ELSEVIER

Mutation Research 410 (1998) 167–183

Reviews in Mutation Research

Mini review

Teratogenic and reproductive effects of low-frequency magnetic fields [1]

H. Huuskonen [a,*], M.-L. Lindbohm [b], J. Juutilainen [c]

[a] National Public Health Institute, Division of Environmental Health, P.O. Box. 95, Kuopio, FIN-70701, Finland
[b] Finnish Institute of Occupational Health, Topeliuksenkatu 41 a A, Helsinki, FIN-00250, Finland
[c] Department of Environmental Sciences, University of Kuopio, P.O. Box 1627, Kuopio, FIN-70211, Finland

Received 20 April 1997; accepted 2 September 1997

Keywords: Electromagnetic field; Fertility; Abortion; Human; Animal

1. Introduction

The public discussion of the health hazards of low-frequency (LF; 0–100 kHz) magnetic fields (MF) has focused on the possible association with cancer, and much less attention has been paid to evaluating their role in reproductive health. However, several studies on the effects of MFs on reproduction have been conducted during the last decade. These studies were initiated by a study reporting that MFs may interfere with chick embryo development [1], small clusters of birth defects and miscarriages observed among operators of video display terminals, and an epidemiological study suggesting that maternal use of electrically heated waterbeds and electric blankets may affect fetal development [2].

The teratogenic effects of chemical and physical environmental agents are often related to their ability to damage DNA. The possibility that MFs induce genotoxic effects is discussed elsewhere in this issue. This paper reviews studies on the possible effects of LF MFs on reproductive outcome, whether the effects are due to genetic mutations (in maternal or paternal germ cells or during early prenatal development) or other MF-induced changes in fetal or maternal physiology. Both experimental and epidemiological studies are reviewed.

Two kinds of MFs are addressed in the studies described in this review: those associated with the use or transmission of electric power and those emitted by video display terminals (VDT). When electric power is used, the conductors carrying the current are surrounded by MFs. The frequency of the field is determined by the frequency of the alternating current, and is 60 Hz in North America and 50 Hz elsewhere. Frequencies between 0 and 300 Hz are conventionally called extremely low frequencies (ELF). The waveform of the MFs produced by alternating current is sinusoidal. Magnetic fields with a triangular (sawtooth) waveform are produced by VDTs, both in the ELF and in the very low frequency (VLF; 300 Hz–100 kHz) range. A few experimental studies have used waveforms and frequencies not related to VDTs or electric power.

The intensity of a magnetic field is usually expressed as magnetic flux density in microtesla (μT)

* Corresponding author.

[1] This is the third in a series of four papers, the first of which was published in *Mutation Res*. 387 (1997) pp. 165–171.

PII S1383-5742(97)00038-0

or millitesla (mT). For MFs with sinusoidal waveforms, the flux density is normally expressed as the root-mean-square (r.m.s.) value, but many studies describe the intensity of non-sinusoidal waveforms by giving the amplitude from the bottom to the top of the wave, the so-called peak-to-peak (p–p) value.

2. Epidemiological studies

2.1. Maternal exposure

2.1.1. Electrically heated beds

Electric blankets and water beds can make a significant contribution to total exposure to ELF magnetic fields because their field strength is quite strong and they are used close to the body for long time periods. Electric blankets produce fields up to about 2.2 μT and the users of water beds are exposed to flux densities of 0.3–0.5 μT [3–5]. It has been estimated that an electric blanket user has on average 1.8-times the exposure of a non-user [6].

The issue of potential harmful effects of the use of electric blankets and heated water beds on reproduction was raised in 1986 by a paper of Wertheimer and Leeper [2]. They examined seasonal patterns of fetal growth and abortion rate among the users of electric blankets and heated waterbeds, and found more abortions and infants who were below average in fetal growth in births conceived in the winter months than during the warmer months. This study has, however, been criticized for several methodological shortcomings [7].

The findings of the studies on electrically heated bed and birth defects have usually been negative (Table 1). The use of electric blankets or heated waterbeds was not related to neural tube defects, oral cleft defects, or urinary tract defects [8–10]. In the study of Li et al. [10] electric blanket use was, however, associated with an increased risk of urinary tract anomalies among women with a history of subfertility. The finding has been questioned because it was observed in a subgroup only and it was based on small numbers (five exposed cases) [11].

Three studies have assessed the association between magnetic fields and childhood cancer. Savitz et al. [12] found indications for an adverse effect of the mother's use of electric blankets during pregnancy, especially for leukemias and brain cancer. In two more recent studies on brain tumors [13,14], no increase was observed for prenatal electric blanket use, but the results of the other study [13] suggested a twofold increase in risk related to maternal use of electric water beds.

