ELSEVIER

Mutation Research 411 (1998) 45–86

Reviews in Mutation Research

The genotoxic potential of electric and magnetic fields: an update

Joyce McCann [a,*], Fred Dietrich [b,1], Charles Rafferty [c,2,3]

[a] *Research Consultant, 5537 East Highway 89, Kanab, UT 84741, USA*
[b] *Electric Research and Management, 2140 William Pitt Way, Pittsburg, PA 15238, USA*
[c] *Electric Power Research Institute (EPRI), 3412 Hillview Avenue, Palo Alto, CA 94303, USA*

Received 28 October 1997; revised 4 February 1998; accepted 4 February 1998

Abstract

We review 23 studies on the potential genotoxicity of electric and magnetic fields that have appeared in the published literature since our 1993 review of 55 published studies (McCann et al., Mutat. Res. 297 (1993) 61–95) and six additional studies published prior to 1993, which were not previously reviewed. As in our previous review, internal electric fields present in media (for in vitro experiments) and in the torso (for in vivo experiments) were estimated. Individual experiments are evaluated using basic data quality criteria. The potential for genotoxicity of electric and magnetic fields is discussed in light of the significant body of genotoxicity data that now exists. Three unsuccessful attempts to replicate previously reported positive results have appeared since our previous review. We conclude that, in spite of the 34 studies reviewed in this and our previous publication that report positive genotoxic effects, none satisfy all of three basic conditions: independent reproducibility, consistency with the scientific knowledge base, and completeness according to basic data quality criteria. As we discuss, these criteria are satisfied for several groups of negative studies in several exposure categories (ELF magnetic fields, 150 μT–5 mT, combined ELF electric and ELF magnetic fields, approx. 0.2 mT, 240 mV/m, and static magnetic fields, 1–3.7 T). The evidence reviewed here strengthens the conclusion of our previous review, that the preponderance of evidence suggests that ELF electric or magnetic fields do not have genotoxic potential. Nevertheless, a pool of positive results remains, which have not yet been tested by independent replication. Among the 12 studies reviewed here, which report statistically significant or suggestive positive results, we point particularly to results from five laboratories [J. Miyakoshi, N. Yamagishi, S. Ohtsu, K. Mohri, H. Takebe, Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations by exposure to high-density 50-Hz magnetic fields, Mutat. Res. 349 (1996) 109–114; J. Miyakoshi, K. Kitagawa, H. Takebe, Mutation induction by high-density, 50-Hz magnetic fields in human MeWo cells exposed in the DNA synthesis phase, Int. J. Radiat. Biol. 71 (1997) 75–79; H. Lai. N.P. Singh, Acute exposure to a 60-Hz magnetic field increases DNA strand breaks in rat brain cells, Bioelectromagnetics, 18 (1997) 156–165; H. Lai, N.P. Singh, Melatonin and

Abbreviations: ELF = Extremely low frequency; dB/dt = The time rate of change of the magnetic field; EMF = Electric and magnetic fields; EMS = Ethyl methanesulfonate; MMS = Methyl methanesulfonate; MF = Magnetic field; MNU = *N*-methyl-*N*-nitrosourea; T = Tesla; TG^r = Thioguanine resistant; HGPRTase = Hypoxanthine-guanine phosphoribosyltransferase; RMS = Root-mean-square; SCEs = Sister chromatid exchanges; UV = Ultraviolet light; V/m = Volts per meter; VDT = Video display terminal

* Corresponding author. Tel.: +1-435-644-5522; fax: +1-435-644-5522; E-mail: jmccann@xpressweb.com
[1] E-mail: 75061.3420@compuserve.com.
[2] E-mail: craffert@epri.com.
[3] Also corresponding author for reprint requests.

PII S1383-5742(98)00006-4

N-tert-butyl-α-phenylnitrone block 60-Hz magnetic field-induced DNA single and double strand breaks in rat brain cells, J. Pineal Res. 22 (1997) 152–162; T. Koana, M. Ikehata, M. Nakagawa, Estimation of genetic effects of a static magnetic field by a somatic cell test using mutagen-sensitive mutants of *Drosophila melanogaster*, Bioelectrochem. Bioenergetics 36 (1995) 95–100; F.L. Tabrah, H.F. Mower, S. Batkin, P.B. Greenwood, Enhanced mutagenic effect of a 60-Hz time-varying magnetic field on numbers of azide-induced TA100 revertant colonies, Bioelectromagnetics 15 (1994) 85–93; S. Tofani, A. Ferrara, L. Anglesio, G. Gilli, Evidence for genotoxic effects of resonant ELF magnetic fields, Bioelectrochem. Bioenergetics, 36 (1995) 9–13], which satisfy most basic data quality criteria and may be of interest.

Keywords: Genotoxic potential; Electric fields; Magnetic fields; Extremely low frequency; ELF; Static magnetic

1. Introduction

A causal relationship between exposure to electric and magnetic fields (EMF) [4] and cancer has been suggested but not unequivocally demonstrated in humans. Some laboratory studies have also suggested that extremely low frequency (ELF) [5] fields may be able to promote neoplasia in experimental animals (reviewed by McCann et al. [3]). An important component in assessing potential cancer risk is knowledge concerning any genotoxic potential of EMF. In 1993, two extensive critical reviews of the published literature on the genotoxic potential of electric and magnetic fields appeared [4,5]. Both reviews reached similar conclusions. In our review, we suggested that the preponderance of evidence indicated that ''neither ELF nor static electric or magnetic fields have a clearly demonstrated potential to cause genotoxic effects''. However, few reports were independently confirmed, and the wide variation in exposure conditions made it difficult to make a definitive overall evaluation. Furthermore, several positive reports had methodological difficulties or presented insufficient information for an adequate evaluation.

Since these reviews have been published, 23 new genotoxicity studies have appeared in the published literature, and 6 additional studies published prior to 1993 have been identified, which were not previously reviewed (see Table 1). Most of these reports (24 of 29) examine ELF magnetic fields, the most significant category in terms of widespread human exposure from power transmission and distribution systems. The total number of studies reviewed, which examine the potential genotoxicity of ELF magnetic fields, is now increased to 43 (plus an additional eight studies that examined ELF magnetic fields in conjunction with co-exposure to ELF electric fields). Thus, the information base for making an overall assessment of the genotoxic potential of ELF magnetic fields is now substantial. In this 'update' report, we assess this new work in the light of previously reviewed results.

2. Methods

A literature search was conducted to retrieve all in vitro and in vivo studies published prior to the Spring of 1997 that measured effects on endpoints relevant to genotoxicity from exposure to electric or magnetic fields. Cancer promotion or reproductive outcome studies were not included. Abstracts were not included unless they appeared in a peer-reviewed journal. Additional studies that have not been cited or published in the open literature, e.g., completed under contract to government agencies, would not have been identified in the search. Genotoxicity assays were grouped into categories as described in our previous review [4].

Electric and magnetic field exposures were grouped into six categories (see McCann et al. [4] for discussion): (1) ELF electric fields; (2) ELF magnetic fields; (3) combined ELF electric and magnetic fields; (4) static magnetic fields; (5) static electric fields; and (6) co-exposures to electric or magnetic fields and ionizing radiation, ultraviolet light, or chemical mutagens. Tofani et al. [33] manipulated the static magnetic field environment, as well as the

[4] For an excellent introduction to the basic physics of electric and magnetic fields, see Polk and Postow [1] and Kaune and Anderson [2].

[5] ELF fields are defined as ac electric and magnetic fields with frequencies between dc and 3 kHz.

Table 1
Genotoxicity reports identified

Report	ELF magnetic	ELF electric	ELF electric and ELF magnetic	Static magnetic[a]	Static electric	Co-exposures
Ager and Radul [6]	X					Ultraviolet light
Antonopoulos et al. [7]	X					
Berg et al. [8]	X				X	
Cantoni et al. [9]	X	X	X			Hydrogen peroxide
Cantoni et al. [10]	X	X	X			MMS, Potassium chromate, Ultraviolet light
Chahal et al. [11]		X				Ultraviolet light, Mitomycin C
Fairbairn and O'Neill [12]	X					Hydrogen peroxide
Fiorani et al. [13]	X	X	X			
Galt et al. [14]	X					
Giorgi et al. [15]				X		
Hintenlang [16]	X					γ-radiation
Kiranmai [17]				X		
Koana et al. [18]				X		
Lai and Singh [19]	X					
Lai and Singh [20]	X					
Miyakoshi et al. [21]	X					X-rays
Miyakoshi et al. [22]	X					
Morandi et al. [23]	X	X	X			
Nafziger et al. [24]	X					
Nordenson et al. [25]	X					
Nordenson et al. [26]	X					
Paile et al. [27]	X	X				
Saalman et al. [28]	X					
Scarfi et al. [29]		X				Mitomycin C
Scarfi et al. [30]	X					
Suri et al. [31]	X					MNU, menadione
Tabrah et al. [32]	X					Sodium azide
Tofani et al. [33]	X					Mitomycin C
Zwingelberg et al. [34]	X					

[a]All studies are believed to have a co-exposure to the static magnetic field of the earth. If the geomagnetic field was reported, experimentally manipulated, or likely to affect the exposure apparatus, that information is noted in the text and in Tables 2–4.

Table 2
Genotoxicity studies of ELF magnetic fields

	Magnetic field exposure[a]	Internal electric field[b]	Result	Reference
Microbial systems				
Positive results—None				
Negative results				
Salmonella TA97a, TA98, TA100, TA102 exposed in top agar Petri plates for 48 h in mutagenesis assay	60 Hz, 600 Hz, and 6000 Hz; 0.33 mT Vertical (0.12, 1.2, and 12 T/s)	0–2.7, 0–27, and 0–270 mV/m at 60, 600, and 6000 Hz, respectively[c]	Negative	[23]
Salmonella TA100 exposed in top agar petri plates for 48 h in mutagenesis assay	60 Hz, 0.2 mT (75 mT/s) (Horizontal) Static: 23.3 μT Horizontal (parallel) and 18.9 μT Vertical	0.1mV/m[d]	Negative	[32]
Salmonella TA100 exposed in top agar petri plates for 6 h in mutagenesis assay	Sawtooth magnetic field 6.2 cm from the face of a VDT[e]	0 – 0.2 mV/m[f]	Negative	[8]
Salmonella TA100, TA97, TA98, and TA102 exposed in top agar petri plates for 48 h in mutagenesis assay	50 Hz, pulsed (2 μs pulse duration, 1 μT peak intensity)	Unknown[g]	Negative	[24]
Repair proficient (RAD^+) and repair deficient (*rad*3) *Saccharomyces cerevisiae* strains exposed for 3 h, 15 min on/off, followed by 3 days continuous exposure in assays for mitotic recombination and mutagenesis	60 Hz, 1 mT (380 mT/s) Vertical	0–9.4 mV/m[h]	Negative	[6]
In vitro chromosome / mutagenesis				
Sinusoidal magnetic fields				
Positive results				
Human peripheral lymphocytes exposed during 72 h culture period in micronucleus assay	32 Hz, 75 μT and 150 μT (15 and 30 mT/s) Static: 42 μT parallel to the ac field	unknown[g]	Positive. 75 μT: 51% average increase over 5 donors ($p < 0.05$); 150 μT: 74% average increase over 5 donors ($p < 0.05$)	[33]
Secondary cultures of human amniotic cells exposed 72 h in chromosome aberration assay	50 Hz, 30 μT (9.4 mT/s) Vertical	0.14 – 0.21 mV/m[h]	Positive. 3-fold increase in mean aberration frequency ($p < 0.001$) averaged over 7–9 donors. Also, a statistically significant increase in aberration frequency for each donor ($p < 0.01$)	[25]

Secondary cultures of human amniotic cells exposed 72 h in chromosome aberration assay	50 Hz, 30 μT (9.4 mT/s), 15 s on/off, Vertical; Static: exposed 44 μT Vertical and controls 37 μT Vertical	0.14 – 0.21 mV/m(15s on/off)[h]	Positive. 1.9-fold increase in mean frequency of aberrations ($p < 0.05$), including gaps; and 3.2-fold increase ($p < 0.05$), excluding gaps	[26]
Secondary cultures of human amniotic cells exposed 72 h in chromosome aberration assay	50 Hz, 30 μT (9.4 mT/s), 2 s on/20 s off, Vertical; Static: exposed 44 μT Vertical and controls 37 μT Vertical	0.14–0.21 mV/m (2 s on/20 s off)[h]	2-fold increase in mean frequency of aberrations ($p < 0.05$), including gaps (results not statistically significant if gaps were excluded)	[26]
Human melanoma cell line (MeWo) exposed for various times and at various induced electric field intensities in HGPRTase mutagenesis assay	50 Hz, 400 mT (126 T/s) Vertical; Static: Not reported but probably severely perturbed by iron pole pieces near cultures[i]	0–1.1, 1.1–1.9, 1.9–3.1, and 3.1–4.7 V/m (range of induced electric fields in each annulus of culture plates)	Positive. Time-dependent increase in mutants. Maximum increase was 6-fold. Statistical significance not reported	[21]
Human melanoma cell line (MeWo) exposed for 2 h at various times after release of cells from synchronization at the G_1/S border in HGPRTase mutagenesis assay	50 Hz, 400 mT (126T/s) Vertical; Static: Not reported but probably severely perturbed by iron pole pieces near cultures[i]	3.1–4.7 V/m (only outer annulus used)	Positive. Up to a 5-fold increase in mutation frequency during S-phase	[22]
Negative results				
Human peripheral lymphocytes exposed during 72 h culture period in micronucleus assay	50 Hz, 150 μT (47 mT/s); or 32 Hz, 75 μT and 150 μT (15 and 30 mT/s) Static: 0 μT (nulled)	Unknown[g]	Negative	[33]
Human peripheral lymphocytes exposed during 48 h culture period in chromosome aberration assay	60 Hz, 0.6 mT, 1.0 mT, or 1.4 mT (230, 380, and 530 mT/s)	Unknown[g]	Negative	[16]
Human peripheral lymphocytes exposed during 48 h culture period (chromosome aberration assay), 67 h culture period (SCE assay), or 65 h culture period (micronucleus assay)	50 Hz, 30 μT, 300 μT, or 1 mT (9.4, 94, or 314 mT/s) Vertical	0–0.06 and 0.08–0.13 mV/m (30 μT); 0–0.6 and 0.8–1.3 mV/m (300 μT); and 0–1.9 and 2.5–4.2 mV/m (1 mT)	Negative. No statistically significant increase in chromosome aberrations or micronuclei. Less than a 2-fold increase in SCEs ($p < 0.05$) in one experiment; negative in second experiment	[27]
Human peripheral lymphocytes exposed during culture for 48–69 h in sister chromatid exchange assay	50 Hz, 5 mT (1.57 T/s) Vertical; Static: Not reported but probably severely perturbed by ferromagnetic shields near the cultures	0–6.3 mV/m[h]	Negative	[7]

Table 2 (continued)

	Magnetic field exposure[a]	Internal electric field[b]	Result	Reference
Chinese hamster V79 cells exposed 1–85 min in assay for 'c-mitotic' effects	50 Hz, 30 μT (9.4 mT/s)	Unknown[g]	Negative	[28]
Secondary cultures of human amniotic cells exposed 72 h in chromosome aberration assay	50 Hz, 300 μT (94 mT/s) Vertical; Static: exposed 44 μT Vertical and controls 37 μT Vertical	1.4–2.1 mV/m[h]	Negative	[26]
Human amniotic cells exposed during 72 h culture period in chromosome aberration assay	50 Hz, 30 μT (9.4 mT/s) Vertical; Static: 4.7–24.6 μT	0.14–0.21 mV/m[h]	Inhibitory. Decrease in chromosome aberrations ($p < 0.05$)	[14]
Rat embryo fibroblasts (R2λLIZ) exposed 120 h in shuttle vector rescue mutagenesis assay	60 Hz, 3 mT (1.1 T/s) Vertical	0–15 mV/m[j]	Negative	[31]
Pulsed or sawtooth-shaped magnetic fields				
Positive results— None				
Negative results				
Human peripheral lymphocytes exposed during 72 h culture period in micronucleus and chromosome aberration assays	50 Hz, sawtooth (1.2 ms rise time, 2.5 mT peak intensity) (2.1 T/s peak)	0–50 mV/m	Negative	[30]
Chinese hamster V79 cells exposed 7 days in HGPRTase mutagenesis assay	50 Hz, pulsed (2 μs pulse duration, 1 μT peak intensity)	Unknown[g]	Negative	[24]
Secondary cultures of human amniotic cells exposed 72 h in chromosome aberration assay	20-kHz, sawtooth fields (rise- and fall-time of 45 μs and 5 μs; 16 μT peak-to-peak) (3.5 T/s peak-to-peak)	20-kHz pulsed, 50–80 mV/m[h] peak-to-peak	Non-statistically significant increase in mean aberration frequency	[25]
In vitro DNA repair				
Sinusoidal magnetic fields				
Positive results—None				
Negative results				
Virus-transformed human lymphoblastoid cells exposed for 7 days in M13 phage assay for DNA damage	50 Hz, 1 μT or 10 μT (0.31 or 3.1 mT/s)	Unknown[g]	Negative	[24]
Human tumor cell line (K562) exposed in suspension culture 4, 6, 12, or 24 h in alkaline elution assay for DNA strand breaks	50 Hz, 0.2, 2, 20, 100, or 200 μT (0.063, 0.63, 6.3, 31, or 63 mT/s)	0–0.4, 0–4, 0–40, 0–80, or 0–200 μV/m[k]	Negative	[13]

Pulsed or sawtooth-shaped magnetic fields				
Positive results—None				
Negative results				
Raji human cells exposed 1 or 24 h in assay for DNA strand breakage	50 Hz, pulsed (3 ms pulse duration, 5 mT peak intensity)	Unknown[g]	Negative	[12]
In vivo chromosome or DNA repair				
Sinusoidal magnetic fields				
Positive results				
Male Sprague–Dawley rats exposed 2 h in 'comet' assay for DNA strand breakage	60 Hz, 0.1 mT, 0.25 mT, and 0.5 mT (38, 94, and 190 mT/s) Horizontal	0–0.7, 0–1.7, and 0–3.5 mV/m[l]	Positive. Dose-dependent increase (up to 78%) in single- and double-stranded DNA breaks in brain cells. 0.1 mT ($p < 0.05$); 0.25 mT and 0.5 mT ($p < 0.01$)	[19]
Male Sprague–Dawley rats exposed 2 h in 'comet' assay for DNA strand breakage. Melatonin or *N-tert*-butyl-α-phenylnitrone injected s.c. immediately before or after magnetic field exposure	60 Hz, 0.5 mT (190 mT/s) Horizontal	0–3.5 mV/m[l]	Positive in the absence of melatonin and *N-tert*-butyl-α-phenylnitrone. Increase in single- and double-strand DNA breaks in brain cells ($p < 0.005$). No significant effects observed in the presence of melatonin or *N-tert*-butyl-α-phenylnitrone	[20]
Negative results				
Female Wistar rats exposed 7 or 28 days in sister chromatid exchange assay	50 Hz, 30 mT (9.4 T/s) Horizontal	0–170 mV/m[l]	Negative	[34]

[a]All studies are believed to have a co-exposure to the static magnetic field of the earth. If the geomagnetic field was reported, experimentally manipulated, or likely to affect the exposure apparatus, that information is noted. The time-rate-of-change of the magnetic field is also given in parentheses when reported or could reliably be calculated.
[b]This column provides the reported or estimated electric field strength within the culture media for in vitro studies or within tissues for in vivo studies.
[c]Calculated from the geometry of the exposure apparatus reported by the study authors and a typical agar plate diameter of 90 mm.
[d]Tabrah et al. reported a value of 2.1 V/m. This value is clearly in error. Based on their reported current density, assumed medium conductivity, and the geometry of their exposure apparatus (which indicates the field was horizontal), we have calculated an internal electric field of 0.1 mV/m.
[e]Exposure is 6.2 cm in front of a monochrome video display terminal and shielded from electric fields. The measured field at the reported location in front of a similar VDT is a 50-Hz sawtooth of 4.3 μT peak-to-peak (8.6 mT/s) oriented principally in the vertical direction. The 18-kHz sawtooth magnetic field from the horizontal deflection system was present but not measured.
[f]Calculated from the geometry of the exposure apparatus reported by the investigators and the field strength measured near a similar VDT (see footnote e above).
[g]The induced electric field cannot reliably be estimated from the information reported.
[h]Calculated from the geometry of the exposure apparatus reported by the study authors (see Section 2).
[i]The geomagnetic field is expected to be very non-uniform throughout the exposure volume; significantly attenuated in some locations and perhaps significantly enhanced in others.
[j]Calculated for a rectangular tissue culture flask of 5 cm$\times$6 cm. Culture dish measurements provided by M.A. Stuchly (personal communication).
[k]Calculated from the geometry of the exposure system reported by Dachà et al. [36].
[l]Calculated assuming an elliptical torso cross-section 5 cm high and 12.5 cm long.

