al. (*59*)	2 mT	Negative	
Co-promotion	Stuchly et al. (*50*) vs McLean et al. (*53*) (intralaboratory comparison)	2 mT	The initial positive report of Stuchly et al. (*50*) was not reproduced in two subsequent replications by members of the same research team	
	Sasser et al. (*52*) and DiGiovanni et al. (*54*) vs McLean et al. (*53*) and Stuchly et al. (*50*)	2 mT	Negative	
Animal models of human leukemia and lymphoma				
Leukemia transplant models	Anderson et al. (*80*), Sasser et al. (*81*), and Morris et al. (*82*) vs Anderson et al. (*79*) (intralaboratory comparison)	1 mT	Negative for a cell inoculum of 2.2×10^7	Differences between the two experiments in some non-neoplastic parameters indicate interexperimental variability

[a]Q/A criteria are as specified in the text. Studies approximately conforming to quality criteria are included for comparative purposes. Studies considered to deviate from Q/A criteria or for other reasons considered to be inappropriate for a comparative analysis (such as available only in abstract form) are as follows. Lifetime or multigeneration exposure studies: Fam and Mikhail (*17*); Kharazi et al. [discussed by the RAPID Working Group (*3*)]. Rat mammary carcinoma model: Ekström et al. (*30*). Mouse skin model: Byus and Ma (*57*); McLean et al. (*49*). Human leukemia/lymphoma models: Svedenstål and Holmberg (*75*); Thomson et al. (*78*).

Mouse Skin Model

For the mouse skin promotion–co-promotion model, three pairwise comparisons are indicated in Table 6: one intralaboratory pairwise comparison involving an assay for co-promotion [(*50*) vs (*53*)] and two independent replication pairs, one involving an assay for promotion activity [(*54*) vs (*58,59*)] and the other an assay for co-promotion [(*52,54*) vs (*50,53*)]. All these studies were conducted using the SENCAR mouse and all involved chronic exposure to 60-Hz, 2-mT (continuous) MFs. All promotion studies were negative, a result confirmed by both intralaboratory and independent replication studies (*54,58,59*). The original positive co-promotion result reported by Stuchly et al. (*50*) was not reproduced in subsequent intralaboratory replications of McLean et al. (*53*) or in the independent replication study (*52,54*).

Animal Models of Human Leukemia and Lymphoma

Finally, an intralaboratory comparison involving two studies using the LGL rat leukemia transplant model [(*80–82*) vs (*79*)] indicated negative results in both assays for chronic exposures to 60-Hz 1 mT (continuous) MFs. As indicated in the text and in Table 6, however, differences between the two experiments in some non-neoplastic parameters indicate significant interexperimental variability.

Summary of Positivity and Negativity

Among the 34 studies reviewed in this and our previous report (*1*) that we consider roughly to meet quality criteria, 12 studies reported positive results and 23 reported uniformly negative results. As discussed above, evidence of independent replication is available only for negative results in two model systems (lifetime or multigeneration exposure studies in rats and mice and promotion–copromotion studies using the mouse skin model). Positive results unconfirmed by independent replication have been reported in 12 studies satisfying basic data quality criteria (see Tables 2 and 5). We discuss each of these positive results briefly below.

Lifetime or multigeneration exposure studies in rats or mice. The statistically significant positive results that form the basis for the NTP conclusion of *equivocal evidence of carcinogenicity* (*11*) are most likely statistical artifacts resulting from biologic variability. This conclusion is strengthened by the failure of this isolated positive result to be confirmed in a similar study by Yasui et al. (*16*).

Rat mammary carcinoma model. All six positive studies are from two laboratories, those of Beniashvili and colleagues and Löscher and colleagues (see Table 2 and text for references). While both laboratories have provided intralaboratory replication studies confirming their positive results, the only attempt at independent replication (*33–35*) was negative. Unfortunately the study protocols used by Beniashvili and colleagues and Löscher and colleagues are too dissimilar to permit direct comparison.

Mouse skin model. Of the three positive results obtained using this system, two results utilized the SENCAR mouse DMBA/TPA co-promotion system. One of these positive studies (*50*) was unconfirmed in subsequent replication attempts performed by members of the same research team. A second positive result used the same model system but involved a different neoplastic end point (*49*), which precluded direct comparison. The third positive result was obtained in an unvalidated assay system employing UV light as inducer (*56*). None of these studies were comparable to the others.

Models of human leukemia and lymphoma in rats or mice. One of the two positive results in this model type occurred in the rat LGL transplant assay in a well-documented study satisfying quality criteria (*79*). The other positive result occurred in a mouse lymphoma assay employing DMBA as inducer (*84*); interpretation of this result is not obvious. As indicated above, the result obtained by Anderson et al. (*79*) is equivocal and its interpretation is complex. Because of the generally high quality of the study, however, the result is possibly significant.

Conclusions

Results of applying data quality and reproducibility criteria to the current data available from *in vivo* animal carcinogenesis bioassays strongly indicate that chronic exposure to continuous MFs in the range of 0.002–5 mT is unlikely to result in carcinogenesis in rats or mice. Although chronic exposure to MFs appears to be clearly negative in one promotion assay (the mouse skin model), results are conflicting in another assay (the rat mammary carcinoma model), and unreplicated weakly positive results have been reported in one treatment group in a third assay (the rat LGL transplant assay). Therefore, a weak promoting effect of MFs under certain exposure conditions cannot be ruled out categorically based on available data.

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