All the above studies were retrospective and assessment of exposure was usually based on self-reported data on the use of electric appliances. Thus, incomplete and biased reporting of exposure may have influenced the findings. In addition, there exists great variability in magnetic field strengths between various types of electric blankets and water beds [3–5]. These difficulties were partly overcome in a prospective study by Bracken et al. [5]. Exposure was estimated by measurements of magnetic fields produced by electric blankets and waterbeds and using interview data on hours of their daily use. Low birth weight and intrauterine growth retardation were not related to electrically heated bed use during pregnancy and no dose–response relation was seen with exposure.

2.1.2. Other residential and occupational exposure

The effects of residential exposure to ELF magnetic fields were investigated in five studies (Table 2). Wertheimer and Leeper [15] observed a positive correlation between a monthly ratio of fetal loss at homes with ceiling cable heat relative to homes without such heating and the increase of heating degree days reported for that month. Ceiling cable heating produces a field of about 1 μT. In another study [14], electric heating sources used in residence during pregnancy were not associated with childhood brain tumors.

The assessment of exposure was based on measurements of the residential magnetic fields in three studies. One study showed a suggestive association between exposure to magnetic fields of ≥ 0.6 μT, measured at the front door, and early pregnancy loss [16], whereas the other found no increases in risk of miscarriage, low birth weight, or preterm delivery for exposure to magnetic fields above 0.2 μT or high wire codes [17]. The interpretation of the results of both studies is, however, limited by the small number of exposed subjects. In a third study, exposure to ≥ 0.2 μT magnetic fields, as measured using personal wrist monitors, was unrelated to low birth weight and intrauterine growth retardation [5].

Table 1
Studies on electrically heated beds and reproductive outcome

Study population	Reproductive outcome	Sources of outcome (O) and exposure (E) data	Result	Reference
Denver; 1256 births and 692 sibling births	Abortions and fetal growth	O: birth announcements and records; E: telephone interview	Frequency of abortions and slow fetal growth correlated with presumed electric bed use	[2]
New Haven; a prospective study of women (2967) receiving prenatal care	Low birth weight (LBW) and intrauterine growth retardation (IUGR)	O: hospital data; E: interview, magnetic field measurements	Time-weighted exposure (high) to electric beds: IUGR: OR 1.6 (0.4-6.5); LBW:no association	[5]
New York State; 535 cases and 55 controls	Neural tube defects (NTD) and oral cleft defects (OCD)	O: malformation registry, birth registration E: mail survey	Electric blanket: NTD: OR 0.9 (0.5–1.6); OCD: OR 0.7 (0.4–1.2). Electric water bed: NTD: OR 1.1 (0.6–1.9); OCD: OR 0.7 (0.4–1.1)	[8]
New England; a cohort of 23491 women	Neural tube defects	O: physicians or women; E:telephone interview	Electric blanket: RR 1.2 (0.5–2.6)	[9]
Washington State; 118 cases and 369 controls, subfertile women: 37 cases and 85 controls	Congenital urinary tract defects	O: birth defect registry and random births in hospitals; E: interview	Electric blanket, all women: OR 1.1 (0.5–2.3); subfertile women: OR 4.4 (0.9–22.7). Water bed, all women: OR 0.8 (0.3–2.7)	[10]
Denver; 252 cases and 222 controls	Childhood cancer	O:cancer registry, random digit dialinf; E: interview	Electric blanket: leukemia OR 1.7 (0.8–.6); brain cancer OR 2.5 (1.1–5.5). Water bed: OR 0.7 (0.4–1.4)	[12]
Los Angeles County; 298 cases and 298 controls	Childhood brain tumors	O: cancer registry random digit dialing; E: interview	Electric blanket: OR 1.2 (0.6–2.2). Electric water bed: OR 2.1 (1.0–4.2)	[13]
Seattle, Washington; 133 cases and 270 controls	Childhood brain tumors	O: cancer registry, random digit dialing; E. interview	Electric blanket: OR 0.9 (0.5–1.6). Electric water bed: OR 0.7 (0.4–1.3)	[14]

The association between occupational exposure to ELF magnetic fields and spontaneous abortion was examined in a retrospective study among employees of semiconductor manufacturers [18]. Exposure assessment was based on women's self-reported work activities and industrial hygienists' evaluation. No increased risk of spontaneous abortion was seen for workers exposed to magnetic fields of 0.2–0.5 μT or >0.5 μT as compared to workers exposed to lower levels of magnetic fields.

2.1.3. Video display terminals

Several epidemiologic investigations have focused on the association between adverse reproductive outcome and the use of VDTs during pregnancy. Exposure to low-frequency electromagnetic fields has been suggested as one causal factor, along with stress and ergonomic factors, for the harmful effects of VDT work on pregnancy outcome. Magnetic fields produced by modern VDTs are usually low and often lower than the fields from other sources in the office environment. The median magnetic field strength measured from 43 different types of VDTs was 0.1 μT at a distance of 50 cm and it ranged from 0.09 to 0.6 μT [19]. Typical ELF magnetic flux densities in office environments range from <0.03 to 1.0 μT [20,21].