Table 3
Other electric and magnetic field exposures

System	Exposure[a]	Internal electric field[b]	Result	Reference
ELF electric				
Salmonella TA97a, TA98, TA100, TA102 exposed in top agar petri plates for 48 h in mutagenesis assay	60 Hz, 600 Hz, or 6000 Hz; 11.8 kV/m Vertical (in air)	0.022, 0.22, and 2.2 mV/m at 60, 600, and 6000 Hz, respectively[c]	Negative	[23]
Escherichia coli strain AB1157 exposed in nutrient broth for 1 h (3 kV/m) or 16 h (1 kV/m) in mutagenesis assay.	1 Hz, 3 kV/m and 1 kV/m (in the medium)	3 kV/m and 1 kV/m	Negative	[11]
Whole blood exposed for approx. 15 s to spark discharges and then cultured 48 h in assay for chromosome aberrations	10 spark discharge pulses, 2.5 - 2.8 μs wide (up to 3.65 kV/cm)	250–370 kV/m	Negative	[27]
Human peripheral lymphocytes from 33 donors exposed for 72 h culture period in micronucleus assay	50 Hz, 0.5, 2, 5, and 10 kV/m (in air)	1.4, 5.6, 14, and 28 μV/m[d]	Negative	[29]
Human tumor cell line (K562) exposed in suspension culture 1, 4, 6, 12, or 24 h in alkaline elution assay for DNA strand breaks	50 Hz, 0.2, 2, 5, 10, 20 kV/m (in air)	0.02, 0.2, 0.5, 1.0, or 2.0 mV/m[e]	Negative	[13]
Combined ELF electric and ELF magnetic				
Salmonella TA97a, TA98, TA100, TA102 exposed in top agar petri plates for 48 h in mutagenesis assay	60 Hz, 600 Hz, or 6000 Hz, 0.33 mT Vertical magnetic field (0.12, 1.2, and 12 T/s) and 60, 600, and 6000 Hz 11.8 kV/m Vertical electric field (in air)	0.02–2.7, 0.2–27, and 2.2–270 mV/m at 60, 600, and 6000 Hz respectively[c,f]	Negative	[23]
Human tumor cell line (K562) exposed in suspension culture 1, 4, 6, 12, or 24 h in alkaline elution assay for DNA strand breaks	50 Hz, 0.2, 2, 5, 10, or 20 kV/m electric field (in air) and 50 Hz, 0.2, 2, 20, 100, or 200 μT magnetic field (0.063, 0.63, 6.3, 31, and 63 mT/s)	0.02–0.2, 0.5, 1.0, or 2.0 mV/m[e]	Negative	[13]
Chinese hamster ovary (CHO) cells exposed for 30 min in assay for DNA double strand breaks	50 Hz, 20 kV/m, 0.2 mT	2 mV/m[g]	Negative	[9]

Static magnetic				
Dry seeds of *Helianthus annus* (sunflower) exposed >90 min in assay for a variety of morphologic characteristics in germinated plants	100 mT, 200 mT, 300 mT	0 V/m[h]	'Positive mutations' reported for 200 mT exposure. Data and experimental procedures not presented.	[17] (abstract)
Flies reared in the magnetic field beginning at the egg stage and continuing for up to 59 generations in assay measuring wing length; or, mating pairs exposed for an unspecified period in the sex-linked recessive lethal assay	0.4–0.7 mT	0 V/m[h]	Positive. 2–3% increase in wing length persisting for multiple generations after removal of the magnetic field; approx. 10-fold increase in sex-linked recessive lethals (statistical significance not reported)	[15]
DNA repair defective larvae and wild type controls from 40 mated females exposed for 24 h in assay for lethality in *Drosophila*	100 mT, 600 mT	0 V/m[h]	Positive. 8% decrease in survival at 600 mT ($p < 0.01$)	[18]
Static electric				
Salmonella TA100 exposed in top agar petri plates for 6 h in mutagenesis assay	250 kV/m Vertical (in air)	0 V/m[i]	Negative	[8]

[a]All studies are believed to have a co-exposure to the static magnetic field of the earth. If the geomagnetic field was reported, experimentally manipulated, or likely affects the exposure apparatus, that information is noted.
[b]This column provides the reported or estimated electric field strength within the culture media for in vitro studies or within tissues for in vivo studies.
[c]Calculated from the exposure geometry and top agar salt concentration.
[d]Calculated from the exposure geometry reported and an assumed media conductivity of 1 S/m.
[e]Calculated values reported by Dachà et al. [36]. These values may overstate the actual field in the medium by two or three orders of magnitude because it appears as though Dachà et al. failed to account for the conductivity of the water-bath water surrounding the culture tube in their calculations.
[f]Calculated from the geometry of the exposure apparatus reported by the investigators and a typical agar plate diameter of 90 mm.
[g]Calculated values reported by Dachà et al. [36]. These values may overstate the actual field in the medium by two or three orders of magnitude because it appears as though Dachà et al failed to account for the conductivity of the water-bath water surrounding the culture tubes in their calculations.
[h]Static magnetic fields do not induce a continuous electric field. The transient electric field which is induced when the exposure is initiated and terminated cannot be calculated from the reported description of the exposure system.
[i]Static electric fields do not induce a continuous electric field in stationary conductive media.

Table 4
Genotoxicity assays of ELF electric or magnetic fields involving co-exposure to ionizing radiation, ultraviolet light, or chemical mutagens

System	Exposure[a]	Internal electric field[b]	Co-exposure	Results	Reference
Human peripheral lymphocytes exposed during 48 h culture period in chromosome aberration assay	60 Hz, 0.6 mT, 1.0 mT, or 1.4 mT (230, 380, and 530 mT/s)	Unknown[c]	γ-irradiation (1, 2, or 3 Gy at 0.0174 Gy/s) of whole blood 2 h prior to establishing lymphocyte cultures	Positive. Dose-dependent increase in 'near tetraploid chromosome complements'. None observed in controls	[16]
Human melanoma cell line (MeWo) exposed 2 h in HGPRTase mutagenesis assay	50 Hz, 400 mT (126 T/s) Vertical; Static: Not reported but probably severely perturbed by iron pole pieces near cultures[d]	0–1.1, 1.1–1.9, 1.9–3.1, and 3.1–4.7 V/m	X-ray (3 Gy) exposure immediately prior to the magnetic field	Positive. 2.7-fold increase in mutation frequency at the HGPRTase locus. Statistical significance not reported.	[21]
Repair proficient (RAD^+) and repair deficient (*rad*3) *Saccharomyces cerevisiae* strains exposed for 3 h, 15 min on/off, followed by 3 days continuous exposure in assays for mitotic recombination and mutagenesis	60 Hz, 1 mT (380 mT/s) Vertical	0–9.4 mV/m[e]	UV, 0.4 J/m^2/s (RAD^+: 12, 25, or 50 J/m^2; *rad*3: 2 or 4 J/m^2) in suspension culture immediately prior to seeding on Petri plates for MF-exposure	Negative	[6]
Escherichia coli strain AB1157 (wild type and several repair defective mutants) exposed in nutrient broth for 1 h (3 kV/m) or 16 h (1 kV/m) in mutagenesis or lethality assays	1 Hz, 3 kV/m and 1 kV/m (in the medium)	3 kV/m and 1 kV/m	Following growth in the electric field, bacteria were exposed to various doses of UV (approx. 10–100 J/m^2) on nutrient agar plates; or bacteria were exposed to the electric field in the presence of Mitomycin C (approx. 0.5–0.2 mg/ml)	Negative	[11]

Three cell lines (CHO, CCRF-CEM, and McCoy's) exposed for up to 100 min in alkaline elution assay for DNA single-strand breaks	50 Hz, 0.2–20 kV/m, or 50 Hz, 2 μT-0.2 mT, or 50 Hz, 20 kV/m and 0.2 mT	0.02, 0.2, and 2.0 mV/m[f]; 0.4, 0–4, 0–40, and 0–400 μV/m[g]; 0.02, 0.2, and 2.0 mV/m[f]	Cells pre-exposed to UV (254 nm, 30 J/m^2)	Negative	[10]
Salmonella TA100 exposed in top agar petri plates for 48 h in mutagenesis assay	60 Hz, 0.2 mT (75 mT/s) Horizontal; Static: 23.3 μT Horizontal (parallel) and 18.9 μT Vertical	0.1 mV/m[h]	Sodium azide at approx. 1 mg/ml included in agar petri plates during 48 h magnetic field exposure	Suggestive. 14% increase in revertants as compared to controls. $p < 0.01$ based on the sign test; $p = 0.078$ based on comparison of aggregate mean of 15 experiments using the *t*-test.	[32]
Salmonella TA97a, TA98, TA100, TA102 exposed in top agar petri plates for 48 h in mutagenesis assay	60 Hz, 600-Hz, and 6000 Hz, 0.33 mT or 60 Hz, 600 Hz, and 6000 Hz, 11.8 kV/m electric fields, or electric and magnetic fields combined	For magnetic fields: 0–2.7, 0–27, and 0–270 mV/m at 60, 600, and 6000 Hz, respectively[i]; for electric fields: 0.022, 0.22, and 2.2 mV/m at 60, 600, and 6000 Hz respectively[j]; for combined magnetic and electric field exposures: 0.02–2.7, 0.2–27, and 2.2–270 mV/m at 60, 600, and 6000 Hz respectively[i,j]	Chemical mutagens included in agar petri plates during 48 h magnetic field exposure at room temperature and for additional 24 h exposure at 37°C. With TA97a, ICR191 (1.0 μg/plate); with TA98, daunomycin (6 μg/plate); with TA100, sodium azide (1.5 μg/plate); with TA102, mitomycin C (0.5 μg/plate)	Negative	[23]

Table 4 (continued)

System	Exposure[a]	Internal electric field[b]	Co-exposure	Results	Reference
Human peripheral lymphocytes exposed during 72 h culture period in micronucleus assay	50 Hz, 150 μT (47 mT/s); or 32-Hz, 75 μT and 150 μT (15 and 30 mT/s) Static: 0 μT (nulled)	Unknown[c]	0.033 μg/ml mitomycin C present during magnetic field exposure	Negative	[33]
Human peripheral lymphocytes exposed during 72 h culture period in micronucleus assay	32 Hz, 75 μT and 150 μT (15 and 30 mT/s) Static: 42 μT parallel to the ac field	Unknown[c]	0.033 μg/ml mitomycin C and 42 μT dc magnetic field parallel to the ac field present during magnetic field exposure	Equivocal. Non statistically significant increase in micronuclei for 150 μT; 11% average increase over 5 donors ($p < 0.05$) for 75 μT	[33]
Human peripheral lymphocytes from 22 donors exposed for 72 h culture period in micronucleus assay	50 Hz, 0.5, 2, 5, and 10 kV/m (in air)	1.4, 5.6, 14, and 28 μV/m[k]	0.033 μg/ml Mitomycin C present during electric field exposure	Negative	[29]
HL-60 human cell line exposed 30 min in assay for DNA strand breakage	50 Hz, pulsed (3 ms pulse duration, 5 mT peak intensity)	Unknown[c]	1.0 mM hydrogen peroxide present during magnetic field exposure	Negative	[12]
HL-60 and HeLa human cell lines and human peripheral lymphocytes exposed 10 min in assay for DNA strand breakage	50 Hz, pulsed (3 ms pulse duration, 5 mT peak intensity)	Unknown[c]	12.5 mM hydrogen peroxide present during magnetic field exposure	Negative	[12]
Rat embryo fibroblast cell line (R2 λLIZ) exposed 120 h in shuttle vector rescue mutagenesis assay	60 Hz, 3 mT (1.1 T/s) Vertical	0–15 mV/m[l]	1.0–5 μg/ml menadione present for 30 min exposure either immediately prior to or during magnetic field exposure	Negative	[31]

Rat embryo fibroblast cell line (R2 λLIZ) exposed 120 h in shuttle vector rescue mutagenesis assay	60 Hz, 3 mT (1.1 T/s) Vertical	0–15 mV/m[l]	20 μg/ml or 100 μg/ml MNU present for 30 min exposure either immediately prior to or during magnetic field exposure	Negative	[31]
Three cell lines (CHO, CCRF-CEM, McCoy's) exposed for varying times up to 300 min in alkaline elution assay for DNA single-strand breaks	50 Hz, 0.2–20 kV/m, or 50 Hz, 2 μT-0.2 mT, or 50 Hz, 20 kV/m and 0.2 mT	0.02, 0.2, and 2.0 mV/m[f]; 0.4, 0–4, 0–40, and 0–400 μV/m[g]; 0.02, 0.2, and 2.0 mV/m[f]	MMS (1 mM) or potassium chromate (200 μM) present for 30 min or 2 h, respectively, immediately prior to ELF field exposures	Negative	[10]
Three cell lines (CHO, CCRF-CEM, McCoy's) exposed for varying times up to 60 min in alkaline elution assay for DNA single-strand breaks and up to 270 min in an assay for DNA double-strand breaks	50 Hz, 0.2–20 kV/m, or 50 Hz, 2 μT–0.2 mT, or 50 Hz, 20 kV/m and 0.2 mT	0.02, 0.2, and 2.0 mV/m[f]; 0.4, 0–4, 0–40, and 0–400 μV/m[g]; 0.02, 0.2, and 2.0 mV/m[f]	Hydrogen peroxide (37.5 μM minus L-histidine, or 15 μM plus L-histidine) present for 10 min immediately prior to ELF field exposures	Negative	[9]

[a]All studies are believed to have a co-exposure to the static magnetic field of the earth. If the geomagnetic field was reported, experimentally manipulated, or likely affected the exposure apparatus, that information is noted.

[b]This column provides the reported or estimated electric field strength within the culture media for in vitro studies or within tissues for in vivo studies.

[c]The induced electric field cannot reliably be estimated from the information reported.

[d]The geomagnetic field is expected to be very non-uniform throughout the exposure volume; significantly attenuated in some locations and perhaps significantly enhanced in others.

[e]Calculated from the geometry of the exposure apparatus reported by the investigators.

[f]Calculated values reported by Dachà et al. [36]. These values may overstate the actual field in the medium by two or three orders of magnitude because it appears as though Dachà et al. failed to account for the conductivity of the water-bath water surrounding the culture tubes in their calculations.

[g]Calculated from the geometry of the exposure apparatus reported by Dachà et al. [36].

[h]Tabrah et al. [32] reported a value of 2.1 V/m. This value is clearly in error. Based on their reported current density, assumed medium conductivity, and the geometry of their exposure apparatus (which indicates the field was horizontal), we have calculated an internal electric field of 0.1 mV/m.

[i]Calculated from the geometry of the exposure apparatus reported by the investigators and a typical agar plate diameter of 90 mm.

[j]Calculated from the exposure geometry and top agar salt concentration.

[k]Calculated from the exposure geometry reported and an assumed media conductivity of 1 S/m.

[l]Calculated for a rectangular tissue culture flask of 5 cm×6 cm. Culture dish measurements provided by M.A. Stuchly (personal communication).

imposed ELF time-varying magnetic field environment during exposure to test the hypothesis that ELF magnetic fields are genotoxic under certain 'ion resonance' conditions. Based on the model proposed by Lednev [35], ELF magnetic fields interact with biologically important ions only when presented at specific frequencies, intensities, and directions relative to and determined by the coexisting static magnetic field. Although the report by Tofani et al. [33] is the only one that selected ELF exposure conditions based on the static geomagnetic field in the laboratory or manipulated the static magnetic field as an exposure parameter, all of the studies reviewed are believed to have been conducted in the presence of the naturally occurring geomagnetic field. Hence, that field can be considered a co-exposure in all of the experiments, although it is often not well documented. Tables 2–4 report the intensity and orientation of the geomagnetic field for those studies in which it was documented. If the design of the exposure system is likely to have materially altered the intensity or direction of the natural geomagnetic field, a comment to that effect is in the tables. Otherwise, no entry is made in the tables, and ambient geomagnetic field conditions in the geographic region of the laboratory can be assumed.

Magnetic field levels, reported in teslas (T), are peak values for static or nonsinusoidal fields and root-mean-square (RMS) values for sinusoidal fields unless otherwise indicated. Electric field levels, reported in volts per meter (V/m), are RMS values for sinusoidal electric fields. Unless otherwise indicated, electric field values reported by investigators in the studies reviewed here are the unperturbed electric field levels that existed in air without the subject present. The time rate of change of the magnetic field (dB/dt) is also provided, as RMS values, in parenthesis in Table 2 for those studies where it was reported, or could be reliably calculated from other reported information.

The induced electric field in tissue or in culture media is tabulated for the ELF magnetic field experiments in column 3 of Tables 2–4 for those experiments where it was stated by the investigators, or where it could be calculated from information provided in the literature. In some cases, where specified, various assumptions, such as concerning the cross-sectional dimensions of culture vessels or subject bodies, were made in order to estimate the magnetically induced electric field.

When cells in a round petri dish are exposed to a vertical magnetic field, the cells in the center of the dish see no induced electric field while those at the periphery of the dish see a large induced electric field. For a round dish in a uniform magnetic field, the strength of the electric field is directly proportional to the distance from the center of the dish. Consequently, the population of cells is exposed to a wide range of induced electric fields. For these conditions, we therefore report the range of exposure rather than the maximum or mean value to indicate that a large range does, in fact, exist. In some experiments, cells are plated on the bottom of the dish or embedded in agar. Since the positions of the cells or micro-organisms are then fixed, their position is an analog of induced electric field strength. Some investigators harvest attached cells from a particular part of the dish to obtain a population with more homogeneous exposure. Cells in suspension can be grown in dishes with concentric rings to have multiple populations with the same magnetic field exposure, but different electric field exposure. Such experiments may help to indicate if an observed effect is due to magnetic field exposure, or induced electric field exposure by evaluating the dose relationships with the two parameters.

Other investigators expose their dishes or flasks to horizontal magnetic fields. If the cross-section of the media in the container is shallow but wide (as it usually is), the induced electric field across the bottom of the dish or across the surface of the medium is relatively uniform and near the maximum value. The zero field area is halfway between the bottom of the dish and the media surface. Although this approach is of no benefit to cells in suspension, cells in top agar, plated on the dish bottom, or merely settled to the bottom, obtain a relatively uniform induced electric field exposure. For these types of exposure geometry, we have reported a single value for induced electric field, indicating a relatively homogeneous exposure.

In assays that exposed *Drosophila* to static magnetic fields, neither the magnitude nor the frequency of the time varying internal electric fields induced in the experiments could be calculated because no movement data were reported.

Each experiment was evaluated against general data quality objectives as previously described [4]. Briefly, criteria included: (1) conformity of exposure conditions and biological tests to accepted protocols for a particular assay; (2) sufficiency of the experimental details reported relative to permitting an adequate characterization of exposure conditions and biological results; (3) inclusion of critical control experiments; (4) reproducibility and/or dose–response character of results; and (5) use of appropriate statistical methodology. We have relied on three basic criteria for making summary judgments concerning the positivity or negativity based on genotoxicity data from multiple, non-identical assay systems and exposure conditions (see Section 4): (1) *Reproducibility*. Greater weight has been given to results that have been independently replicated, or which have been tested in more than one laboratory in the same or similar assay systems under similar exposure conditions; (2) *Consistency*. Greater weight has been assigned to results that are consistent with current knowledge of assay endpoints and genotoxicity mechanisms; and (3) *Completeness*. Studies that lack information needed for an adequate assessment, or which do not satisfy basic data quality objectives, have been given less weight in an overall assessment.

3. Results

As shown in Table 1, 29 previously unreviewed reports were identified. Though most studies used ELF magnetic field exposures (24 of 29), all exposure categories are represented (ELF electric—7 studies; combined ELF electric and ELF magnetic—4 studies; static electric—1 study; and static magnetic—3 studies). Some of these reports also employed co-exposures to ultraviolet light (UV), ionizing radiation (γ- or X-irradiation), or chemical mutagens. As shown in Table 5, most experiments utilized in vitro assays in mammalian cells (tests for chromosome aberrations, sister-chromatid exchanges (SCEs), micronuclei, mutagenesis, or DNA strand breaks). However, assays using microbial (particularly the *Salmonella* (Ames) mutagenesis assay), plant, *Drosophila*, and in vivo systems were also represented.

The results of studies that examined the genotoxic potential of electric and magnetic fields are presented below, organized according to the exposure and assay system categories indicated in Section 2.

3.1. ELF magnetic fields (see Table 2)

Twenty-two previously unreviewed reports were available for analysis [6–8,12–14,16,19–28,30–34]. Genotoxicity assays employed were the *Salmonella* (Ames) bacterial mutagenesis assay, assays for mutagenesis and mitotic recombination in the yeast *Saccharomyces cerevisiae*, in vitro chromosome or mutagenesis studies in human or non-human mammalian cells in culture, and in vivo chromosome and DNA strand breakage studies in rats.

3.1.1. Microbial systems

Four studies were identified which employed the *Salmonella* (Ames) bacterial mutagenesis assay

Table 5
Types of genotoxicity experiments, by exposure category

Assay type	ELF magnetic	ELF electric	ELF electric and ELF magnetic	Static magnetic	Static electric
Microbial systems	5 (3)[a]	2 (2)	1(1)		1
Plants				1	
Drosophila				2	
In vitro chromosome/mutagenesis	17 (6)	2 (1)			
In vitro DNA repair	3 (5)	1 (3)	2 (3)		
In vivo chromosome or DNA repair	3				

[a] Numbers in parenthesis indicate additional experiments involving co-exposure to ionizing radiation, ultraviolet light, or chemical mutagens.

[8,23,24,32]. All four studies exposed bacterial tester strains in top agar on petri plates. Nafziger et al. [24] and Tabrah et al. [32] exposed plates during a 48-h incubation period at 37°C, whereas Morandi et al. [23] exposed plates at room temperature for 48 h, and then subsequent to exposure incubated plates at 37°C for an additional 24 h. Berg et al. [8] exposed plates for 6 h at room temperature. All four studies employed the TA100 tester strain. In addition, the Nafziger et al. [24] study used the tester strains TA97, TA98, and TA102 and Morandi et al. [23] used tester strains TA97a, TA98, and TA102. Magnetic field exposures were somewhat similar in the Morandi et al. [23] and Tabrah et al. [32] studies. Tabrah et al. [32] used 60-Hz Horizontal sinusoidal fields of 0.2 mT (75 mT/s) and, included among the several exposure conditions employed by Morandi et al. [23] was exposure to 60-Hz Vertical 0.33 mT (120 mT/s) fields. Internal fields were also comparable in the two studies (0–2.7 mV/m in Morandi et al. and 0.1 mV/m [6] in Tabrah et al.). Neither Tabrah et al. [32] nor Morandi et al. [23] reported an effect on mutagenesis in the *Salmonella* strains exposed to the magnetic field. (A co-mutagenic effect reported by Tabrah et al. [32] is discussed separately below). Morandi et al. [23] also exposed the bacterial tester strains to 0.33 mT at 600-Hz and 6000-Hz frequencies, also with no effects on mutagenesis.

Exposures employed by Nafziger et al. [24] were quite different from those employed by Morandi et al. [23] and Tabrah et al. [32] (see Table 2); these investigators also reported no mutagenic effects. Electric field strength in the culture medium could not be estimated from the information provided by Nafziger et al. [24].

Magnetic field exposures in the Berg et al. study were quite different from the other reports reviewed. In this study, bacteria in agar petri dishes were exposed to a sawtooth magnetic field for 6 h by placing them 6.2 cm from the face of a monochrome video display terminal (VDT) shielded from electric fields. Berg et al. [8] did not report a field strength, but we measured the field at the reported location in front of a similar VDT as a 50-Hz sawtooth of 4.3 μT peak-to-peak (8.6 mT/s) oriented principally in the vertical direction. An 18-kHz sawtooth magnetic field from the horizontal deflection system was present but not measured. An internal electric field of 0–0.2 mV/m was calculated from the geometry of the exposure apparatus reported by the investigators and the measured field strength near a similar VDT as discussed above. After incubation of the exposed plates for 48 h at 37°C, the means of three exposed and five unexposed controls were compared, with no significant difference in revertant numbers noted.

These four reports are the first of which we are aware that have used the *Salmonella* (Ames) assay to examine the potential genotoxicity of ELF magnetic fields at power frequencies. One of the two reports identified in our previous review [37], which examined ELF magnetic fields using the *Salmonella* (Ames) assay, used somewhat similar exposure conditions (100-Hz, sinusoidal, 0.13 μT – 0.13 mT) to those employed by Tabrah et al. [32]. Juutilainen and Liimatainen [37] also did not report any mutagenic effects, nor did a second study, previously reviewed, that employed quite different exposure conditions (see McCann et al. [4] for reference and discussion).

One study [6] examined radiation damage repair proficient (RAD^+) and deficient (rad3) mutants of the yeast *S. cerevisiae* in assays for mutagenesis and mitotic recombination after exposure to 60-Hz, 1 mT (380 mT/s) (Vertical) magnetic fields for 3 h using a 15 min on/15 min off protocol, followed by continuous exposure to the same field for 3 days. An internal field of 0–9.4 mV/m was calculated from the geometry of the exposure apparatus reported by the investigators. Assays for mitotic recombination, mutation, and gene conversion were negative in both repair proficient and repair deficient yeast strains. Experiments that were also conducted using co-exposure to UV-irradiation are discussed separately below. In our previous review [4], we did not identify any genotoxicity studies of electric or magnetic fields that employed a yeast assay system.

3.1.2. Summary

All eight studies reviewed (three previously, and five in the present review) reported negative results. Six of these employed the *Salmonella*/Ames test. Three of these studies [32,23,37] roughly satisfy independent reproducibility requirements, all studies

[6] See footnote in Table 3.

reporting negative results at exposures of 60-Hz 0.3 mT, 60-Hz 0.2 mT, and 100-Hz 0.13–130 μT, respectively, at similar estimated internal electric field strengths in the top agar of the assay plates. However, the experimental protocols in the Morandi et al. [23] report differs in one potentially important respect. Whereas exposures in the Tabrah et al. [32] and Juutilainen and Liimatainen [37] studies were at 37°C, where normal bacterial growth would have occurred, exposure in the Morandi et al. [23] study was at room temperature, where minimal growth would have occurred. Exposure conditions used in the third and fourth reports reviewed here [8,24] are also not comparable to either of these reports, nor to each other, since one study [8] exposed petri dishes in front of a VDT and the other [24] employed a 50-Hz, pulsed (2 μs pulse duration, 1 μT peak intensity) field. The other report previously reviewed, which employed the Salmonella/Ames assay system, used quite different exposure conditions from all other studies reviewed (see McCann et al. [4] for details) and is difficult to compare to the other studies. A negative study in the *Saccharomyces* system [6] also suggests no genotoxic effect at somewhat higher flux densities (1 mT), but other similar reports are not available for confirmation.

3.2. In vitro chromosome or mutagenic effects

3.2.1. Sinusoidal magnetic fields

Eleven previously unreviewed reports were identified [7,14,16,21,22,25–28,31,33].

3.2.1.1. Human peripheral lymphocytes. In four studies, human peripheral lymphocytes were exposed in vitro [7,16,27,33].

Tofani et al. [33] exposed human peripheral lymphocytes in vitro during a 72-hour culture period to a 32-Hz, 75 μT or 150 μT (15 and 30 mT/s) sinusoidal magnetic field in the presence of a 42 μT parallel static magnetic field or with the dc field nulled, and assayed for induction of micronuclei. The induced electric field in the culture medium could not reliably be estimated from the information reported. Experiments were intended to test the genotoxic potential of magnetic field exposures corresponding to postulated cyclotron and parametric resonance conditions for Ca^{2+}. (In a second series of experiments mitomycin C was also present during the culture period. These experiments are discussed below in Section 3.4.) Parallel control cultures were grown in a separate incubator in which the geomagnetic field was 23.5 μT, and the background ac electric and magnetic fields were less than 1 V/m and 12 nT, respectively. Lymphocytes obtained from 5 donors were assayed, and results were presented for each donor. Magnetic field effects were not observed in experiments where the geomagnetic field was nulled and the samples were exposed only to either the 32-Hz, 75 μT or 150 μT ac fields. However, in the presence of the static field, investigators reported an increase in the frequency of micronuclei in lymphocytes from all donors at both ac flux densities (75 μT or 150 μT) as compared to cultures unexposed to either the sinusoidal or the dc magnetic fields. In the cultures exposed to the 150 μT field there was an average increase of 74%, and in the cultures exposed to 75 μT the average increase was 51%. Although the percentage increases were small, the results were statistically significant ($p < 0.05$) using the Wilcoxon signed rank test. (For the cultures in which mitomycin C was present in addition to the dc and ac fields, there was an average increase of 18% for the 150 μT exposed group (which was not statistically significant), and an average increase of 11% for the 75 μT exposed groups, which was statistically significant ($p < 0.05$), again using the Wilcoxon signed rank test.) Investigators speculate that resonant exposure conditions may have resulted in changes in the movement of Ca^{2+} through cell membranes, possibly altering cell functions related to micronuclei induction.

In a second set of experiments, Tofani et al. [33] exposed human peripheral lymphocytes to 50-Hz, 150 μT fields with the geomagnetic field nulled, and reported no effects on the frequency of micronuclei as compared to controls exposed to neither the 50-Hz sinusoidal nor the dc field.

Hintenlang [16] assayed for clastogenic effects in human peripheral lymphocytes by exposing cells during a 48-h culture period to 60-Hz magnetic fields with field strengths of 0.6, 1.0, and 1.4 mT (230, 380, and 530 mT/s), considerably higher than the 150 μT flux density employed by Tofani et al. [33] in their experiments using 50-Hz fields. The

induced electric field in the culture medium could not be reliably estimated from the information reported by Hintenlang [16]. Hintenlang [16] reported no genotoxic effects of the 60-Hz magnetic field on exposed cells, but did report clastogenic effects in a second series of experiments involving co-exposures to γ-irradiation. Further details of these experiments and a criticism based on data quality criteria are included below in Section 3.4.

Paile et al. [27] exposed human peripheral lymphocytes to 50-Hz, 30 μT, 300 μT, or 1 mT (9.4, 94, or 314 mT/s) (Vertical) magnetic fields during a 48-h culture period (in an assay for chromosome aberrations), a 67-h culture period (in an SCE assay), and a 65-h culture period (in a micronucleus assay). Each culture dish contained a central well separated from an outer channel, so that the same cell culture could simultaneously be exposed at two different induced electric field intensities. Average internal field strengths in the culture medium in the central well are shown in Table 2. No statistically significant effects on the frequencies of chromosome aberrations or micronuclei were observed. A weak effect (less than a twofold increase in frequency) on SCEs was observed in one experiment ($p < 0.05$), but this was not observed in a second experiment.

Among the in vitro chromosome studies previously reviewed [4], in only one report were human peripheral lymphocytes exposed to sinusoidal magnetic fields in the absence of electric field or chemical mutagen co-exposures. This study [38] used 50-Hz, 5 mT fields. The assay protocol used by Rosenthal and Obe [38] was similar to that used in the studies of Tofani et al. [33] and Hintenlang [16] with the exception that the genotoxicity endpoint was SCEs. Recently, the negative result of Rosenthal and Obe [38] was confirmed by Antonopoulos et al. [7] who demonstrated the lack of effect of 50-Hz, 5 mT (1.57 T/s) magnetic fields on SCEs in a study using an expanded protocol involving two different exposure systems and culture times ranging from 48–69 h [7]. An internal electric field of 0–6.3 mV/m was calculated from the geometry of the exposure apparatus reported by Antonopoulos et al. [7].

3.2.1.2. Other cell types. In 1992, Nordenson et al. reported that exposure of established cultures of human amniotic cells for a 72-h culture period to a 50-Hz Vertical, 30 μT (9.4 mT/s) homogeneous magnetic field resulted in clastogenic effects [25]. Internal electric fields calculated from the geometry of the exposure apparatus reported by investigators were 0.14–0.21 mV/m. A total of 12 experiments were conducted on cells obtained from 7 donors, and a total of 1300 cells were scored. The mean number of aberrations per 100 cells analyzed in the exposed cultures was 5.4, and the mean value for sham-exposed controls was 1.8. This difference was statistically significant ($p < 0.001$). If chromosome and chromatid gaps are excluded from the analysis, results are still statistically significant. Because of high inter-individual variation in aberrations among the 7 donor cultures, exposed and sham-exposed aberration frequencies were also compared for each donor. In all cases the frequency of aberrations was significantly greater in exposed as compared to sham-exposed controls ($p < 0.01$).

Recently, the Nordenson group has extended its earlier work to report that at 10-fold greater flux densities (50-Hz Vertical, 300 μT (94 mT/s) (Vertical)), there is no evidence of a clastogenic effect in the human amniotic cell system [26]. (The intensity of the parallel geomagnetic field was also reported in this study as 44 μT for exposed cultures and 37 μT for controls, and the internal electric field calculated from the geometry of the exposure apparatus reported was 1.4–2.1 mV/m.) Unfortunately, the 30-μT continuous exposure condition employed in their earlier study was apparently not repeated in this new work. However, effects of two intermittent exposure conditions at the 50-Hz, 30 μT intensity (15 s on/off, Vertical, and 2 s on/20 s off, Vertical) were examined in cell cultures from eight donors. (The internal electric fields calculated were the same as for the 30 μT continuous exposure condition discussed above.) Other aspects of the protocol were as in their previous experiments [25]. For the 15-s on/off exposure, a 1.9-fold increase in mean aberration frequency was reported that is weakly statistically significant ($p < 0.05$), regardless of whether chromatid and chromosome gaps are included in the totals. Exposed and sham-exposed control cell cultures were paired for each of the eight donors. For 6 of the 8 donor cell cultures, there were slightly more chromosome aberrations in the exposed as compared to the paired control cultures. For the 2-s on/20-s

off exposure, a significant increase was observed only if gaps were included.

Stimulated by preliminary reports [39] of the 1992 results of Nordenson et al., Saalman et al. [28] assayed for 'c-mitotic' effects of exposure to 50-Hz, 30 μT (9.4 mT/s) fields by examination of the integrity of mitotic figures immediately following short-term exposure to the magnetic field. (The induced electric field could not be estimated from the information provided.) Chinese hamster V79 cells (a fibroblast cell line) were exposed to the magnetic field for various times ranging from 1 to 85 min. Sham controls were exposed in the same incubator to magnetic field levels less than 0.7 μT. Cells were immediately fixed, and the frequencies of 'disturbed' mitotic cells were compared in exposed and control cultures. No statistically significant differences between exposed and control cultures were reported. The study cannot adequately be assessed because it lacks sufficient information on the experimental protocol, on scoring criteria, and on other data quality objectives. It is not comparable to the Nordenson study that used a different cell type, employed much longer exposure times, and examined chromosome aberrations in mitotic figures allowed to accumulate by treatment of cultures with colcemid.

Recently, an attempt was made independently to replicate the 1992 Nordenson study employing the 50-Hz Vertical, 30 μT continuous exposure condition [14]. Internal electric fields calculated from the geometry of their exposure apparatus also replicated those reported by Nordenson et al. [25]. Galt et al. were unable to confirm the positive findings of Nordenson et al. [25], and in fact reported a statistically significant ($p < 0.05$) *decrease* in chromosome aberrations in exposed human amniotic cells as compared to sham-exposed controls.

A comparison of the assay protocols and exposure conditions in these two studies suggests several differences: (1) The human amniotic cells used by Galt et al. [14] apparently grew faster and were passaged more times prior to exposure than the cells used by Nordenson et al. [25,26]. Galt et al. [14] indicate cells were subcultured 3–4 times in a period of 3 weeks, whereas Nordenson et al. [26] indicate 1–2 subcultures over a 1-month period. Numerous changes occur in cells as they progress through primary to secondary and tertiary cultures, and possible differences between the two target cell cultures at the time of magnetic field exposure cannot be discounted. (2) Nordenson et al. [26] indicate that there were transients of unknown magnitude present in their exposure system, and the possibility that these influenced the observed results also cannot be excluded. (3) Finally, as Galt et al. [14] discuss, the geomagnetic fields in the two exposure systems were different: dc fields were ~ 44 μT in the Nordenson et al. [25,26] studies and, depending upon where measurements were taken in the incubator chambers, varied between 4.7 and 24.6 μT in the experiments of Galt et al. [14].