Most epidemiologic studies have examined the effects of VDTs according to the amount of time

Table 2
Studies on residential ELF magnetic fields and reproductive outcome

Study population	Reproductive outcome	Sources of outcome (O) and exposure (E) data	Result	Reference
Oregon; a cohort of 1879 livebirths and 142 abortions	Fetal loss	O: birth certificates; E: assessor's office files	Apositive correlation between fetal loss ratio for ceiling cable heated homes and the increase of heating degree days	[15]
Finland; 89 cases and 102 controls in a cohort of women attempting to become pregnant	Early pregnancy loss	O: pregnancy test; E: magnetic field measurements	Magnetic field ≥ 0.63 μT: OR 5.1 (1.0–25). Magnetic field 0.1–0.62 μT: OR 1.0 (0.6–1.9)	[16]
Denver: 257–396 pregnancies of a previous case control study on childhood cancer	Miscarriage (M), low birth weight (LBW), preterm delivery (PD)	O: interview; E: interview, measurement, wire configuration code	Magnetic field ≥ 0.2 μT: M: OR 0.8 (0.3–2.3); PD: OR 0.7 (0.1–4.0). High wire code: M: OR 0.7 (0.3–1.8); LBW: OR 0.7 (0.2–2.3)	[17]
New Haven; a prospective study of women (2967) receiving prenatal care	Low birth weight (LBW) and intra-uterine growth retardation (IUGR)	O: hospital data; E: interview, magnetic field measurements	Magnetic field ≥ 0.2 μT: IUGR: OR 1.2 (0.4–3.1); LBW: OR 1.4 (0.3–6.1)	[5]
Seattle, Washington; 98 cases and 208 controls	Childhood brain tumors	O: cancer registry, random digit dialing; E:mail questionaire	Electric heating source in mother's bedroom: OR 1.5 (0.8–2.9). Any electric heating: OR 0.7 (0.4–1.2)	[14]

spent working at the terminal. The majority of these studies suggest that VDT work is not associated with spontaneous abortion, congenital malformation or fetal growth retardation (see reviews [7,22–26]). Only a few studies showed an excess of some reproductive outcomes, but the effects of recall bias could not be excluded in these investigations. Usually, these studies have not included any magnetic field measurements.

Two studies investigated the association between the magnetic fields of VDTs and spontaneous abortion. In an US study [27], no association was observed between the electric (< 1.0 V/m) or magnetic fields (< 0.1 μT) emitted by VDTs and spontaneous abortion. In a Finnish study [28], working with a VDT was not related to spontaneous abortion. However, the odds ratio of spontaneous abortion for a small group of workers who had used a VDT with a high level of ELF magnetic fields (> 0.3 μT) was increased compared with workers using a terminal with a low level of magnetic fields. No significant associations were found between VLF magnetic fields and spontaneous abortion. The findings of the two studies do not necessarily contradict each other, since in the US study, there were no VDT models with ELF magnetic fields reaching the lower bound for the highest exposure category of the Finnish study.

2.2. Paternal exposure

Paternal employment in industries involving potential electromagnetic field exposure has been related to childhood cancer [29]. The results of various studies are, however, contradictory. In an initial study of paternal occupation and neuroblastoma, elevated risks were observed for employment in electrical occupations [30]. Two subsequent studies did not demonstrate significantly increased risks [31,32]. Elevated risks of central nervous system tumors were found for some electrical occupations in two studies [33,34], while a third study showed no association [35].

Other reproductive outcomes have also been occasionally related to paternal magnetic field exposure.

An Italian study [36] found that cases with infertility reported radioelectric work as their usual occupation more often than the controls. One study showed an excess of birth defects in the children of electronic equipment operators [37]. Decreased frequency of 'normal' pregnancy outcome, mainly due to increased frequency of congenital malformations, and fertility difficulties were observed among high-voltage switchyard workers [38]. No association was observed between semen abnormalities and job titles suggesting magnetic field exposure [39].

The present data for an increased risk of childhood cancer and adverse pregnancy outcome associated with electrical occupations are inconclusive, although there are some indications of elevated risks. The studies are subject to several methodological limitations. Exposure assessment is the most critical, because occupation is used as a surrogate for magnetic field exposure. There may also be some other important exposures in electrical occupations, which may have contributed to the increased risks.