Recently, Miyakoshi et al. [21], using fields of much greater flux density (50-Hz Vertical, 400 mT (126 T/s), Vertical), exposed a human melanoma cell line (MeWo cells) for various time periods up to 20 hours. Annular culture plates were used, which permitted simultaneous exposure of cultures to four internal electric fields (see Table 2). The geomagnetic field present is not reported, but was probably severely perturbed by iron pole pieces described by investigators as present near the cell cultures. The geomagnetic field is expected to have been very non-uniform throughout the exposure volume; significantly attenuated in some locations and perhaps significantly enhanced in others. A time dependent increase in the frequency of 6-TG resistant cells using the HGPRTase mutation assay system was observed, as was a dose-dependent increase in 6-TG resistant cells with increasing induced current intensity. No effect of magnetic field exposure on cell killing or cell growth was noted; however, the increase in 6-TG resistant cells was not observed if DNA synthesis was inhibited during the period of magnetic field exposure. These findings were confirmed in a more recent report from the same group [22], in which MeWo cultures synchronized at the G_1/S boundary were exposed to 50-Hz, 400 mT magnetic fields for 2 h at various times after release from synchrony. Investigators [21,22] suggest that since ELF magnetic fields are not believed to induce DNA damage directly, the increase in mutation frequency may be due to an increase in DNA replication errors possibly due to a disturbance in mismatch repair systems. It should be pointed out, however, that since the HGPRTase assay system measures mutations based on detection of a phenotypic change

(6-TG resistance), it is not a direct measure of a genotypic change at the DNA level. Thus, it is theoretically possible that the increase in 6-TG resistance observed could have been due to epigenetic alterations in the expression of the HGPRTase gene at the transcriptional, translational, or post-translational levels ([40]; J.E. Trosko, personal communication). Experiments by Miyakoshi et al. [21] involving co-exposure to X-rays are discussed separately below in the Section 3.4.

Suri et al. [31] grew a rat embryo fibroblast cell line (R2 λLIZ) containing multiple copies of an integrated bacteriophage λ/*lac*I shuttle vector to confluence (120 h) in the presence of a 60-Hz, 3 mT (1.1 T/s) vertical sinusoidal field. Electric fields in the culture media were calculated to be 0–15 mV/m, based on rectangular tissue culture flask dimensions of 5 cm × 6 cm (M.A. Stuchly, personal communication). Controls were incubated in a separate incubator in which background fields were 0.2 μT. Mutants in the *lac*I gene were detected by plaque assay after transfection of a *lac*I-deficient *E. coli* strain with DNA isolated from the exposed fibroblasts. No significant differences in mutation frequency between control and exposed cultures were noted. Investigators also employed co-exposures to chemical mutagens, also with negative results (see Section 3.4).

3.2.2. Summary

There are a relatively large number of reports reviewed, which include experiments using sinusoidal magnetic fields (13 in this review and 8 in our previous review). Among these 21 reports, there are five which have assayed for effects of ELF magnetic fields in human peripheral lymphocytes in vitro using sinusoidal 50-Hz or 60-Hz fields of similar flux densities [7,16,27,33,38]. Although the flux densities employed in all five studies were not identical, overlapping ranges were employed (see Table 2). Only one of these studies [16] was criticized on the basis of failure to adequately satisfy data quality criteria. Although different genetic toxicity endpoints were assayed for in the remaining four studies (SCEs, chromosome aberrations, and micronuclei), these are compatible endpoints that detect a similar spectrum of genotoxic agents. All four studies reported negative results (the Hintenlang study was also negative).[7] This suggests that it is reasonable to conclude that ELF magnetic fields of 50-Hz or 60-Hz are not genotoxic in human peripheral lymphocytes in vitro at the overlapping flux densities employed in these four assays (150 μT–5 mT).

The positive results reported by Tofani et al. using 32-Hz frequency fields that require the presence of a parallel dc field must be considered uncertain without independent confirmation. As noted, the increase in frequency of micronuclei was small (less than 2-fold) and results were not consistently statistically significant ($p < 0.05$) among all groups co-exposed to the ac and dc fields. Unfortunately, we are aware of no other experiments conducted at 32-Hz for comparison.

Three positive results have been reported using sinusoidal fields in in vitro chromosome or mutagenesis systems employing other cell types. The positive results reported by Nordenson [25,26], using either continuous or on/off application of 30 μT fields in assays for chromosome aberrations using human amniotic cells, were not replicated in an experiment designed to independently replicate the continuous exposure conditions [14]. Negative results were also obtained at 30 μT in another report using human peripheral lymphocytes [27]. As discussed above, results of Nordenson et al. cannot be discounted. However, the negative findings of Galt et al. [14] and Paile et al. [27] suggest that the positive results reported by Nordenson may reflect subtle aspects of their system that, as yet, are unidentified and uncontrolled.

Recent studies using a human melanoma cell line [21,22] report positive, time-dependent increases in mutation frequency at the HGPRTase locus from exposure to 50-Hz, high-flux density fields (400 mT). These reports are of interest, and should be followed up. Unfortunately, we are aware of no other studies employing ELF magnetic fields at such high flux densities in mammalian cell assays in vitro for comparison.

Thus, except for the positive results obtained by Nordenson et al. [25,26] at 50-Hz (30 μT), Tofani et

[7] Note that two of these studies [16,33] reported positive results dependent on co-exposures. These results are discussed separately.

al. [33] at 32-Hz (75 μT and 150 μT) in combination with a parallel dc field, and that of Miyakoshi et al. [21,22] at 50-Hz (400 mT), all other studies that satisfy basic data quality objectives that employ ELF sinusoidal magnetic fields in genotoxicity assays using human or non-human mammalian cells in vitro have been negative (see Table 2). These negative studies span a flux density ranging from 0.2–3 mT.

3.2.3. Pulsed or sawtooth-shaped magnetic fields

In our 1993 review, two of the eight studies that examined effects of ELF magnetic fields in human or mammalian cells in vitro used 50-Hz pulsed or sawtooth-shaped ELF magnetic fields [41,42]. One of these reported positive results [41]. For several reasons pertaining to questions regarding methodology and consistency, we suggested that ''while the work cannot be discounted, it would be prudent to view it with some caution unless it is independently replicated'' (see McCann et al. [4] for discussion). Khalil and Qassem [41] used 50-Hz, pulsed (10 ms pulse duration, 1.05 mT peak intensity) fields. In a new report, Scarfi et al. [30] have discussed the Khalil and Qassem [41] result in the context of their and other work. They also report results of new studies in which human peripheral lymphocytes were exposed during a 72-h culture period to 50-Hz, sawtooth (1.2 ms rise time, 2.5 mT peak intensity) (2.1 T/s) magnetic fields. The induced electric field was reported to be 0–50 mV/m. These are similar exposure conditions to those used by Khalil and Qassem [41]. Under these conditions, Scarfi et al. [30] found no significant increase in chromosome aberrations, the endpoint reported positive by Khalil and Qassem [41], nor in micronuclei.

Nordenson et al. [25] exposed established cultures of human amniotic cells to a sawtooth-shaped field (20-kHz, rise- and fall-time of 45 μs and 5 μs, 16 μT peak-to-peak) (3.5 T/s peak-to-peak) for 72 h. Induced electric fields in the culture media were estimated to be 20-kHz pulsed, 50–80 mV/m peak-to-peak. Thirteen experiments were conducted on cell cultures obtained from 8 donors. A total of 1400 cells were scored. The mean number of chromosome aberrations was somewhat higher in magnetic-field-exposed cultures than in sham-exposed controls (2.7 vs 1.4), but this difference was not statistically significant.

Nafziger et al. [24] exposed Chinese hamster V79 cells, an established fibroblastic cell line, to a pulsed 50-Hz magnetic field (2 μs pulse duration, 1 μT peak intensity) for 7 days (the induced electric field could not reliably be estimated from the information reported). After a zero- or 7-day post-exposure expression period mutation frequencies at the HGPRTase locus were assayed by selection of 6-TG^r colonies. Sham-exposed control and positive control (exposed to the mutagen ethyl methanesulfonate (EMS)) cultures were included. In the cultures that were not allowed a post-exposure expression period, investigators noted a statistically significant 25% decrease in cloning efficiency in the MF-exposed cells ($p < 0.0001$), and a small (about 2-fold) increase in mutation frequency which, apparently, was not statistically significant. Cultures allowed a post-exposure expression period did not demonstrate any change in cloning efficiency or mutation frequency. To our knowledge, these experiments have not been independently replicated.

3.2.4. Summary

The negative report of Scarfi et al. [30] suggests that ELF pulsed or sawtooth magnetic fields at high flux densities are nongenotoxic to mammalian cells exposed in vitro. However, as Scarfi et al. [30] point out, the earlier positive result reported by Khalil and Qassem [41] could be due to minor differences in the field exposure conditions, or to different sensitivities of the human peripheral lymphocytes used in the assay. Although the criterion of independent reproducibility is not satisfied, this new negative study, together with reservations stated previously about the Khalil and Qassem [41] report (see McCann et al. [4] for discussion), suggest that 50- or 60-Hz pulsed or sawtooth magnetic fields at high flux densities are most likely nongenotoxic in mammalian cells in vitro.

3.2.5. In vitro DNA repair effects

3.2.5.1. Sinusoidal magnetic fields. Two assays for DNA strand breaks using field exposures ranging from 0.2–200 μT over periods from 4 h to 7 days were identified [13,24]. Both studies were negative. Nafziger et al. [24] exposed the Epstein–Barr virus-

transformed human lymphoblastoid cells to a sham field or to 50-Hz, 1 μT or 10 μT (0.31 or 3.1 mT/s) magnetic fields for 7 days (the induced electric field could not reliably be estimated from the information reported). Single-stranded M13 phage DNA, commonly used as a probe to detect somatic mutations in human DNA, was then used in a Southern blot analysis to detect possible changes in the length or number of DNA fragments resulting from the magnetic field exposures. No changes were noted according to a visual comparison of the DNA fingerprints prepared from the magnetic field exposed and sham-exposed cells.

Fiorani et al. [13] exposed a human tumor cell line (K562) grown in suspension culture to 50-Hz, 0.2, 2, 20, 100, or 200 μT (0.063, 0.63, 6.3, 31, or 63 mT/s) magnetic fields for 4, 6, 12, or 24 h in an alkaline elution assay for DNA strand breaks. The induced electric field calculated from the geometry of the exposure system reported by Dachà et al. [36] was 0–0.4, 0–4, 0–40, 0–80, or 0–200 μV/m, respectively. No increase in strand breaks was observed in cultures exposed to the magnetic field as compared to controls.

These two studies partially satisfy requirements for independent reproducibility, though the Nafziger et al. [24] report did not supply sufficient information on the exposure system employed to satisfy data quality criteria. Both studies assayed for DNA strand breaks using human cell lines in suspension culture and both exposed cells to similar intensity magnetic fields (1 and 10 μT and 2 and 20 μT, respectively). However, there were significant differences in exposure times (7 days vs. 4–24 h) and possible differences in assay sensitivity, suggesting caution in concluding that conditions for independent reproducibility have been met. In our earlier review [4], we did not identify any DNA repair assays that employed sinusoidal magnetic fields

3.2.5.2. Pulsed or sawtooth-shaped magnetic fields. One study was identified. Fairbairn and O'Neill [12] exposed Raji cells, a human cancer cell line, for 1 or 24 h at 37°C on agarose slides to a 50-Hz, pulsed (3 ms pulse duration, 5 mT peak intensity) magnetic field (the induced electric field could not reliably be estimated from the information reported). Cells were assayed in situ for DNA strand breakage using a sensitive microgel electrophoresis method termed the 'comet' assay, which allows detection of DNA damage in individual cells. Investigators employed alkaline electrophoresis and ethidium bromide staining coupled with laser scanning microscopy to quantify DNA migration. For further discussion of the comet assay see Section 3.2.6. The ratio of the width to the length of comet tails was determined for exposed and sham-exposed samples. No significant DNA damage was observed in the magnetic field exposed samples as compared to sham-exposed controls. No similar studies were identified in our previous review [4].

3.2.6. In vivo chromosome effects

Since our 1993 review, we have identified three new studies [19,20,34] involving in vivo exposure to ELF magnetic fields. Zwingelberg et al. [34] exposed 9 female Wistar rats for 7 or 28 days 24-h per day to a homogeneous 50-Hz 30 mT (9.4 T/s) (Horizontal) magnetic field. We calculated an internal electric field of 0–170 mV/m assuming an elliptical torso cross-section 5 cm high and 12.5 cm long. Peripheral blood was sampled one day prior to and immediately following exposure. Cyclophosphamide, a potent inducer of SCEs, was used as a positive control. Investigators report that neither exposure period resulted in a statistically significant increase in SCEs in peripheral blood lymphocytes in any of the exposed animals when compared to rates determined prior to exposure. Six additional animals were used as sham-exposed controls, with similar results (data not shown).

Lai and Singh [19,20] exposed male Sprague–Dawley rats to a 60-Hz magnetic field of flux densities 0.1 mT, 0.25 mT, or 0.5 mT (38, 94, and 190 mT/s) (Horizontal), for a period of 2 h. Assuming an elliptical torso cross-section 5 cm high and 12.5 cm long, we calculated internal electric fields of 0–0.7 mV/m (0.1 mT), 0–1.7 mV/m (0.25 mT), and 0–3.5 mV/m (0.5 mT). Four hours after exposure, cell suspensions were prepared from the whole rat brain for assay using the comet assay (see Fairbairn et al. [43] and McKelvey-Martin et al. [44] for review). This method is in wide use, employing a variety of protocols. The version used by Lai and Singh [19,20] is a modification of a protocol designed for sensitive detection of DNA strand breaks

recently described by Singh et al. [45]. This procedure results in a several fold increase in sensitivity over Singh's original protocol [46]. The comet assay is usually considered to be comparable in sensitivity to the alkaline elution assay [44], although the modified form used by Lai and Singh is expected to be greater in sensitivity. In the protocol used by Lai and Singh, cells embedded in agar on microscope slides are lysed and electrophoresed under alkaline conditions to detect single-stranded DNA breaks and under neutral conditions to detect double-stranded DNA breaks. The extent of DNA strand breakage is inferred from the length of DNA migration in the gel.

In the study with ELF magnetic fields, migration lengths of 50 representative cells were measured on each slide; two slides were prepared from each animal. Controls included an unexposed, unhandled baseline control and a sham-exposed control. In the sham-exposed control the two sets of coils in each Helmholtz coil in the exposure chamber were set to a 'bucking' mode, in which the coils are activated in an anti-parallel direction, resulting in cancellation of the fields generated by each coil. Unlike many exposure systems that have two parallel windings within each coil that can be connected in series with opposing phase to produce little or no magnetic field in the sham mode, Lai and Singh had only one winding per coil and connected the coils in antiparallel. This sham condition produced little or no magnetic field in the exact center of the animal cage, but produced a material residual field elsewhere in the cage. The unexposed control animals received no magnetic field exposure other than the background field level in the laboratory.

The lengths of DNA migration for the various treatment and control groups were compared using averages compiled from multiple experiments, and frequency distributions of DNA migration length were presented for each exposure group. Data for individual animals were not presented, although confidence limits presented on some averages indicate surprisingly similar DNA migrations within each group (see Williams [47] for further discussion on this point). Based on the summary data, authors report statistically significant increases in single-strand DNA breaks at all magnetic field exposures, and statistically significant increases in DNA double-strand breaks at the two higher flux densities. They also report a dose-dependent increase in average migration length with increasing flux density, particularly for single-stranded DNA. Statistically significant increases in average migration length in magnetic field exposed samples as compared to anti-parallel controls ranging from 12% to 78% are reported at all three magnetic field flux densities (0.1 mT, $p < 0.05$; 0.25 mT and 0.5 mT, $p < 0.01$). It should be noted that others have cautioned against relying only on migration length as an indicator of DNA damage, because comet length is dramatically affected by experimental parameters [48]. When comet length is used, median migration length has been suggested as a more appropriate measure than mean migration length [44].

These results are quite interesting and could suggest that acute exposure to ELF magnetic fields at flux densities as low as 100 μT could result in DNA strand breakage in the rat brain. Lai and Singh [19] suggest that an inhibition of DNA repair by 60-Hz magnetic fields could explain the observed results. Recently, Lai and Singh have provided confirmation of this work, and have also demonstrated that the effect they observe is blocked by the free radical scavenging agents melatonin and *N-tert*-butyl-α-phenylnitrone [20]. The observations of Lai and Singh are potentially quite important, but for several reasons need independent replication.

First, there is a preponderance of evidence in in vitro systems that exposure to sinusoidal ELF magnetic fields at comparable flux densities does not result in SCEs, chromosome aberrations, or micronuclei (see discussion above), or in effects on DNA repair as measured by the alkaline elution assay for DNA strand breaks (see particularly the studies of Fiorani et al. [13] discussed above and that of Reese et al. [49] discussed in our previous review [4]). Lai and Singh evidently did not assay for strand breaks in any tissues other than brain. This would have been an important set of experimental controls, especially in view of this significant body of negative data. In addition, though DNA strand breaks are known to be associated with comet formation, changes in DNA conformation (caused by strand breakage and possibly other factors) are believed to contribute significantly to the origin or comets (see reviews previously cited for discussion). Lai and Singh do not discuss whether the effects they observed from expo-

sure to ELF magnetic fields could possibly have been due to factors other than DNA strand breakage.

Second, the significance of work of Lai and Singh suggesting that low intensity microwaves result in DNA strand breakage in the rat brain [50] has recently been questioned [47]. Williams points primarily to two features of the microwave work that lead him to conclude it is equivocal: (1) statistical significance of modest increases in DNA migration length as compared to 'substantial background(s)' made possible by small standard deviations 'indicating a very uniform distribution of DNA migrations'; and (2) the unusual kinetics of strand breakage observed by Lai and Singh as compared to DNA damage and repair induced by other physical or chemical agents. Lai and Singh reply to the latter criticism [51] by pointing out that the kinetics of strand breakage and repair can vary with the duration of exposure, and that most DNA repair studies using ionizing radiation utilize much shorter exposures than were used for the microwave work. They also offer several examples of 'non-standard' kinetics of DNA repair after UV and gamma irradiation, as well as citations reporting an effect of microwaves on DNA repair in bacteria.

The first of William's comments also applies to the ELF magnetic field work. The backgrounds do appear to be substantial as compared to migration patterns reported elsewhere for the comet assay. However, Lai and Singh are using a longer electrophoresis time than in most other protocols which could account for the higher backgrounds. Also, where confidence intervals are displayed, they are quite small, indicating uniform migration. All of the increases in DNA migration length reported are also less than 2-fold, indicating a weak effect.

Finally, there are unfortunately no in vivo studies sufficiently similar to the Lai and Singh study for definitive comparison. The negative study of Zwingleberg et al. [34] reviewed above could be considered somewhat contradictory. However, the flux density used is much higher (30 mT vs. 0.1–0.5 mT), the exposure times are much longer (7 or 28 days vs. 2 h), and the assay employed may be less sensitive than in the Lai and Singh study. In our previous review, four in vivo chromosome studies were identified. However, none is suitable for comparison to the Lai and Singh work, as they all involved complex, largely undefined occupational exposures (see McCann et al. [4] for references and discussion).

3.3. Other electric and magnetic field exposures (see Table 3)

3.3.1. ELF electric

We identified five previously unreviewed reports that assayed for genotoxic effects of ELF electric fields [11,13,23,27,29].