2.3. Summary of the epidemiological studies

The epidemiologic evidence on the potential adverse effects of ELF magnetic fields on the reproductive health is controversial and inconclusive. The findings of the studies on birth defects, low birth weight, intrauterine growth retardation and preterm birth have mainly shown no association with exposure. The results on childhood cancer have been inconsistent. Spontaneous abortion is the only outcome for which there is some suggestive evidence of an association with ELF magnetic field exposure. An increased risk of spontaneous abortion was observed in three out of four study populations [15,16,28] exposed to high levels of magnetic fields (> 0.3 μT).

The validity of most of the epidemiologic investigations on ELF magnetic fields is weakened by methodological shortcomings. The most important weakness is inaccurate assessment of exposure. The studies have usually been retrospective. In this design, the assessment of exposure is particularly difficult, as all humans are, to some extent, exposed to magnetic fields from a wide variety of sources. Except for one investigation, the study subjects total field exposure, including all fields both in the work and home environment, has not been considered. Another limitation in many studies is small numbers of highly exposed subjects, making it impossible to draw conclusions on the effects of high levels of magnetic field exposure. Use of self-reported data on exposure makes also the results of several studies open to bias.

3. Animal studies

3.1. Studies using non-mammalian models

Several experiments have shown abnormalities in chick embryos following exposure to weak (about 1 μT) pulsed or sinusoidal MFs [1,40–44]. Other studies using chick eggs have not reported any significant increases in developmental abnormalities following exposure to MFs [45–47]. The conclusion of our earlier review [22] was: 'There are variations in the results, but the combined data suggest that there is a real effect modulated by some unknown biological or environmental variables'. Very little research on chicken embryos has been published since then. The present review focuses on studies on mammals.

3.2. Effects on prenatal development

Studies that have evaluated MF effects on prenatal development are summarized in Table 3. Tribukait et al. [48] exposed pregnant C_3H mice continuously from gestation day 0–14 either to 0.5 ms wide 100-Hz rectangular-shaped pulses (amplitude 1 μT or 15 μT, 2 μs rise and fall time) or to 20-kHz sawtooth MFs (1 μT or 15 μT p–p, rise time 45 μs and fall time of 5 μs). Increased number of fetuses with external malformations was noted when dams were exposed to the 15-μT sawtooth pulses. The increase was statistically significant when the analysis was based on individual fetuses but not when it was based on the number of affected litters. The number of fetuses with skeletal malformations was similar in the control and exposure groups. The frequency of malformations found in Tribukait's study, although statistically significant, was rather low suggesting that MF exposure was capable of influencing the development of only a few most sensitive individuals. The increase of external mal-

Table 3
Effects of alternating magnetic fields on prenatal development

Animal strain	Exposure time[a]	Frequency (Hz)	Waveform	Flux density (μT)	Number of litters[b]	Gross external or visceral malformations	Skeleton anomalies or malformations	Resorptions	Other	Reference
Mouse										
C_3H	0–14	100	Rectangular	1 (p–p)	109/28	–	–	–	–	[48]
	0–14	100	Rectangular	15 (p–p)	109/35	–	–	–	–	
	0–14	20 k	Sawtooth	1 (p–p)	109/76	–	–	–	–	
	0–14	20 k	Sawtooth	15 (p–p)	109/81	+	–	–	–	
CBA/S	0–18	20 k	Sawtooth	15 (p–p)	154/211	–	–	+	Dead fetuses ↑	[49]
	0–18	20 k	Sawtooth	15 (p–p)	111/142	–		+	–	
	1–18	20 k	Sawtooth	15 (p–p)	99/117	–		+	–	
	4–18	20 k	Sawtooth	15 (p–p)	98/137	–		+	–	
	6–18	20 k	Sawtooth	15 (p–p)	81/100	–		–	Body weight ↓ Length of fetuses ↓	
CBA/S	0–4.5	20 k	Sawtooth	15 (p–p)	100/113	–		–	Dead fetuses ↑ Body weight ↓ Length of fetuses ↓	[50]
	0–6	20 k	Sawtooth	15 (p–p)	103/120	–		–	–	
CBA/S	0–18	20 k	Sawtooth	15 (p–p)	75/84	–	–	(+)	–	[51] and unpublished
CBA/Ca	0–18	50	Sinusoidal	12.6	41/55	–	+	–	–	[51] and unpublished
	0–18	20 k	Sawtooth	15 (p–p)	41/53	–	+	–	–	
	0–18	50	Sinusoidal	126	34/31	–	+	–	–	
CD-1	0–17	20 k	Sawtooth	3.6	141/151	–	–	–	–	[56]
	0–17	20 k	Sawtooth	17 (p–p)	141/163	–	–	–	–	
	0–17	20 k	Sawtooth	200 (p–p)	141/144	–	–	–	–	
CD-1	0–17	50	Sinusoidal	20 000	86/90	– ↓	(+)	–	Body weight ↑ Length of fetuses ↑ (live implants ↑)	[55]