3.3.1.1. Microbial. Using the *Salmonella* (Ames) assay, Morandi et al. [23] exposed several bacterial tester strains (TA100, TA97a, TA98, and TA102) to an 11.8 kV/m, vertical (in air) electric field at three frequencies (60 Hz, 600 Hz, and 6000 Hz). We calculated internal electric fields in the top agar from the exposure geometry and top agar salt concentration as: 0.022, 0.22, and 2.2 mV/m at 60, 600, and 6000 Hz, respectively. Bacteria were exposed in top agar on duplicate Petri plates at room temperature for 48 h, and then revertants were allowed to grow by incubating plates for an additional 24 h at 37°C. No effect on reversion frequency was observed in any tester strain.

Chahal et al. [11] exposed *E. coli* strain AB1157 (rifampicin sensitive) in nutrient broth culture at 37°C for 1 h to a 1-Hz, 3 kV/m electric field or for 16 h to a 1-Hz, 1 kV/m field. Treated and control cultures were plated on agar Petri dishes containing various concentrations of rifampicin to detect drug resistant mutants. No effects of electric field exposure on mutation frequency were noted. Investigators also assayed for effects of electric field exposure on UV-sensitivity and mitomycin C induced mutagenesis (discussed in Section 3.4). Since the frequencies employed in the Morandi et al. [23] and Chahal et al. [11] experiments were so different (60–6000-Hz vs. 1-Hz, respectively) it is difficult to compare the two studies. We did not identify any studies in our previous review [4], which used a microbial system to test for genotoxic effects of exposure to ELF electric fields.

3.3.1.2. In vitro chromosome. Nordenson et al. reported in 1984 that exposure of human peripheral

lymphocytes in vitro to 10 spark discharge pulses resulted in a statistically significant increase in chromosome aberrations [52]. We discussed this study in our previous review, and concluded that generalized cell destruction was of concern at the very high field strengths employed, and that chromosome breaks reported at the high dose tested may have been secondary to more generalized cytotoxicity [4]. A recent study using very similar exposure conditions to those employed by the Nordenson group has reinforced this concern [27]. Paile et al. exposed samples of human peripheral blood to 10 spark discharge pulses (2.5–2.8 μs wide) at intensities up to 3.65 kV/cm, and then cultured samples 48 h (with colcemid added for the final 2 h) in an assay for chromosome aberrations. Internal electric fields of 250–370 kV/m were reported, which, as Paile et al. [27] indicate, are at or above the threshold reported for haemolysis in erythrocytes. The mitotic index was severely reduced at all intensities tested and extensive haemolysis indicated cellular destruction, but there was no effect observed on the rate of either chromatid or chromosome breaks.

Scarfi et al. [29], using much lower intensity fields, exposed human peripheral lymphocytes obtained from 33 healthy donors to 50-Hz electric fields of 0.5, 2, 5, and 10 kV/m (in air) during a 72-h culture period. We calculated internal electric fields of 1.4, 5.6, 14, and 28 μV/m based on the exposure geometry reported, and an assumed media conductivity of 1 S/m. As in their work previously reviewed [53], the electric field was applied through capacitive coupling. The frequency of micronuclei was not increased in electric field exposed cultures as compared to controls. Results are reported for each of 10 (0.5 kV/m), 8 (2 kV/m), 8 (5 kV/m), and 7 (10 kV/m) donors representing 33 separate individuals. As authors discuss, these results are in contrast to their earlier report [53] that electric fields of similar intensity (6.5 kV/m in air) significantly increased the frequency of chromosome aberrations in bovine lymphocytes exposed for similar periods in vitro. As we discussed previously [4], the positive results reported earlier by these authors is difficult to interpret due to the relatively high incidence of chromosome aberrations in control cultures, and the unusually low frequency of gaps scored. Similar experiments were conducted by Scarfi et al. [29] involving co-exposure to Mitomycin C (see Section 3.4).

In an alkaline elution assay for DNA strand breakage, which utilized similar intensity electric fields to those used by Scarfi et al. [29], Fiorani et al. [13] cultured a human tumor cell line (K562 cells) for 1, 4, 6, 12, or 24 h in the presence of a 50-Hz electric field of 0.2, 2, 5, 10, or 20 kV/m (in air) intensity, and reported no significant effects of any exposure condition on the elution of DNA fragments. Calculated values for internal electric fields reported by Dachà et al. [36] (see Table 2) may overstate the actual field in the medium by two or three orders of magnitude because it appears as though Dachà et al. failed to account for the conductivity of the water-bath water surrounding the culture tube in their calculations.

3.3.2. Summary

The previous report of Nordenson et al. [52] that spark discharges results in chromosome aberrations in human peripheral lymphocytes in vitro has recently been contradicted by Paile et al. [27], who used very similar exposure and assay conditions. As discussed previously [4], chromosome breakage observed by Nordenson et al. [52] was most likely a secondary consequence of generalized cellular destruction from very high internal electric fields. Additionally, the positive studies of D'Ambrosio et al. [53,54], previously reviewed, have been brought into question by a more recent study from the same laboratory [29]. A study using similar exposure conditions and a related endpoint (DNA strand breakage) [13] was also negative, but, as discussed, because of uncertainties regarding experimental exposures, did not satisfy data quality criteria. The previously reviewed positive in vivo studies in mice of El Nahas et al. [55,56] are of possible interest, particularly the 1989 study, which satisfied data quality criteria and reported a dose-dependent increase in micronuclei for high exposures (at or above 170 kV/m in air, 0.03 V/m (torso) and 2.4 V/m (paws)). In this and our previous review, eleven negative studies have now been identified. Seven of these satisfied basic data quality criteria [11,23,27,29,57–59]. Assays included microbial mutagenesis tests [11,23], in vitro assays in human peripheral lymphocytes [27,29,58,60], and a domi-

nant lethal assay in mice [59]. Among the in vitro assays, estimated electric fields in the culture media varied widely, ranging from 1.4 μV/m to 370 kV/m.

3.3.3. Combined ELF electric and ELF magnetic fields

Using the *Salmonella* (Ames) assay, Morandi et al. [23] exposed several bacterial tester strains (TA100, TA97a, TA98, and TA102) to a 0.33 mT (Vertical) magnetic field (0.12, 1.2, and 12 T/s) in combination with an 11.8 kV/m (Vertical) electric field (in air) at three frequencies (60 Hz, 600 Hz, and 6000 Hz). We calculated internal electric fields from the exposure geometry, top agar salt concentration, and a typical agar plate diameter (90 mm) (see Table 2). Bacteria were exposed in top agar on duplicate Petri plates at room temperature for 48 h, and then revertants were allowed to grow by incubating plates for an additional 24 h at 37°C. No effect on reversion frequency was observed in any tester strain.

Fiorani et al. [13] exposed a human tumor cell line (K562) grown in suspension culture to various combinations of 50 Hz, 0.2, 2, 20, 100, or 200 μT magnetic fields (0.063, 0.63, 6.3, 31, and 63 mT/s) and 50 Hz, 0.2, 2, 5, 10, or 20 kV/m electric fields (in air) for 1, 4, 6, 12, or 24 h in an alkaline elution assay for DNA strand breaks. Calculated values for internal electric fields reported by Dachà et al. [36], as discussed above, may overstate the actual field in the medium by two or three orders of magnitude. No increase in strand breaks was observed as compared to controls exposed to neither the magnetic nor the electric field, or to controls exposed to either field alone.

Cantoni et al. [9] exposed Chinese hamster ovary (CHO) cells for 30 min to a combined 50-Hz electric (20 kV/m) and magnetic (0.2 mT) field and assayed for DNA double strand breaks using a pulsed field gel electrophoresis assay, in which double stranded DNA fragments are detected using ethidium bromide staining. Internal electric fields in the culture media reported by Dachà et al. [36], as discussed above, may overstate the actual field in the medium by two or three orders of magnitude. No significant increase in DNA double strand breaks were noted in the samples exposed to the electric and magnetic fields, as compared to unexposed controls. See Section 3.4 for experiments involving co-exposures to hydrogen peroxide.

3.3.4. Summary

Morandi et al. [23] is the only study of which we are aware that employed combined ELF magnetic and ELF electric fields in a microbial assay for genotoxicity. Although, as discussed above, actual exposures used in both reports are uncertain, the experiments of Fiorani et al. [13] and Cantoni et al. [9] using mammalian cell lines are similar in some respects. However, conditions for independent reproducibility are not met because Cantoni et al. [9] assayed only for DNA double-strand breaks in experiments that did not also involve co-exposure to chemical mutagens, and Fiorani et al. [13] only assayed for DNA single-strand breaks. All six studies reviewed previously [4], which employed combined ELF magnetic and ELF electric fields in genotoxicity assays using mammalian cells in culture, were negative. The internal electric fields calculated in the culture media in all six of these studies were much higher than in the reports reviewed here, spanning a range from 24-38,000 mV/m (see McCann et al. [4] for details). Studies from two research groups [60,61] roughly satisfy the criterion of independent reproducibility. These studies, both negative, were conducted using the same cellular system (human peripheral lymphocytes), assay endpoint (SCEs), overlapping exposure periods, and similar calculated internal electric fields.

3.3.5. Static magnetic fields

3.3.5.1. Plants. One study was identified [17], appearing in abstract form, in which dry seeds of two varieties of the sunflower *Helianthus annus* were exposed to 100 mT, 200 mT, or 300 mT static magnetic fields for an unspecified period of more than 90 min, and germinated plants were screened for a number of plant characteristics such as germination percentage, plant height, and days to flowering. No internal continuous electric field is expected from exposure to static magnetic fields. The transient electric field, which is induced when the exposure is initiated and terminated, could not be calculated because information on the exposure system was not provided. Details of the experimental protocol and

results were also not provided. The investigator reports that a number of different mutant types were obtained for the group of seeds exposed to 200 mT, and that mutants were 'screened by biochemical analysis'. Insufficient information is provided in this abstract to evaluate the study.

In our earlier review [4] two cytogenetic studies in plants were identified [62,63], both employing high flux density fields (45–1200 mT). One of these studies [62], in which exposures spanned the intensities employed by Kiranmai, reported statistically significant increases in some cytogenetic endpoints, but the investigators cautioned that effects were too small to support the conclusion that there was a cytogenetic effect. We concluded that results were most likely due to random experimental variability. The other study [63], which did not meet data quality criteria, employed a much higher intensity magnetic field (900–1200 mT) than the Kiranmai study, and was negative.

3.3.5.2. Drosophila. Since our earlier review, we have identified two additional studies using static magnetic fields with the *Drosophila* system [15,18].

Giorgi et al. [15] used static magnetic fields of 0.4–0.7 mT. [8] Internal continuous electric fields are expected to be zero. Transient electric fields could not be calculated from the reported description of the exposure system. In the first series of experiments, flies were reared in the magnetic field beginning at the egg stage and continuing for up to 59 generations. During this extended exposure period, body size was monitored by measuring wing length, and the total cell number was calculated from wing dimensions determined by macroscopic and microscopic observations. In all stocks, an increase in wing length (2–3%) was observed, which began in the first generations, and then plateaued throughout the remaining generations. When flies were removed from the magnetic field, as early as the third generation, the longer wing length persisted as long as stocks were followed (up to 56 additional generations). This result may be of interest; however, without additional information, it is difficult to evaluate its significance.

In a second series of experiments, a sex-linked recessive lethal assay, 30 pairs from two *Drosophila* stocks were exposed to the magnetic field for an unspecified period of time. The exposed male progeny were then mated with virgin females, and the number of males among F_2 progeny was subsequently determined. Relatively few X-chromosomes were examined (only 1345 in one treated *Drosophila* stock and 1153 in another independent stock). The values presented are summed over 4 separate experiments, suggesting that in each individual experiment, even fewer chromosomes were examined. Authors report large increases (about 10-fold) in lethals in both stocks as compared to untreated controls. Data from the individual experiments are not presented, nor is information provided on whether clusters could have been present. Although this report cannot be discounted, the experiment requires independent confirmation.

Koana et al. [18] used a DNA repair assay employing a double mutant of *Drosophila melanogaster* known to be defective in excision and post-replication repair. This *Drosophila* strain was previously developed for use in mutagen screening [64], and has been used to assay a number of known genotoxic agents (e.g., see Fujikawa et al. [65]). In the experiment of Koana et al. [18] larvae from 40 mated females were exposed either to static magnetic fields of 100 mT or 600 mT for 24 h. As for all experiments employing a static magnetic field, the internal continuous electric field is assumed to be zero. The transient electric field could not be estimated from the reported description of the exposure system. Non-exposed controls were incubated separately in the exposure room, but were not sham-exposed. After treatment, larvae were allowed to mature, and the ratio of male and female survivors was deter-

[8] Although Georgi [15] states very clearly that exposures are to static fields, the description of the exposure system includes references to '50-Hz' and 'stabilized by a continuous current' which could suggest an ac field was employed. We have assumed that these potentially contradictory references indicate that the generator and amplifier are powered from a commercial 50-Hz power system but produce a stable continuous current (dc) to the coils for generation of static fields. Further evidence for this interpretation comes from the statement that the solenoid coils are wound on aluminum tubes, which would drastically attenuate ac fields, resulting in a failure to achieve the reported agreement between calculated and measured field levels.

mined for treated and control groups. In this assay, males carry the repair defective genes, and females are normal. Therefore, a significant reduction in the male:female ratio as compared to controls indicates increased lethality in the DNA repair-defective males. Koana et al. report a very small (8%) decrease in the male:female ratio for the group of larvae exposed to 600 mT, which they indicate, is statistically significant ($p < 0.01$). However, it should be noted that the small ratio difference reported appears to be within the range of variation for unexposed mutants in this system (e.g., see Nguyen et al. [64] and Fujikawa et al. [65]). Koana et al. [18] do not report a statistically significant reduction in the male:female ratio for the group exposed to 100 mT. A similar experiment was performed using the wild type strain, with no observable effects of the magnetic field exposure. This experiment utilizes a well-established genotoxicity assay system, but the very weak results reported relative to those obtained for known genotoxic agents in this system suggests that it may not be definitive.

3.3.6. Summary

A recent study using repair deficient strains of *Drosophila* was weakly positive [18]. We previously evaluated seven static magnetic field studies in *Drosophila*, and concluded that the three positive studies were of uncertain validity, and two of the negative studies were of insufficient size to detect any but a very potent effect (see McCann et al. [4] for discussion). We concluded that the results of two of the negative reports [66,67] satisfied basic data quality criteria and provided convincing evidence that static magnetic fields from 1.0–3.7 T did not have genotoxic effects in *Drosophila* (see McCann et al. [4] for discussion). However, all reports previously reviewed used wild-type flies, whereas the *Drosophila* strains used by Koana et al. [18] were deficient in two major DNA repair pathways. Therefore, the positive results reported by Koana et al. [18] are not necessarily contradicted by the earlier negative reports because the sensitivity of the assay used by Koana et al. [18] may be greater than those of assays conducted using wild-type flies.

Although the positive results reported by Giorgi et al. [15] could be of interest, particularly a persistent, multi-generation increase observed in wing length, the report taken by itself is difficult to interpret due to methodological questions discussed above regarding certain aspects of the study.

Two of the other three negative studies in our 1993 review which satisfied basic data quality criteria [68,69], were similar in that they employed human peripheral lymphocytes exposed for similar time periods (1 or 3 h) in assays for SCEs and chromosome aberrations. The field intensities employed, however, differed by at least a factor of four (0.5 T as compared to 0.125 T, respectively), suggesting that the two experiments do not meet requirements for independent reproducibility. The other negative experiment that satisfied data quality criteria [70] employed a bacterial system (see McCann et al. [4] for discussion).

3.3.7. Static electric fields

3.3.7.1. Microbial. In response to concerns that electrostatic fields from VDTs might be associated with skin deterioration, Berg et al. [8] examined static electric fields for their ability to damage DNA. Using the *Salmonella* (Ames) mutagenesis assay, the tester strain TA100 was exposed in top agar on Petri plates for 6 h at room temperature to a static electric field of approximately 250 kV/m (Vertical) (in air). (Since static electric fields do not induce a continuous electric field in stationary conductive media, the internal electric field in the agar media is expected to be 0 V/m.) After incubation of the exposed plates for 48 h at 37°C, the mean number of revertants among 13 exposed and 5 control plates were compared. No significant differences in revertant numbers were noted.

3.3.8. Summary

In our previous review [4], we discussed one study which employed the *Salmonella* (Ames) assay in exposures to static electric fields [71]. In contrast to the Berg et al. [8] report, Hungate et al. [71] reported significant increases in revertant numbers in bacterial cultures exposed to the static field. The two studies are not strictly comparable, however, as Hungate et al. [71] employed higher field strengths (800 kV/m), a longer exposure period (20 h), and exposed bacteria in suspension culture instead of in top agar. In our earlier review [4], we also concluded that an assessment of the Hungate et al. [71] report

was complicated by the absence of detailed data in the report and, because of the probable presence of corona during exposure, the difficulty in determining actual exposures. Although the experiments of Berg et al. [8] are less likely to have been subject to corona, exposures were still near the level where auxiliary effects might be expected to begin. The only other study we have identified which met data quality criteria was the negative study of Diebolt [67] using the *Drosophila* sex-linked recessive lethal assay system (see McCann et al. [4] for discussion). In our earlier review, four additional studies that failed to meet data quality criteria reported positive results using exposures ranging from 8–330 kV/m in *Drosophila* and in in vivo chromosome effects studies in mice (see McCann et al. [4] for detailed discussion).

3.4. Co-exposure to electric or magnetic fields and ionizing radiation, ultraviolet light, or chemical mutagens (see Table 4)

3.4.1. Co-exposure to γ- or X-irradiation

Since our earlier review, we have identified two new studies that assayed for genotoxic effects of ELF magnetic fields in conjunction with exposure to γ- or X-irradiation [16,21]. Hintenlang [16] utilized 60-Hz sinusoidal magnetic fields of 0.6 mT, 1 mT, and 1.4 mT (230, 380, and 530 mT/s). The induced electric field could not be estimated from the information reported. Whole blood obtained from a single donor was irradiated using a Cesium-137 source (0.0174 Gy/s) to deliver doses of 1, 2, or 3 Gy, apparently at room temperature. After a period of 2 h, also at room temperature, lymphocytes were isolated and then cultured 48 h in the magnetic field. Cells were then prepared for cytogenetic analysis. The protocol for the cytogenetic analysis is not presented, nor are detailed results included. Controls were incubated in an adjacent chamber of the exposure incubator, where no measurable 60-Hz magnetic field was detected. No clastogenic effects were observed in control cultures exposed neither to γ-irradiation, nor to the magnetic field (i.e., the spontaneous incidence was zero), nor were any aberrations observed in cultures exposed only to the magnetic field. In the control cultures exposed to γ-irradiation at 3 Gy, the investigator indicates that a variety of aberration types were observed, primarily dicentrics, at a frequency of 0.3/cell. Results are not reported for γ-irradiation exposures of 1 Gy or 2 Gy. In cultures exposed to both γ-irradiation and the magnetic field, the investigator reports no increase in aberrations of the types observed in the γ-irradiated controls (data not shown), but the presence of near tetraploids. This type of aberration was observed only in the samples exposed both to γ-irradiation and the magnetic field. A dose-dependent increase in the frequency of near tetraploids up to 0.065/cell was reported both for magnetic field flux densities from 0.6–1.4 mT and 3 Gy γ-irradiation and for γ-irradiation from 1–3 Gy and 1.4 mT magnetic field flux density. The investigator reports that 1–6 replicates were included at each exposure point, and that nine sets of experiments were performed over the period of a year, with consistent results. Data reported were averaged over these multiple experiments. The small numbers of total cells that authors report were examined for each exposure group (− γ-irradiation, − MF = 140 cells; + γ-irradiation, − MF = 185 cells; − γ-irradiation, + MF = 200 cells; + γ-irradiation, + MF = 367 cells) suggest that each of these nine experiments were done under different exposure conditions (i.e., either that control experiments were not concurrent, or that an insufficient number of cells were examined in each experiment). It is not indicated whether the same donor was used for all experiments. In conclusion, although these results could be of interest, they lack sufficient detail for an adequate analysis, and also appear to have been obtained after examination of either a limited number of cells, or without concurrent controls.