Swiss Webster	5–16	15.6	Sawtooth	40 (p–p)	24/21	(+)	(+)	–	–	[62]
Rat										
SRPD	−15–21	18 k	Sawtooth	5.7 (p–p)	20/20	–	–	–	–	[52]
	−15–21	18 k	Sawtooth	23 (p–p)	20/20	–	–	–	–	
	−15–21	18 k	Sawtooth	66 (p–p)	20/20	–	+	–	Maternal hematology	
SRPD	0–20	60	Sinusoidal	0.6	170/174	–	–	–	–	[59]
	0–20	60	Sinusoidal	1000	170/175	–	–	–	–	
SPRD	6–19	60	Sinusoidal	2	55/48	–	–	–	–	[57]
	6–19	60	Sinusoidal	200	55/46	–	–	–	–	
	6–19	60	Sinusoidal	1000	55/51	–	–	–	–	
	6–19	60	Intermittent	1000	55/51	–	–	–	–	
SPRD	multi-generation	60	Sinusoidal	2	40/40[c]				–	[58]
		60	Sinusoidal	200	40/40				–	
		60	Sinusoidal	1000	40/40				–	
		60	Intermittent	1000	40/40				–	
Wistar	0–20	50	Sinusoidal	12.6	58/64	–	+	–	Implants ↑	[53]
	0–20	20 k	Sawtooth	15 (p–p)	58/64	–	+	–	–	
Wistar	0–19	50	Alternating	30 000	12/12	–	+	–	–	[54]

[a] Days of gestation starting from day 0.
[b] Number of litters in the control groups/number of litters in the exposure group.
[c] Number of breeding pairs.
+ = findings; (+) = a trend; − = no findings; empty = not determined; ↑ = increased; ↓ = decreased.

formations reported by Tribukait et al. [48] has not been confirmed by other studies.

Frölén et al. [49] used CBA/S mice and exposed them to a 20-kHz sawtooth field similar to that used by Tribukait et al. [48]. In the first two experiments, pregnant animals were exposed throughout the entire gestational period (days 1–19 postconception (pc)). In the other three experiments, the onset of MF exposures was on day 2, 5 or 7 pc. All exposures were continuous and terminated on day 19 pc at which time the fetuses and the uteri were examined. External or skeletal (skeletons were examined only in Expt. 1) malformations were not significantly increased. In all groups in which MF exposure started on day 5 pc or earlier, the placental resorptions (fetal loss) were significantly more frequent than in controls. The increased resorption rate was not reflected in a reduction in litter size or in the number of litters. An increased number of dead fetuses was noted in the exposed group in the first experiment. The body mass and the length of exposed mouse fetuses were significantly reduced when the MF treatment began on day 7 pc.

Svedenstål and Johanson [50] continued the studies of Frölén et al. [49] to determine the critical exposure time. Additionally, they studied whether implantation time, serum progesterone or Ca^{2+} levels were affected by MFs. Pregnant CBA/S mice were exposed or sham-exposed to a 20-kHz, 15 μT MF continuously from day 1 pc until day 5.5 pc or until day 7 pc. No significant increase in resorption rate was found in the exposed animals at termination on day 19 pc. The percentage of dead fetuses was significantly increased after exposure on days 1 to 5.5, but only a tendency was seen after exposure on days 1 to 7. The body weight and length of the living fetuses were also significantly decreased in animals exposed during days 1–5.5 pc. No significant differences in progesterone or calcium were found. The implantation time was not affected, but only 5 to 11 animals were used per group and the evaluation was done only once daily. The authors reported a significantly increased number of implants when Frölén's [49] and their data were analyzed together.

Since Frölén's study reported, in contrast to most other studies, robust effects on prenatal development in mammals, an attempt was made to replicate the findings [51]. A slight increase of resorptions was observed, but the difference was smaller than that found in Frölén's study. The result was not significantly different either from the no effect hypothesis or from Frölén's data. The authors concluded that, together with the observations of Frölén et al., the results were more for than against increased resorptions in CBA/S mice exposed to 20-kHz MFs. In addition to replicating Frölén's experiment with CBA/s mice, the study also included experiments with a closely related strain CBA/Ca. No increase of resorptions was found in the CBA/Ca mice exposed to the 20-kHz magnetic field or to 50-Hz sinusoidal fields at 13 or 130 μT, suggesting that MF-induced resorptions are highly strain-specific.