The recent study of Miyakoshi et al. [21] discussed above, which employed 50-Hz sinusoidal magnetic fields at high flux density (400 mT, 126 T/s) and reported an increase in mutations at the HGPRT locus in human melanoma MeWo cells, also assayed for effects of pre-exposure to X-rays. In these experiments, about 5×10^6 cells were irradiated with X-rays (3 Gy) and then immediately placed in the magnetic field for 2 h. Authors indicate that experiments were repeated twice. Average results indicate a modest increase in mutation frequency (2.7-fold) at the HGPRTase locus in the cells exposed to both X-rays and magnetic fields as compared to cells exposed only to X-rays. Very small

error bars presented in the figure suggest statistical significance, but this is not reported. This experiment appears to be well done, and the results are quite interesting. As discussed above, it has been suggested that these results could be the result of possible epigenetic effects of the magnetic field ([40]; J.E. Trosko, personal communication).

3.4.2. Summary

Four studies have now been identified, which employed co-exposures to ionizing radiation and electric or magnetic fields. Two were identified in this review [16,21] and two in our previous review [58,72]. Among these four, only the studies by Miyakoshi et al. [21] and Frazier et al. [58] satisfied all data quality criteria. The positive results of Miyakosi et al. [21], as discussed above, are of possible interest; however, no comparable experiments are available for comparison. Note that Miyakoshi et al. [21,22] also observed significant dose-related increases in 6-TG^R colonies in the absence of co-exposure to X-irradiation (see Sections 3.2 and 3.3). The Hintenlang [16] study also reported a positive result, but did not meet data quality criteria, and must be considered uncertain unless independently replicated. The other two studies reported negative results. The experimental protocol of Frazier et al. [58] does not sufficiently overlap with that of Hintenlang [16] to permit comparison. The work of Cossarizza et al. [72] employed an experimental protocol with some similarities to that used by Hintenlang [16] and used sawtooth fields of similar maximum field strength. Though the work by Cossarizza et al. [72] was reported negative by authors, as we discuss above, their data could suggest a positive trend. It is, nevertheless, difficult to attempt a comparison of the two studies, due particularly to the uncertainties raised regarding the validity of the Hintenlang [16] report, and to the fact that the Cossarizza et al. [72] study did not supply enough information to meet data quality criteria.

3.4.3. Co-exposure to ultraviolet light

Since our previous review, we have identified three studies that assayed for genotoxic effects of electric or magnetic fields in conjunction with exposure to ultraviolet light [6,10,11]. Chahal et al. [11] exposed *E. coli* strain AB1157 (wild type and several repair defective mutants) in nutrient broth at 37°C to a 1-Hz, 3 kV/m and 1 kV/m (in the medium) electric field for 1 or 16 h, respectively. Following growth in the electric field, bacteria were exposed to various doses of UV (254 nm, 10–100 J/m^2) on nutrient agar plates, and then assayed for viability. No effects on UV sensitivity due to the electric field exposures were noted.

Ager and Radul [6] assayed for effects on mutagenesis and mitotic recombination in two strains of *S. cerevisiae*, one repair-proficient (RAD^+) and the other defective in excision repair (*rad*3). Cells in suspension culture were exposed to ultraviolet light (at 0.4 $J\ m^{-2}\ s^{-1}$) immediately prior to seeding on Petri plates for magnetic field exposure. The RAD^+ strain received 12, 25, or 50 J/m^2, and the *rad*3 strain (which is sensitive to UV-light) received 2 or 4 J/m^2. Cell cultures were exposed to a 60-Hz, 1 mT (380 mT/s) (Vertical) magnetic field for 3 days. We calculated an internal electric field of 0–9.4 mV/m from the geometry of the exposure apparatus reported by investigators. For the first 3 h of this exposure, the field was in a 15-min on/off cycle, and thereafter, exposure was to continuous fields. Following exposure, cultures were incubated an additional 3 days. No alterations in UV-induced mutagenesis, gene conversion, or mitotic recombination were noted in either yeast strain in cultures also exposed to the magnetic field when compared to sham-exposed controls.

A similar study involving pre-exposure to ultraviolet light (254 nm, 30 J/m^2) was conducted using several cell lines (CHO, CCRF-CEM, McCoy's) by Cantoni et al. [10]. In this study, pre-irradiated cells were exposed for up to 100 min to 50-Hz electric (0.2–20 kV/m) or magnetic (2 μT–0.2 mT) or combined electromagnetic (20 kV/m, 0.2 mT) fields, and then assayed for DNA single-strand breaks using the alkaline elution procedure. For cultures exposed to magnetic fields alone, internal electric fields in the culture media were 0–0.4, 0–4, 0–40, 0–400 μV/m, as calculated from the exposure apparatus reported in an earlier publication [36]. For cultures exposed either to electric fields alone or to combined electric and magnetic fields, internal electric fields in the culture media were 0.02, 0.2, and 2 mV/m as reported by Dachà et al. [36]. However, it should be noted, as discussed above, that these values may

overstate the actual fields in the medium by two or three orders of magnitude. No significant differences in the rate of repair of single-strand breaks were noted in field-exposed, as compared to unexposed controls.

3.4.4. Summary

Four studies of which we are aware, three discussed in this report [6,10,11], and one in our previous review [73], tested electric or magnetic fields for genotoxicity in conjunction with ultraviolet light. All of these studies were negative. The studies of Cantoni et al. [10] and Whitson et al. [73] are roughly similar. Both employed ELF electric fields possibly resulting in similar internal electric fields, both pre-exposed cell cultures to UV at 254 nm, and both assayed for DNA strand breaks. However, neither of these studies provided adequate information concerning actual exposures to satisfy data quality criteria (discussed above for Cantoni et al. [10] and in McCann et al. [4] for Whitson et al. [73]) and are thus difficult to compare.

3.4.5. Co-exposure to chemical mutagens

Seven studies among those identified since our 1993 review employed ELF magnetic fields with co-exposure to chemical mutagens [11,12,23,29,31–33].

3.4.5.1. Microbial. A total of three studies employed co-exposures to chemical mutagens with ELF magnetic [23,32], ELF electric [11,23], or combined ELF magnetic and ELF electric [23]. Tabrah et al. [32] used the *Salmonella* (Ames) test and exposed the bacterial tester strain TA100 in top agar on Petri plates to a 60-Hz, 0.2 mT (75 mT/s) (Horizontal) magnetic field during a 48-h incubation period in the presence of the mutagen sodium azide (approx. 1.0 mg/plate). The horizontal and vertical components of the geomagnetic field were 23.3 μT (Horizontal) and 18.9 μT (Vertical). As discussed above, the induced internal electric field of 2.1 V/m reported by Tabrah et al. [32] is clearly in error, and we have calculated an internal electric field of 0.1 mV/m. Control plates were incubated in a 'reference' incubator. A separate control experiment was also conducted, where revertant numbers were compared on plates sham-exposed and plates incubated in the reference incubator, with no significant differences in revertant number observed. In multiple co-exposure experiments, a small but consistent increase (avg. 14%) in revertant colonies was observed on the Petri plates exposed to both the chemical mutagen and the magnetic field, as compared to Petri plates exposed in the reference incubator. Although the comparison of overall means was not statistically significant using a *t*-test ($p = 0.078$), the consistency of the small increase over 15 independent experiments resulted in statistical significance ($p < 0.01$) using the sign test. Authors also conducted experiments to ensure that the small enhancement in revertant number was not due to temperature differences between the two incubators, which, if higher in the magnetic field exposure incubator, could have resulted in increased growth rates, and hence an increase in the number of spontaneous revertants observed at 48 h. The results of these experiments indicated that temperature differences were unlikely to have produced the observed results. In spite of the weakness of the enhancement observed, the results reported in this paper are quite interesting, and are consistent with a weak enhancement in cell growth caused by exposure to ELF magnetic fields. Although investigators argue against this interpretation, the evidence they present is not convincing, because it is based on growth on the Petri plates beyond the 48-h incubation period for the reversion assay. Since histidine, an essential amino acid for these mutant bacterial strains, is limiting on these plates, the type of growth under these conditions may not be adequate to support any conclusion as to the possible effects of the magnetic field on cell growth. An alternative possible mechanism suggested by authors is an effect on azide ion transfer through bacterial cell wall channels.

Morandi et al. [23] also exposed *Salmonella* tester strain TA100 to a very similar magnetic field (60-Hz, 0.33 mT) for 48 h in the presence of sodium azide (1.5 μg/plate), but reported no enhancement of the reversion rate. In the same study, investigators also employed field frequencies of 600 Hz and 6000 Hz, also with no reported enhancement of sodium azide-induced revertants. We calculated internal electric fields in the top agar, as discussed above (see Table 2). For two reasons, this result does not necessarily contradict the observation of Tabrah et al. [32]. First,

Morandi et al. [23] exposed Petri plates at room temperature instead of 37°C, which could have affected the result. And, secondly, the increase reported by Tabrah et al. [32] was quite small (avg. 14%). Since Morandi et al. [23] report results of only one experiment, it is possible that a very weak effect might have not been detected. Morandi et al. [23] also exposed three other *Salmonella* tester strains treated with chemical mutagens (TA97a (ICR191); TA98 (daunomycin); and TA102 (mitomycin C)) to the 0.33 mT magnetic field, with no reported effects on reversion rate. Morandi et al. [23] also conducted the assays, using the same set of tester strains and chemical mutagens, using either electric fields (11.8 kV/m), or combined magnetic and electric fields (0.33 mT, 11.8 kV/m) at 60, 600, and 6000 Hz, also with negative results.

Chahal et al. [11] exposed *E. coli* strain AB1157 (rifampicin-sensitive) to a 1-Hz, 1-kV/m (in the medium) electric field during 16 h of growth in nutrient broth at 37°C in the presence of several different concentrations of mitomycin C (approx. 0.05–0.2 mg/ml). No effects of electric field exposure on the frequency of rifampicin resistant mutants induced by mitomycin C were observed.

3.4.5.2. In vitro chromosome. Six previously unreviewed studies were identified, employing co-exposures to chemical mutagens with ELF magnetic fields [9,10,12,29,31,33]. Tofani et al. [33] exposed human peripheral lymphocytes during a 72-h culture period to either 50 Hz, 150 μT (47 mT/s) or 32 Hz, 75 μT and 150 μT (15 and 30 mT/s) in the presence of mitomycin C (0.033 μg/ml). Induced electric fields could not reliably be estimated from the information reported. Control cultures were incubated in a separate incubator from that used for the magnetic field exposures. At the 50-Hz frequency, neither flux density had a statistically significant effect on the frequency of micronuclei induced by mitomycin C. However, at the 32-Hz frequency, very small increases in micronuclei were observed at both 75 μT and 150 μT (11% and 18%, respectively). The 11% increase was statistically significant ($p < 0.05$). These small increases were only observed if a parallel geomagnetic field was present (see the section on Section 3.2 above for further discussion).

Fairbairn and O'Neill [12] conducted two experiments using the 'comet' assay for DNA strand breaks, in which several human cell types were exposed at 37°C on agarose slides to a 50-Hz, pulsed (3 ms pulse duration, 5 mT peak intensity) magnetic field in the presence of hydrogen peroxide, an agent known to induce oxidative damage in cells. (The induced electric field could not reliably be estimated from the information provided). In the first experiment, HL-60 cells, a human promyelocytic leukemic cell line, were exposed for 30 min in the presence of 1.0 mM hydrogen peroxide. In the second series of experiments, HL-60 cells, HeLa cells (a human cervix carcinoma cell line), and human peripheral lymphocytes (HPL), were exposed for 10 min in the presence of 12.5 mM hydrogen peroxide. Cells were assayed in situ for DNA strand breakage using alkaline electrophoresis and ethidium bromide staining coupled with laser scanning microscopy to quantify DNA migration. The ratio of the width to the length of comet tails was determined for exposed and sham-exposed samples. No significant effects on DNA strand breakage were observed in any of the magnetic field exposed samples as compared to sham-exposed controls.

Scarfi et al. [29] exposed human peripheral lymphocytes obtained from healthy donors to 50-Hz electric fields of 0.5, 2, 5, and 10 kV/m (in air) during a 72-h culture period, during which Mitomycin C was present (0.033 μg/ml). We calculated internal electric fields of 1.4, 5.6, 14, and 28 μV/m based on the geometry reported, and an assumed media conductivity of 1 S/m. The frequency of micronuclei was not increased in electric field exposed cultures co-exposed to Mitomycin C as compared to Mitomycin C controls. Results are reported for each of 3 (0.5 kV/m), 5 (2 kV/m), 7 (5 kV/m), and 7 (10 kV/m) donors representing 22 separate individuals. See Section 3.3.1 for further discussion of the experimental protocol, and for experiments conducted without co-exposure to Mitomycin C.

An additional recent report [31] employed co-exposures to MNU using ELF magnetic field exposures (60-Hz, 3 mT (1.1 T/s) Vertical), and reported negative results. A rat embryo fibroblast line was used in a mutagenesis assay involving a *lac*I shuttle vector. Suri et al. [31] also employed co-exposures to menadione, a known free-radical generator, also with

negative results. For further description of the assay system used by Suri et al. [31], see Section 3.2.

Cantoni et al. [9,10] examined the possible effects of 50-Hz electric (0.2–20 kV/m), magnetic (2 μT–0.2 mT), or combined electric and magnetic (20 kV/m, 0.2 mT) field exposures on the rate of repair of DNA single and double strand breaks induced by hydrogen peroxide, and single strand breaks induced by either MMS or potassium chromate. These three mutagens induce DNA strand breaks by different mechanisms. No differences in repair rates were noted between ELF field-exposed and unexposed controls. However, as discussed in previous sections reporting results of the Cantoni et al. experiments, it is not clear what actual exposures were, since internal electric fields in culture media were probably severely attenuated.

3.4.6. Summary

The small but consistent increases in revertants in the *Salmonella*/Ames test observed by Tabrah et al. [32] after co-exposure to sodium azide and a 60-Hz 0.2 mT magnetic field are of possible interest. Unfortunately, in our previous review, the only studies that employed microbial systems in assays involving co-exposure to chemical mutagens used static magnetic fields, and were available only in abstract form, making a critical assessment difficult (see McCann et al. [4] for discussion). In our 1993 review, three studies were identified which employed in vitro chromosome assays in mammalian cells with co-exposures to magnetic fields and chemical mutagens [38,42,74] (no studies were identified which employed chemical co-exposures with ELF electric fields or to combined ELF magnetic and ELF electric fields).

Rosenthal and Obe [38] observed small but statistically significant increases in SCEs in human peripheral lymphocytes pretreated with MNU or trenimon (known SCE-inducers) and subsequently cultured for up to 72 h in a 50-Hz, 5-mT sinusoidal field as compared to cultures treated only with the chemical mutagens. Investigators suggested that the increase could be due to uncontrolled factors, specifically to stimulation of cell cycle progression by the magnetic field. Recently, in further support of their proposed mechanism, the same laboratory reported effects on the stimulation of the cell cycle by magnetic fields (50-Hz, 5 mT). Unfortunately, in this new study they did not repeat the experiment involving co-exposure to the chemical mutagens [7]. Whereas the negative experiments of Suri et al. [31] also employed co-exposures to MNU and a magnetic field condition similar to that used by Rosenthal and Obe [38], the cell culture system and assay endpoint used were quite different from those used by Rosenthal and Obe [38], preventing direct comparisons.

Scarfi et al. [42] exposed human peripheral lymphocytes in vitro to sawtooth fields (2.5 mT maximum amplitude, pulse width 1.2 ms) after treatment with mitomycin C, and observed no change in the rate of induction of micronuclei. These experiments are somewhat similar to those of Fairbairn and O'Neill [12] discussed above, as the latter investigators also employed human peripheral lymphocytes and 50-Hz pulsed fields with a twofold greater maximum amplitude (5 mT) as compared to Scarfi et al. [42]. However, the use of quite different chemical mutagens in the two studies (hydrogen peroxide and Mitomycin C) makes comparison difficult. Exposures in the occupational study of Butler et al. [74] were difficult to quantify, and the study also did not meet other quality control criteria (see McCann et al. [4] for discussion).

4. Discussion and conclusions

In this report, 29 previously unreviewed [4,5] published articles were identified, testing ELF magnetic, ELF electric, combined ELF magnetic and ELF electric, static magnetic, and static electric fields for genotoxic effects (Table 1). All five exposure categories are represented in these 29 reports, but the great majority (83%) involve ELF magnetic field exposures. Although a number of biological assay systems are represented (Table 5), the majority of experiments (68%) utilize in vitro mammalian cell assays for mutagenesis, sister chromatid exchanges (SCEs), micronuclei, chromosome aberrations, or DNA strand breaks.

The new reports identified in this review bring the total we have now reviewed to 84. It is of interest to determine if this substantial body of genotoxicity data supplies sufficient evidence to conclude that electric or magnetic fields under any exposure condi-

tion have genotoxic potential, or, conversely, if evidence is sufficient for any convincing conclusions regarding the absence of genotoxic activity. For any potentially genotoxic agent, particularly an agent for which activity is expected to be negative or weak, such an analysis is complex. For ELF fields, the great variety of exposure conditions possible further complicate the analysis. While a variety of quantitative, graphic and composite scoring approaches are available (reviewed by Brusick et al. [75]), it is not clear that it would be advantageous to apply them to ELF fields because of the immense variety of exposure conditions. Following the recommendations of EPA in their newly proposed risk assessment guidelines [76], we have adopted a relatively straightforward narrative approach, which combines the use of data quality and independent reproducibility criteria.

The data quality criteria employed are grounded in three basic principles: reproducibility, consistency and completeness. They are specified in Section 2 of this report and in the Methods section of our previous review [4]. An important limitation in applying data quality criteria to experiments from the published literature is that experiments which do not meet data quality criteria due to 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.

The criterion adopted for independent reproducibility attempts to take into account the infrequency with which studies are precisely replicated in the open literature. Thus, since there are so many exposure and biological variables in any genotoxicity assay, unless a study has been specifically designed to test for reproducibility (of which there are only two examples in the entire data base [14,27]), it is unlikely that any two study protocols will be exactly the same. Therefore, we have attempted to determine when the criterion for independent reproducibility has been 'roughly' satisfied. We consider that this 'rough' criterion is met when both exposure and assay conditions are 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.

Clearly, decisions as to whether or not 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 genotoxicity data from multiple non-identical assay systems and exposure conditions. Scientific judgment must be applied, which, of necessity, will be subjective to some degree. In making the judgments necessary for the analysis presented here, we have paid particular attention to four factors.