Stuchly et al. [52] exposed Sprague-Dawley (SPRD) rats to 18-kHz MFs with sawtooth waveform (44 μs rise time, 12 μs fall time) at three magnetic field intensities (5.7, 23, or 66 μT p–p) for 7 h per day. The exposure started 2 weeks prior to mating and continued throughout pregnancy. No treatment-related differences were noted in maternal parameters (except for erythrocyte, leucocyte and lymphocyte counts), fetal weight, or malformations. A significant decrease in the incidence of bipartite or semipartite thoracic centra was noted in the two highest exposure groups and significantly increased number of fetuses (but not litters) with minor skeletal anomalies in the highest exposure group. The authors concluded that the skeletal findings were just statistical noise.

Huuskonen et al. [53] reported that the number of fetuses with minor skeletal anomalies was significantly higher than in controls when Wistar rats were exposed to a 50-Hz sinusoidal MF with a flux density of 12.6 μT r.m.s. or to a 20-kHz sawtooth MF with a flux density of 15 μT (p–p) on days 0–20 of gestation for 24 h/day. There was a tendency towards slightly different effects at the two frequencies. At 50 Hz, minor skeletal malformations were significantly increased. At 20 kHz, most of the increase was due to an increased number of variations that occur also spontaneously in unexposed animals. The number of implants was slightly increased at 50 Hz. No effects on the incidence of external or visceral malformations or resorptions were found.

Minor skeletal fetal anomalies were increased in Wistar rats exposed to a 50-Hz MF with a flux density of 30 mT from day 1 to day 20 of pregnancy

[54]. No other effects were found. Increased skeletal ossification was noted, possibly indicating an accelerated prenatal development (extra thoracic ribs, particularly comma-shaped). A significantly lower number of fetuses with reduced ossification of pelvic bones were also observed indicating that ossification was accelerated by magnetic field exposure.

Increased skeletal variations have been observed also in mice, in connection with the studies on increased resorptions in mice [51]. Unpublished observations from these experiments showed an increased number of fetuses with skeletal variations in CBA/Ca mice (45 to 56 animals per group) exposed to 50-Hz (13 μT or 130 μT) or 20-kHz (15 μT p–p) magnetic fields.

Pregnant CD-1 mice were exposed or sham-exposed from day 0 to day 17 of gestation to a 50-Hz sinusoidal MF at 20 mT and the development of the fetuses was evaluated [55]. Magnetic field exposure was associated with longer and heavier fetuses at term, even when adjusted for litter size, and with fewer external abnormalities. The most common external malformations in control animals were exencephaly, cleft palate and open eye. The incidence of fetuses with brain abnormalities was not significantly different in the exposed group compared with the sham-exposed group. The incidence of fetuses with one or more cervical ribs was statistically significantly increased, but this was not significant when analyzed using techniques accounting for possible litter effects. The number of resorptions and other parameters measured were unaffected.

Several studies in mice or rats have been negative in all parameters studied (e.g. [56–59]). Wiley et al. [56] tested the teratogenic potential of VDT-like sawtooth MFs on CD-1 mice. Animals were exposed throughout gestation to 20-kHz fields (45 μs rise time, 5 μs fall time, [60]) with field strengths of 0, 3.6, 17, or 200 μT (p–p). No treatment-related adverse effects were found on maternal weight gain, fetal weight, number of implants, or number of live and/or dead embryos/fetuses, or gross external, visceral or skeletal malformations.

Continuous or intermittent (1 h on/1 h off) exposure to 60-Hz MFs during the period of major organogenesis did not have adverse impact on fetal development in Sprague-Dawley rats [57]. In this study, timed-pregnant females received continuous (18.5 h/day) exposure to linearly polarized, sinusoidal 60-Hz MF at field strengths of 0, 2, 200 or 1000 μT, or intermittent (1 h on/1 h off) exposure at 1000 μT from gestation days 6 through 19. Statistically significant differences were seen in several parameters (e.g. decreased preimplantation loss at 200 and 1000 μT) but were considered non-significant by the authors.

A reproductive assessment by continuous breeding (RACB) study on the reproductive toxicity of 60-Hz magnetic fields was conducted by Ryan et al. [58]. The RACB protocol permits the evaluation of reproductive performance over multiple generations. Rats were exposed continuously for 18.5 h per day to continuous 60-Hz MFs at field strengths of 0, 2, 200 or 1000 μT or to an intermittent (1 h on, 1 h off) MF at 1000 μT. No statistically significant effects on any reproductive parameter (malformations or anomalies were not studied) were found in any generation.

Rommereim et al. [59] reported no effects in Sprague-Dawley rats exposed throughout gestation 20 h per day to 60-Hz MFs at field strengths of 0.1, 0.6 or 1000 μT. A decrease in the number of fetuses per litter was found in the first study, but this decrease did not repeat in a replicate study.

A prenatal exposure to low-frequency MFs seems not to result in strong effects on prenatal development in mammals. Gross external, visceral or skeletal malformations are not increased by fields up to 20 mT. The only findings that show some consistency are minor skeleton alterations in several experiments and increased resorptions in CBA/S mice.