(1) Within each of the five basic exposure categories (ELF magnetic, ELF electric, combined ELF magnetic and ELF electric, static magnetic, and static electric) exposure conditions vary widely. Although a number of studies may have been conducted in a particular exposure category, exposure conditions may not be sufficiently similar to permit cross-comparisons for purposes of determining whether observed effects are reproducible. In cases where the criterion for independent reproducibility is satisfied, we have thus emphasized that conclusions apply only to the specific frequencies and intensities of exposure satisfying the condition. As an aid to comparing studies using different applied exposure conditions, when possible, we have calculated the internal electric fields present in the culture media (for in vitro experiments), and in the torso and extremities (for in vivo experiments).

(2) Despite the apparent simplicity of many genotoxicity assays there are subtleties of experimental procedure, that, if not carefully controlled, can lead to erroneous results. Thus, the detection and the potency of a genotoxic effect may be contingent on the duration of exposure or on other protocol variables such as cell type, metabolic state, stage of DNA replication, or whether (and how long) cells are allowed to grow after exposure. When such differences pertain among studies that otherwise satisfy reproducibility requirements, they have been noted.

(3) While all genotoxicity assays are related, in that they assay for endpoints either directly represen-

tative of, or believed to be associated with, mutagenesis, they are by no means the same in sensitivity and specificity (for example, see the results of a multi-laboratory comparison of tests on a number of chemicals across many different genotoxicity assays [77]). Thus, an agent detected as genotoxic in one assay system will not necessarily be detected in other systems. Some assays, however, are more closely related than others (e.g., see Lohman et al. [78] for discussion). For example, we have grouped together genotoxicity assays for mutagenesis and endpoints involving clastogenic effects using human or non-human mammalian cells in vitro, and we have also grouped in vivo assays together. The complete classification scheme we have used is specified in Section 2 and in the Methods section of our previous review [4]. The sensitivity and specificity of assays thus grouped are not perfectly overlapping, but there are sufficient similarities to justify using multiple results in assays within the same grouping as at least partially indicative of a reproducible effect.

(4) Hundreds of genotoxic and nongenotoxic agents (mostly chemicals) have been tested in genotoxicity assays, and many of the assay systems represented in this report have been very widely used. As a result, a significant body of knowledge has developed concerning the relative sensitivities of different endpoints to genotoxic agents, and, to some extent, concerning mechanistic relationships between endpoints. When possible, we have attempted to draw on this body of knowledge. However, it is important to note that a great deal is still to be learned, and important uncertainties remain. Therefore, some assumptions that have been made, particularly concerning 'rough' reproducibility requirements for multiple non-identical assays may prove to be incorrect.

4.1. Summary of results and reproducibility analysis

Table 6 presents a combined summary of results from our 1993 review [4] and the current report. (Results included in Table 6 do not include experiments involving co-exposures to ionizing radiation, ultraviolet light, or chemical mutagens. These experiments are discussed separately below.) As shown, ELF magnetic fields is the exposure category most represented, for which 37 reports from the published literature have now been reviewed. The number of studies reviewed involving other exposure categories are also substantial (ELF electric = 15; Combined ELF magnetic and ELF electric = 15; Static magnetic = 20; and Static electric = 7). The percentage of studies satisfying basic data quality criteria (as specified in Section 2) ranges between 40 and 53 per cent in all exposure categories, except static electric, where only 29% of the studies reviewed satisfied

Table 6
Combined summary of review results from McCann et al. [4] and from the current report

Field exposure	Total studies reviewed[a]	% of studies satisfying basic data quality criteria	Number of studies reporting positive results[ab]	Criterion for independent reproducibility satisfied? (Y, N, R)[c]	Number of studies reporting negative results[ab]	Criterion for independent reproducibility satisfied? (Y, N, R)[c]
ELF magnetic	37	51%	**6** (5)	N	**13** (13)	R
ELF electric	15	53%	**1** (4)	N	**7** (4)	N
Combined ELF magnetic and ELF electric	15	47%	**0** (2)	N	**7** (6)	R
Static magnetic	20	40%	**3** (7)	N	**5** (5)	R[d]
Static electric	7	29%	**0** (5)	N	**2** (0)	N

[a] Note that reports which included multiple types of exposures are listed in more than one exposure category.
[b] Results from experiments satisfying basic data quality criteria are in boldface; other results are in parentheses.
[c] Y = Yes; N = No; R = Criterion roughly satisfied. See text for discussion.
[d] Note that although two studies using the *Drosophila* sex-linked recessive lethal system satisfied the 'rough' criterion for independent reproducibility, another study, as yet unreplicated, using possibly more sensitive *Drosophila* mutant strains, has reported a weakly positive result (see text for discussion).

these criteria. In all but a few cases (which are noted in the text), studies that did not satisfy data quality criteria did so because they failed to meet more than one criterion.

Table 6 tabulates the number of studies reporting positive or negative results, and whether any of these studies meet a criterion of independent reproducibility. Below, we briefly summarize these conclusions for each of the five exposure categories considered.

4.2. ELF magnetic

The six positive studies satisfying basic data quality criteria represent the work of three laboratories [19–22,25,26]. As discussed in detail in the text, the differences among these studies are significant, preventing any conclusion as to independent reproducibility. As shown in Table 6, the only examples of studies employing ELF magnetic fields that satisfy the condition of independent reproducibility are studies that report the absence of a genotoxic effect. Among the 13 negative studies that met data quality objectives, the 'rough' criterion for reproducibility was met for two groups of experiments. First, two of the eight studies reviewed (all of which were negative), which utilized the *Salmonella*/Ames bacterial mutagenesis assay system, reported negative results at roughly similar exposures (60 Hz 0.2 mT [32] and 100 Hz 0.13 μT–0.13 mT [37]), and at similar estimated internal electric field strengths in the top agar of the assay plates (0.1 mV/m and 0.2–200 μV/m, respectively). Second, six negative studies satisfying data quality criteria used similar exposure conditions (50 Hz or 60 Hz; 0.03 – 5 mT) in in vitro assays for chromosome effects, DNA strand breaks, or mutagenesis [7,13,14,27,31,38]. Although the flux densities employed in all of these studies were not identical, overlapping ranges were employed (see Table 2). The same cellular system, human peripheral lymphocytes, was also used in several of these studies [7,27,38]. A conclusion that ELF magnetic fields are non-genotoxic under these assay and exposure conditions thus appears to be justified. Note, however, that weakly positive results that were contingent on co-exposure to chemical mutagens were reported by both Tabrah et al. [32] and Rosenthal and Obe [38]. These experiments are discussed separately below.

4.3. ELF electric

As shown in Table 6, only one of the five reports of positive effects (all reviewed previously) satisfied data quality criteria [56] (see text and McCann et al. [4] for discussion), whereas these criteria were satisfied for seven of the eleven negative studies identified in our previous review and in the current report [11,23,27,29,57–59]. Unfortunately, among these seven studies, none were sufficiently similar to satisfy the 'rough' requirement for independent reproducibility (see text for discussion).

4.4. Combined ELF magnetic and ELF electric

The only positive studies identified were two occupational studies of Nordenson et al. [52,79] reviewed previously. Both of these studies involved complex exposures difficult to quantify (see McCann et al. [4] for discussion). Among the seven negative studies that satisfied basic data quality criteria, two were conducted under similar exposure conditions using similar assay systems and endpoints. These studies are those of Cohen et al. [60] and Livingston et al. [61]. Both studies employed human peripheral lymphocytes in similar in vitro assays for SCEs, employing combined ELF magnetic and ELF electric fields (0.1–0.2 mT, 240 mV/m and 0.22 mT, 24–24,000 mV/m).

4.5. Static magnetic fields

The three positive studies identified in our previous and current reviews that satisfied basic data quality criteria [18,62,80] used very different assay systems (human peripheral lymphocytes, root meristems of *Allium cepa*, and the *Drosophila* sex-linked recessive lethal system), preventing cross-comparison. Among the five negative studies identified, which satisfied data quality criteria, two studies [66,67] using the *Drosophila* sex-linked recessive lethal assay system roughly satisfy requirements for independent reproducibility (see McCann et al. [4] for discussion). Both studies used very high magnetic field exposures (1.0–3.7 T), and both used sufficient numbers of flies to detect relatively weak effects. It is of interest that a recent study reviewed in this report, which used repair deficient strains of

Drosophila, was weakly positive [18]. Since the Kale and Baum [66] and Diebolt [67] studies both used wild type flies, and the *Drosophila* strains used by Koana et al. [18] were deficient in two major DNA repair pathways, the positive results reported by Koana et al. [18] are not necessarily contradicted by the negative reports because the sensitivity of the assay used by Koana et al. [18] may be greater than that of assays conducted using wild type flies.

4.6. Static electric fields

All five positive studies were identified in our earlier review [4], and none satisfied basic data quality criteria (see McCann et al. [4] for discussion). Both negative studies identified, one in our previous review [67] and one in the current report [8], did satisfy these criteria, but the two studies used very different assay systems (*Drosophila* and the *Salmonella*/Ames bacterial mutagenesis assay), preventing cross-comparison.

4.7. Co-exposure to ELF electric or magnetic fields and ultraviolet light, γ-irradiation, X-irradiation, or chemical mutagens

Three studies meeting quality control criteria report positive effects that appear to be dependent on co-exposure to ionizing radiation, UV-light, or chemical mutagens. These are the ELF magnetic field studies of Tabrah et al. [32] using the *Salmonella*/Ames assay system with co-exposures to sodium azide, Rosenthal and Obe [38] using an assay for SCEs in human peripheral lymphocytes in vitro with co-exposures to trenimon and NMU, and the static magnetic field study of Takatsuji et al. [80] using a chromosome aberration assay in human peripheral lymphocytes with co-exposure to protons and α-particles. [9]

The studies by Tabrah et al. [32] and Rosenthal and Obe [38] reported very weak effects, and both investigators suggested that the effects observed could be due to an enhancement in cell proliferation caused by exposure to the magnetic field. Magnetic field exposures were somewhat similar in these two studies (60 Hz, 0.2 mT and 50 Hz, 5 mT, respectively). Our estimates of the internal electric fields in the culture media for these two experiments are also not greatly different (0.1 mV/m and 0.6–2.0 mV/m). However, the assay systems are so different, and the effects observed are so weak that it is difficult to draw any conclusions as to the significance of the positive results observed. We previously discussed the weak positive results of Takatsuji et al. [80], which involved static magnetic fields of 1.1 T [4].

The only other positive results reported involving co-exposures were those of Miyakoshi et al. [21] involving co-exposures to X-rays, and Tofani et al. [33] involving co-exposures to Mitomycin C. However, the positive effects observed in both of these studies were also observed (though at a lower response level in the Miyakoshi et al. studies) in the absence of the co-exposures (see text for discussion).

The six other reports reviewed here and previously which satisfied basic data quality criteria and involved co-exposures to ionizing radiation, ultraviolet light, or chemical mutagens, were all negative [6,11,29,31,42,58]. Unfortunately, none of these studies are sufficiently similar to permit cross-comparisons.

4.8. Mechanistic analysis

Despite the strong evidence discussed above suggesting that, at least under the exposure and assay conditions specified, ELF magnetic fields and combined ELF magnetic and ELF electric fields are nongenotoxic, a pool of positive results remains from studies that satisfy data quality criteria, but have not yet been tested by independent replication. It may be helpful to consider whether physical models of electric and magnetic field coupling to biological systems offer any further insight into the plausibility of any of these positive results. First, the response threshold related to endogenous electric field signal levels resulting from thermal noise of cell membranes at physiological temperatures provides a fundamental limit to the detection of external fields by

[9] The positive report of Hintenlang [16], in which positive effects were reported, depending on co-exposure to γ-irradiation, did not meet quality control criteria and is thoroughly discussed in the text.

biological systems, since internal electric fields due to externally applied fields must be similar or larger than the endogenous fields before the biological system can respond [81–83]. For typical single cells in tissues or in culture, the electric field detection threshold due to membrane thermal noise is calculated to be in the range of 0.1–1.0 V/m for 60-Hz fields. Biological responses below this threshold are implausible based on this physical argument. About 46% of the articles reviewed in this and our previous report [4] involving exposures to ELF magnetic or ELF electric fields, for which internal electric fields could be estimated, were conducted at exposures resulting in internal fields exceeding 0.1 V/m. The majority (about 70%) of results obtained at these high exposures were negative, but several positive results were reported. These include the reports of Miyakoshi et al. [21,22] reviewed here, and several experiments from the Nordenson group [52,79] reviewed previously. The estimated internal electric fields for the other positive reports reviewed here were two to three orders of magnitude below this calculated physical threshold.

Second, several mechanisms for the direct coupling of magnetic fields to biological systems (not involving induced electric fields) have been proposed (for review see Valberg et al. [83], Grissom [84], Polk [85], and Tenforde [86]). Two of these mechanisms, interaction of magnetic fields at certain resonance frequencies affecting either calcium ion movement through membranes or calcium binding to proteins, and magnetic field effects on the rate of radical pair recombination, are supported to varying extents by experimental data. However, both the experimental and theoretical basis of resonance types of mechanism remain controversial (for discussion see reviews cited above). On the other hand, supporting evidence for a free radical pair recombination mechanism from in vitro experiments involving purified physicochemical or biochemical systems is strong (for review see Brocklehurst and McLauchlan [87], Valberg et al. [83], Scaiano et al. [88], Walleczek [89], and Grissom [84]). This evidence suggests that magnetic fields above approximately 1 mT are at least theoretically capable of affecting free radical reactions in living systems. Recent calculations suggest that such effects may be physically feasible at flux densities as low as 20 μT [87]. A number of both positive and negative studies in this and our previous review were conducted using magnetic field exposures at these and higher flux densities. For example, all of the positive studies using ELF or static magnetic fields, which satisfied data quality criteria [18–22,25,26,32,38,62,80], were conducted using magnetic fields exceeding 20 μT, and all but two of these reports [25,26] employed fields exceeding 0.1 mT. However, the same can be said of the negative reports reviewed. In fact, all negative reports that used ELF magnetic or static magnetic field exposures and satisfied data quality criteria, whether reviewed previously or in the present report, used flux densities that exceeded 0.1 mT. Thus, while a radical pair recombination mechanism may potentially explain the positive results obtained, the large number of negative reports at relatively high flux densities suggest that additional factors are involved.

4.9. Conclusion

It is perhaps surprising that, although we have now identified 32 separate reports that electric or magnetic fields have induced genotoxic effects (10 in this report and 22 in our 1993 review), none of these reports have been independently confirmed. To date, the few attempts to replicate positive results have failed. Therefore, given this lack of evidence for a genotoxic effect through independent replication, the weakly positive results in the few positive reports that satisfy data quality criteria, and the relatively large number of negative reports that satisfy both data quality criteria and a 'rough' criterion for independent reproducibility, we believe that the evidence reviewed here strengthens the conclusion of our previous review [4], that the preponderance of evidence suggests that ELF electric or magnetic fields do not have genotoxic potential. Nevertheless, it would be quite inappropriate to discount the current batch of positive reports, which should be confirmed by independent replication.

Extensive efforts are now underway to assess the carcinogenic potential of EMF in animal model systems (reviewed in Refs. [3,90]). Interpreting results from these animal studies in the light of potential risk to humans will require a risk assessment strategy for EMF (e.g., see DOE [91]). Whether EMF is

classified genotoxic or nongenotoxic is likely to have a significant impact on the choice of plausible risk assessment strategies, particularly on the choice of dose–response extrapolation models. If appropriate independent replication should establish the definitive presence of genotoxic activity of electric or magnetic fields in any assay system (and our conclusions here by no means rule this out), it will be important to assess these positive results in the light of the existing body of information on known genotoxic agents. If this step becomes necessary, it will be important to undertake it with an understanding that a key result of tests of hundreds of chemicals across a wide spectrum of genotoxicity assays is that agents do not appear to be divided clearly into those that are 'genotoxic' and those that are 'nongenotoxic' [92–94]. Instead, there appears to be a continuum of activity, from the very potent that are positive in almost all genotoxicity assays, to the very, very weak, which may have borderline activity in only a few assays. This observation has important implications for risk assessment, which have yet to be confronted by regulatory agencies (e.g., see EPA [76]).

Acknowledgements

This work was supported by the Electric Power Research Institute, Palo Alto, CA 94304, Project No. 6424-WO2965 to J. McCann and Project No. 2965-03 to Electric Research and Management.

References

[1] Polk, C., Postow, E. (Eds.), Handbook of Biological Effects of Electromagnetic Fields, CRC Press, New York, NY, 1996.
[2] Kaune, W.T., Anderson, L.E., Physical aspects of ELF electric and magnetic fields: measurements and dosimetry, in: B.W. Wilson, R.G. Stevens, L.E. Anderson (Eds.), Extremely Low Frequency Electromagnetic Fields: The Question of Cancer, Battelle Press, Columbus/Richland, 1990, pp. 17–45.
[3] J. McCann, R. Kavet, C. Rafferty, Testing EMF for potential carcinogenic activity: a critical review of animal models, Environ. Health Perspect. 105 (1997) 81–103, Suppl. 1.
[4] J. McCann, F. Dietrich, C. Rafferty, A.O. Martin, A critical review of the genotoxic potential of electric and magnetic fields, Mutat. Res. 297 (1993) 61–95.
[5] J.C. Murphy, D.A. Kaden, J. Warren, A. Sivak, Power frequency electric and magnetic fields: a review of genetic toxicology, Mutat. Res. 296 (1993) 221–240.
[6] D.D. Ager, J.A. Radul, Effect of 60-Hz magnetic fields on ultraviolet light-induced mutation and mitotic recombination in *Saccharomyces cerevisiae*, Mutat. Res. 283 (1992) 279–286.
[7] A. Antonopoulos, B. Yang, A. Stamm, W-D. Heller, G. Obe, Cytological effects of 50 Hz electromagnetic fields on human lymphocytes in vitro, Mutat. Res. 346 (1995) 151–157.
[8] M. Berg, B. Lindelöf, I. Langlet, K. Victorin, Absence of mutagenic response to radiation from a video display terminal, Scand. J. Work Environ. Health 14 (1988) 49–51.
[9] O. Cantoni, P. Sestili, M. Fiorani, M. Dachà, The effect of 50 Hz sinusoidal electric and/or magnetic fields on the rate of repair of DNA single/double strand breaks in oxidatively injured cells, Biochem. Mol. Biol. Int. 37 (1995) 681–689.
[10] O. Cantoni, P. Sestili, M. Fiorani, M. Dachà, Effect of 50 Hz sinusoidal electric and/or magnetic fields on the rate of repair of DNA single strand breaks in cultured mammalian cells exposed to three different carcinogens: methylmethane sulphonate, chromate and 254 nm U.V. radiation, Biochem. Mol. Biol. Int. 38 (1996) 527–533.
[11] R. Chahal, D.Q.M. Craig, R.J. Pinney, Investigation of potential genotoxic effects of low frequency electromagnetic fields on *Escherichia coli*, J. Pharm. Pharmacol. 45 (1993) 30–33.
[12] D.W. Fairbairn, K.L. O'Neill, The effect of electromagnetic field exposure on the formation of DNA single strand breaks in human cells, Cell Mol. Biol. 40 (1994) 561–567.
[13] M. Fiorani, O. Cantoni, P. Sestili, R. Conti, P. Nicolini, F. Vetrano, M. Dachà, Electric and/or magnetic field effects on DNA structure and function in cultured human cells, Mutat. Res. 282 (1992) 25–29.
[14] S. Galt, J. Wahlström, Y. Hamnerius, D. Holmqvist, T. Johannesson, Study of effects of 50 Hz magnetic fields on chromosome aberrations and the growth-related enzyme ODC in human amniotic cells, Bioelectrochem. Bioenergetics 36 (1995) 1–8.
[15] G. Giorgi, D. Guerra, C. Pezzoli, S. Cavicchi, F. Bersani, Genetic effects of static magnetic fields. Body size increase and lethal mutations induced in populations of *Drosophila melanogaster* after chronic exposure, Genet. Sel. Evol. 24 (1992) 393–413.
[16] D.E. Hintenlang, Synergistic effects of ionizing radiation and 60 Hz magnetic fields, Bioelectromagnetics 14 (1993) 545–551.
[17] V. Kiranmai, Induction of mutations by magnetic field for the improvement of sunflower, J. Appl. Phys. 75 (1994) 7181, (abstract).
[18] T. Koana, M. Ikehata, M. Nakagawa, Estimation of genetic effects of a static magnetic field by a somatic cell test using mutagen-sensitive mutants of *Drosophila melanogaster*, Bioelectrochem. Bioenergetics 36 (1995) 95–100.
[19] H. Lai, N.P. Singh, Acute exposure to a 60-Hz magnetic field increases DNA strand breaks in rat brain cells, Bioelectromagnetics 18 (1997) 156–165.

[20] H. Lai, N.P. Singh, Melatonin and *N-tert*-butyl-*a*-phenylnitrone block 60-Hz magnetic field-induced DNA single and double strand breaks in rat brain cells, J. Pineal Res. 22 (1997) 152–162.
[21] J. Miyakoshi, N. Yamagishi, S. Ohtsu, K. Mohri, H. Takebe, Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations by exposure to high-density 50-Hz magnetic fields, Mutat. Res. 349 (1996) 109–114.
[22] J. Miyakoshi, K. Kitagawa, H. Takebe, Mutation induction by high-density, 50-Hz maganetic fields in human MeWo cells exposed in the DNA synthesis phase, Int. J. Radiat. Biol. 71 (1997) 75–79.
[23] M.A. Morandi, C.M. Pak, R.P. Caren, L.D. Caren, Lack of an EMF-induced genotoxic effect in the Ames assay, Life Sci. 59 (1996) 263–271.
[24] J. Nafziger, H. Desjobert, B. Benamar, J.J. Guillosson, DNA mutations and 50 Hz electromagnetic fields, Bioelectrochem. Bioenergetics 30 (1993) 133–141.
[25] Nordenson, I., Mild, K.H., Sandström, M., Mattsson, M-O., Effect of low-frequency magnetic fields on the chromosomal level in human amniotic cells, in: B. Nordén, C. Ramel (Eds.), Interaction Mechanisms of Low-Level Electromagnetic Fields in Living Systems— Resonant Phenomena, Oxford Univ. Press, Stockholm, 1992, pp. 240–250.
[26] I. Nordenson, K.H. Mild, G. Andersson, M. Sandström, Chromosomal aberrations in human amniotic cells after intermittent exposure to fifty Hertz magnetic fields, Bioelectromagnetics 15 (1994) 293–301.
[27] W. Paile, K. Jokela, A. Koivistoinen, S. Salomaa, Effects of 50 Hz sinusoidal magnetic fields and spark discharges on human lymphocytes in vitro, Bioelectrochem. Bioenergetics 36 (1995) 15–22.
[28] E. Saalman, A. Önfelt, B. Gillstedt-Hedman, Lack of c-mitotic effects in V79 chinese hamster cells exposed to 50 Hz magnetic fields, Bioelectrochem. Bioenergetics 26 (1991) 335–338.
[29] M.R. Scarfi, F. Bersani, A. Cossarizza, D. Monti, O. Zeni, M.B. Lioi, G. Franceschetti, M. Capri, C. Franceschi, 50 Hz AC sinusoidal electric fields do not exert genotoxic effects (micronuclei formation) in human lymphocytes, Radiat. Res. 135 (1993) 64–68.
[30] M.R. Scarfi, M.B. Lioi, O. Zeni, G. Franceschetti, C. Franceschi, F. Bersani, Lack of chromosomal aberration and micronucleus induction in human lymphocytes exposed to pulsed magnetic fields, Mutat. Res. 306 (1994) 129–133.
[31] A. Suri, J. deBoer, W. Kusser, B.W. Glickman, A 3 milliTesla 60 Hz magnetic field is neither mutagenic nor comutagenic in the presence of menadione and MNU in a transgenic rat cell line, Mutat. Res. 372 (1996) 23–31.
[32] F.L. Tabrah, H.F. Mower, S. Batkin, P.B. Greenwood, Enhanced mutagenic effect of a 60 Hz time-varying magnetic field on numbers of azide-induced TA100 revertant colonies, Bioelectromagnetics 15 (1994) 85–93.
[33] S. Tofani, A. Ferrara, L. Anglesio, G. Gilli, Evidence for genotoxic effects of resonant ELF magnetic fields, Bioelectrochem. Bioenergetics 36 (1995) 9–13.
[34] R. Zwingelberg, G. Obe, M. Rosenthal, M. Mevissen, S. Buntenkötter, W. Löscher, Exposure of rats to a 50-Hz, 30-mT magnetic field influences neither the frequencies of sister-chromatid exchanges nor proliferation characteristics of cultured peripheral lymphocytes, Mutat. Res. 302 (1993) 39–44.
[35] V.V. Lednev, Possible mechanism for the influence of weak magnetic fields on biological systems, Bioelectromagnetics 12 (1991) 71–75.
[36] M. Dachà, A. Accorsi, C. Pierotti, F. Vetrano, R. Mantovani, G. Guidi, R. Conti, P. Nicolini, Studies on the possible biological effects of 50 Hz electric and/or magnetic fields: evaluation of some glycolytic enzymes, glycolytic flux, energy and oxido-reductive potentials in human erythrocytes exposed in vitro to power frequency fields, Bioelectromagnetics 14 (1993) 383–391.
[37] J. Juutilainen, A. Liimatainen, Mutation frequency in *Salmonella* exposed to weak 100-Hz magnetic fields, Hereditas 104 (1986) 145–147.
[38] M. Rosenthal, G. Obe, Effects of 50-Hertz electromagnetic fields on proliferation and on chromosomal alterations in human peripheral lymphocytes untreated or pretreated with chemical mutagens, Mutat. Res. 210 (1989) 329–335.
[39] I. Nordenson, K.H. Mild, in: BEMS 11th Annual Meeting, Tucson, AZ, June 18–22, 1989.
[40] J.E. Trosko, Challenge to the simple paradigm that 'carcinogens' are 'mutagens' and to the in vitro and in vivo assays used to test the paradigm, Mutat. Res. 373 (1997) 245–249.
[41] A.M. Khalil, W. Qassem, Cytogenetic effects of pulsing electromagnetic field on human lymphoctes in-vitro: chromosome aberrations. Sister-chromatid exchanges and cell kinetcs, Mutat. Res. 247 (1991) 141–146.
[42] M.R. Scarfi, F. Bersani, A. Cossarizza, D. Monti, G. Castellani, R. Cadossi, G. Franceschetti, C. Franceschi, Spontaneous and Mitomycin-C-induced micronuclei in human lymphocytes exposed to extremely low frequency pulsed magnetic fields, Biochem. Biophys. Res. Commun. 176 (1991) 194–200.
[43] D.W. Fairbairn, P.L. Olive, K.L. O'Neill, The comet assay: a comprehensive review, Mutat. Res. 339 (1995) 37–59.
[44] V.J. McKelvey-Martin, M.H.L. Green, P. Schmezer, B.L. Pool-Zobel, M.P.D. Méo, A. Collins, The single cell gel electrophoresis assay (comet assay): a European review, Mutat. Res. 288 (1993) 47–63.
[45] N.P. Singh, R.E. Stephens, E.L. Schneider, Modifications of alkaline microgel electrophoresis for sensitive detection of DNA damage, Int. J. Radiat. Biol. 66 (1994) 23–28.
[46] N.P. Singh, R.R. Tice, R.E. Stephens, E.L. Schneider, A microgel electrophoresis technique for the direct quantitation of DNA damage and repair in individual fibroblasts cultured on microscope slides, Mutat. Res. 252 (1991) 289–296.
[47] G.M. Williams, Comment on 'Acute Low-Intensity Microwave Exposure Increases DNA Single-Strand Breaks in Rat Brain Cells' by Henry Lai and Norendra P. Singh, Bioelectromagnetics 17 (1996) 165.
[48] M. Klaude, S. Eriksson, J. Nygren, G. Ahnström, The comet assay: mechanisms and technical considerations, Mutat. Res. 363 (1996) 89–96.
[49] J.A. Reese, R.F. Jostes, M.E. Frazier, Exposure of mam-

malian cells to 60-Hz magnetic or electric fields: analysis for DNA single-strand breaks, Bioelectromagnetics 9 (1988) 237–247.
[50] H. Lai, N.P. Singh, Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells, Bioelectromagnetics 16 (1995) 207–210.
[51] H. Lai, N.P. Singh, Reply to comment on acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells, Bioelectromagnetics 17 (1996) 166.
[52] I. Nordenson, K.H. Mild, S. Nordstrom, A. Sweins, E. Birke, Clastogenic effects in human lymphocytes of power frequency electric fields: in vivo and in vitro studies, Radiat. Environ. Biophys. 23 (1984) 191–201.
[53] G. D'Ambrosio, A. Scaglione, D. DiBernardinio, M.B. Kioi, L. Iannuzzi, E. Mostacciuolo, M.R. Scarfi, Chromosomal aberrations induced by ELF electric fields, J. Bioelect. 4 (1985) 279–284.
[54] G. D'Ambrosio, R. Massa, D. DiBerardino, M.B. Lioi, A. Scaglione, M.R. Scarfi, Chromosomal aberrations in bovine lymphocytes exposed to 50-Hz electric currents, J. Bioelect. 7 (1989) 239–245.
[55] S. ElNahas, H. Anis, Mutagenic effects of exposure to power frequency electric fields, in: IASTE International Symposium on High Technology in the Power Industry, Bozeman, MT, 1986, pp. 305–308.
[56] S. ElNahas, H.A. Oraby, Micronuclei formation in somatic cells of mice exposed to 50-Hz electric fields, Environ. Mol. Mutagen. 13 (1989) 107–111.
[57] M.M. Cohen, In vitro genetic effects of electromagnetic fields, Contractors Final Report to New York State Power Lines Project, Wadsworth Center for Laboratories and Research, New York, 1986.
[58] M.E. Frazier, J.A. Reese, J.E. Morris, R.F. Jostes, D.L. Miller, Exposure of mammalian cells to 60-Hz magnetic or electric fields: analysis of DNA repair of induced, single-strand breaks, Bioelectromagnetics 11 (1990) 229–234.
[59] C.I. Kowalczuk, R.D. Saunders, Dominant lethal studies in male mice after exposure to a 50-Hz electric field, Bioelectromagnetics 11 (1990) 129–138.
[60] M.M. Cohen, A. Kunska, J. Astemborski, D. McCulloch, The effect of low-level 60-Hz electromagnetic fields on human lymphoid cells: II. Sister-chromatid exchanges in peripheral lymphocytes and lymphoblastoid cell lines, Mutat. Res. 172 (1986) 177–184.
[61] G.K. Livingston, K.L. Witt, O.P. Gandhi, I. Chatterjee, J.L.R. Roti, Reproductive integrity of mammalian cells exposed to power frequency electromagnetic fields, Environ. Mol. Mutagen. 17 (1991) 49–58.
[62] F.J. Peteiro-Cartelle, J. Cabezas-Cerrato, Influence of a static magnetic field on mitosis in meristematic cells of *Allium cepa*, J. Bioelect. 8 (1989) 167–178.
[63] V.V. Shevchenko, L.I. Grinikh, V.Y. Strekova, On the problem of induction of chromosome aberrations in plants in a constant magnetic field, Genetika 14 (1978) 1101–1103.
[64] T.D. Nguyen, J.B. Boyd, M.M. Green, Sensitivity of *Drosophila* mutants to chemical carcinogens, Mutat. Res. 63 (1979) 67–77.
[65] K. Fujikawa, F.L. Fort, K. Samejima, Y. Sakamoto, Genotoxic potency in *Drosophila melanogaster* of selected aromatic amines and polycyclic aromatic hydrocarbons as assayed in the DNA repair test, Mutat. Res. 290 (1993) 175–182.
[66] P.G. Kale, J.W. Baum, Genetic effects of strong magnetic fields in *Drosophila melanogaster*: I. Homogeneous fields ranging from 13,000 to 37,000 Gauss, Environ. Mutagen. 1 (1979) 371–374.
[67] J.R. Diebolt, The influence of electrostatic and magnetic fields on mutation in *Drosophila melanogaster* spermatozoa, Mutat. Res. 57 (1978) 169–174.
[68] P. Cooke, P.G. Morris, The effects of NMR exposure on living organisms: II. A genetic study of human lymphocytes, Br. J. Radiol. 54 (1981) 622–625.
[69] F.J. Peteiro-Cartelle, J. Cabezas-Cerrato, Absence of kinetic and cytogenetic effects on human lymphocytes exposed to static magnetic fields, J. Bioelect. 8 (1989) 11–19.
[70] A. Thomas, P.G. Morris, The effects of NMR exposure in living organisms: I. A microbial assay, Br. J. Radiol. 54 (1981) 615–621.
[71] F.P. Hungate, M.P. Fujihara, S.R. Strankman, Effects of high-strength electric fields, in: R.D. Phillips, M.F. Gillis, W.T. Kaune, D.D. Mahlom (Eds.), Biological Effects of Extremely Low Frequency Electromagnetic Fields, Proceedings of the 18th Annual Handford Life Sciences Symposium, Richland, WA, 1979, pp. 530–537.
[72] A. Cossarizza, D. Monti, P. Sola, G. Moschini, R. Cadossi, F. Bersani, C. Franceschi, DNA repair after γ irradiation in lymphocytes exposed to low-frequency pulsed electromagnetic fields, Radiat. Res. 118 (1989) 161–168.
[73] G.L. Whitson, W.L. Carrier, A.A. Francis, C.C. Shih, S. Georghiou, J.D. Regan, Effects of extremely low frequency (ELF) electric fields on cell growth and DNA repair in human skin fibroblasts, Cell Tissue Kinet. 19 (1986) 39–47.
[74] M.G. Butler, J. Yost, B.B. Jenkins, Chromosome breakage and sister chromatid exchange analysis in computer operators, J. Environ. Sci. Health A 22 (1987) 729–741.
[75] D.J. Brusick, J. Ashby, F.J. deSerres, P.H.M. Lohman, T. Matsushima, B.E. Matter, M.L. Mendelsohn, D.H. Moore II, S. Nesnow, M.D. Waters, A method for combining and comparing short-term genotoxicity test data: preface, Mutat. Res. 266 (1992) 1–6.
[76] E.P.A. Proposed Guidelines for Carcinogen Risk Assessment EPA/600/P-92/003C, Office of Research and Development, Environmental Protection Agency, Washington, DC, 1996.
[77] J. Ashby, F.J. deSerres, M. Draper, M. Ishidate Jr., B.H. Margolin, B.E. Matter, M.D. Shelby, Evaluation of Short-term Tests for Carcinogens, Report of the International Programme on Chemical Safety's Collaborative Study on In Vitro Assays, Vol. 5, Elsevier, Amsterdam, 1985.
[78] P.H.M. Lohman, M.L. Mendelsohn, D.H. Moore II, M.D. Waters, D.J. Brusick, J. Ashby, W.J.A. Lohman, A method for comparing and combining short-term genotoxicity test data: the basic system, Mutat. Res. 266 (1992) 7–25.
[79] I. Nordenson, K.H. Mild, U. Ostman, H. Ljungberg, Chro-

mosomal effects in lymphocytes of 400-kV substation workers, Radiat. Environ. Biophys. 27 (1988) 39–47.
[80] T. Takatsuji, M.S. Sasaki, H. Takekoshi, Effect of static magntic field on the induction of chromosome aberrations by 4.9 MeV protons and 23 MeV alpha particles, J. Radiat. Res. 30 (1989) 238–246.
[81] J.C. Weaver, D. Astumian, The response of living cells to very weak electric fields: the thermal noise limit, Science 247 (1990) 459–462.
[82] R.K. Adair, Constraints on biological effects of weak extremely low-frequency electromagnetic fields, Phys. Rev. A 43 (1991) 1039–1048.
[83] P.A. Valberg, R. Kavet, C.N. Rafferty, Can low level 50/60 Hz electric and magnetic fields cause biological effects?, Radiat. Res. 148 (1997) 2–21.
[84] C.B. Grissom, Magnetic field effects in biology: a survey of possible mechanisms with emphasis on radical-pair recombination, Chem. Rev. 95 (1995) 3–24.
[85] C. Polk, Dosimetry of extremely-low-frequency magnetic fields, Bioelectromagnetics Suppl. 1 (1992) 209–235.
[86] T.S. Tenforde, Interaction of ELF magnetic fields with living systems, in: C. Polk, E. Postow (Eds.), Handbook of Biological Effects of Electromagnetic Fields, 2nd edn., CRC Press, Boca Raton, FL, 1996, pp. 185–230.
[87] B. Brocklehurst, K.A. McLauchlan, Free radical mechanism for the effects of environmental electromagnetic fields on biological systems, Int. J. Radiat. Biol. 69 (1996) 3–24.
[88] J.C. Scaiano, F.L. Cozens, N. Mohtat, Influence of combined AC–DC magnetic fields on free radicals in organized and biological systems. Development of a model and application of the radical pair mechanism to radicals in micelles, Photochem. Photobiol. 62 (1995) 818–829.
[89] J. Walleczek, Magnetokinetic effects on radical pairs: a paradigm for magnetic field interactions with biological systems at lower than thermal energy, 1995, pp. 395–420.
[90] L. Hardell, B. Holmberg, H. Malker, L-E. Paulsson, Exposure to extremely low frequency electromagnetic fields and the risk of malignant diseases—an evaluation of epidemiological and experimental findings, Eur. J. Cancer Prev. 4 (1995) 3–107.
[91] D.O.E. EMF RAPID Program: Research Agenda and Communication Plan DOE/EE-0021, EMF RAPID Program Interagency Committee, Washington, DC, 1994.
[92] M.L. Mendelsohn, D.H. Moore II, P.H.M. Lohman, A method for comparing and combining short-term genotoxicity test data: results and interpretation, Mutat. Res. 266 (1992) 43–60.
[93] D. Brusick, A proposed method for assembly and interpretation of short-term test data, Environ. Health Perspect. 96 (1991) 101–111.
[94] J. McCann, L.S. Gold, L. Horn, R. McGill, T.E. Graedel, J. Kaldor, Statistical analysis of *Salmonella* test data and comparison to results of animal cancer tests, Mutat. Res. 205 (1988) 183–195.