Minor skeletal changes have been observed in several rat and mouse strains, at both ELF and VLF frequencies. Skeletal variations are a relatively common finding in teratological studies and all of the skeletal changes reported were minor and unlikely to impair later development. Many of the skeletal anomalies were significant only if statistical analyses were done on individual fetuses rather than on litters. Nevertheless, some subtle effect of magnetic fields on skeletal development cannot be ruled out. The successful use of low-frequency MFs for facilitating bone healing [61] also suggests that MF may affect growth and proliferation of bone tissue.

The finding of increased resorptions in CBA/S mice was robust and repeatable in one laboratory, but the replication study [51] gave only limited support to this finding. The finding of no resorptions in a closely related strain (CBA/Ca) suggests that the effect may be strain specific. The possible effects of MFs on the survival of early embryos should be further investigated.

3.3. Interactions with known teratogens

Chiang et al. [62] exposed Swiss Webster mice to a 15.6-kHz MF with a sawtooth waveform (52 μs rise time, 12 μs decay time, peak magnetic flux density 40 μT) for 4 h daily on days 6–17 of gestation. The development of cytosine arabinoside induced cleft lip and/or cleft palate was enhanced in the MF-exposed animals. The incidence of these malformations was increased also in MF only exposed fetuses, but this finding was not significant when the analysis was done on litters. This interesting finding indicates that MFs might interact with known teratogenic agents in a way analogous to their suspected interaction with carcinogenic agents (tumor promotion). The possible mechanisms of the co-carcinogenic effects of MFs are discussed by Löscher and Liburdy elsewhere in this issue. Interaction with other teratogens might also partly explain the inconsistent findings of studies on the teratogenic effects of MF; due to differences in food and environmental conditions, the presence of weak embryotoxic agents may vary between studies. No supporting evidence for the interaction of MFs and teratogenic chemicals is available from other studies. The possible co-teratogenic effects of MFs should be further evaluated.

3.4. Postnatal and behavioral effects

Several authors have reported changes in body weights or organ weights and controversial effects on a number of other developmental and behavioral indices in rodents following a prenatal, and sometimes postnatal, exposure (Table 4).

Rivas et al. [63] exposed Swiss mice to 50-Hz pulsed (5 ms) MF at either 2.3 mT or 83 μT from birth to day 120 for the first generation and from the conception and throughout embryological development up to day 120 for the second generation. In the first generation no changes were observed in body weights, serum glucose, protein, cholesterol, or triglyceride levels. In the second generation, body weights and serum glucose levels of the exposed mice were significantly lower after 60 and 120 days and the triglyceride level was decreased at 120 days.

Zusman et al. [64] found that the weight of Sprague-Dawley rat offspring was reduced at day 1 of age after continuous exposure to a pulsed 20-Hz electromagnetic field throughout gestation, but increased after exposure to a 100-Hz field. The weights of rat offspring exposed to a 50-Hz field were decreased only from 21 to 28 days of age. Delayed eye opening was observed but no effect on the surface righting reflex. The field intensities used in this study are not known due to inadequate data given in the article.

The brain weight was decreased on postnatal day 308 in C57/Bl mice after prenatal exposure (gestation days 0–19) to a 20-kHz (15 μT) magnetic field. Decreased DNA level and increased activities of 2′,3′-cyclic nucleotide 3′-phosphodiesterase (a marker for oligodendrocytes), acetylcholine esterase and nerve growth factor protein were observed on postnatal days 21 and/or 308 in brain cortex [65].

Increased male accessory-sex organ weights were noted in Sprague-Dawley rats prenatally exposed to a 15-Hz pulsed magnetic field with 0.3 ms pulse duration, 330 μs rise time and peak intensity of 800 μT [66]. Pregnant animals were exposed for two 15-min periods on days 15–20 of gestation. At birth, no treatment-related effects on offspring of exposed dams were noted for number of live fetuses, average weight, or anogenital distance. At day 120 postpartum, circulating testosterone, LH and FSH, testis and accessory sex organ weights and scent marking behaviors were analyzed in males. Exposed male rats exhibited diminished territorial scent marking behavior as adults. The authors concluded that MF exposure had caused an incomplete masculinization in the animals. Maternal stress is known to affect masculinization in rodents [67].

Effects on postnatal development and behavior of prenatally exposed CD1 mice were studied by Sienkiewicz et al. [68]. The animals were exposed or sham-exposed throughout gestation to a 50-Hz, 20 mT MF. Three possible field-dependent effects were found: the exposed animals performed the air righting reflex earlier (about 2 days), the exposed males were significantly lighter in weight at 30 days of age

Table 4
Effects of prenatal exposure of alternating magnetic fields on postnatal development

Animal strain	Exposure time[a]	Frequency (Hz)	Waveform	Flux density (μT)	No. of dams[b]	Body weight changes	Changes in developmental indices	Behavioral changes	Other	Reference
Mouse										
Swiss	Pre- and postnatal	50	Pulsed	83	28/29[c]	+ ↓			Serum chemistry	[63]
		50	Pulsed	2300	29/29[c]	+ ↓			Serum chemistry	(2nd generation)
CD-1	Gestation	50	Sinusoidal	20 000	21/23	+ ↓	+	+	−	[68]
CD-1	Gestation	50	Sinusoidal	5000	8/7			−		[70]
C57/Bl	0–19	20 k	Sawtooth	15 (p–p)	15/15				Brain weight ↑ neurochemical changes	[65]
Rat										
Wistar	0–19	Static		30 000	12/12	+ ↑	−	−	−	[54]
SPRD	15–20	15	Pulsed	800 (p–p)	6/6	−	−	+	Organ weights	[66]
SPRD	Gestation	20	Pulsed	?	9/10	+ ↑ ↓	+		Litter average ↓	[64]
	Gestation	50	Pulsed	?	9/11	+ ↑ ↓	+		Litter average ↓	
	Gestation	100	Pulsed	?	9/12	+ ↑ ↓	+		Litter average ↓	
SPRD	Pre- and postnatal	60	?	100	20/21[c]	−	+	−		[69]

[a] days of gestation starting from day 0.
[b] number of litters in the control group/number of litters in the exposure group.
[c] number of animals examined.
+ = findings; (+) = a trend; − = no findings; empty = not determined; ↑ = increased; ↓ = decreased.

and the exposed animals remained on a Rota-rod for less time as juveniles. No field-dependent effect on the surface righting reflex or eye opening was reported, in contrast to the findings of Zusman et al. [64]. There was a suggestion that exposed animals took slightly longer to avoid a cliff edge, although this difference was of borderline significance. A slight increase in activity (in the activity wheel) by the exposed females and a slight decrease in activity by the exposed males was noted, but these were considered by the authors not to be of any biological significance. A reduction in running time on a Rota-rod which was found in juvenile mice may represent a MF-induced impairment in motor coordination during adolescence. Any gross impairments in the postnatal development or behavior of mice were not found.

Altered behavior several months after combined, fetal–neonatal exposure to an electromagnetic field has been reported [69]. Rats were sham-exposed or exposed perinatally to a 60-Hz electromagnetic field, for 22 days in utero and the first 8 days postpartum. Each of the 30 once-daily exposures was 20 h in duration. The electric component of the field was vertical 30 kV/m r.m.s., and the magnetic field component was 100 μT r.m.s. Later, as adults, male rats were trained to emit an operant response when reinforced with food on a multiple, random-interval schedule. Exposed rats gradually came to respond at significantly lower rates than did sham-exposed controls. After a sequence including operant conditioning followed by experimental extinction of responding and then by a suspension of conditioning and finally by more than a month of reconditioning, slower rates of responding were found to persist in the previously exposed adult animals. Field-exposed rats did not differ from sham-exposed rats in terms of body mass, physical appearance, grossly observed activity level, or incidence of disease.

Prenatal exposure to a 50-Hz, 5 mT MF had no effect on spatial learning in adult CD-1 mice [70].

The reported effects on body weight after prenatal exposure to MF are controversial. Effects on developmental indices, behavior and learning have been reported in several studies. Changes in postnatal behavior and performance might indicate subtle changes in the brain during prenatal development. Neurochemical changes have been reported in mice after prenatal exposure [65]. Neural tube changes have been observed in early chicken embryos exposed to MF [42]. Evaluation of the consistency of the findings is difficult due to the different methods used in different studies, but slight effects cannot be excluded.

3.5. Effects on male reproduction

A flow cytometry study was performed to monitor the effects of 50-Hz MF (1.7 mT) on mouse spermatogenesis [71]. In groups exposed for 4 h a statistically significant decrease in elongated spermatids was observed at 28 days after the treatment, suggesting a possible cytotoxic and/or cytostatic effect on differentiating spermatogonia.

3.6. In *vitro* effects

Exposure of day 10.5 Hebrew University Sabra strain rat embryos in vitro to a 50-Hz or 70-Hz pulsed electromagnetic field resulted in retarded development and an increased incidence of developmentally malformed embryos after 48 h of exposure [64]. The main malformations were absence of telencephalic, optic and otic vesicles and of forelimb buds. In Hebrew University mouse preimplantation embryos, a significant increase in the percentage of embryos with arrested development was seen after 72 h of exposure to 20-Hz or 50-Hz fields. More than 50% of blastocysts were inhibited from hatching and further development. Among those embryos which continued to develop, no exposure-related differences were noted in the rate of development. The field intensity used in the experiments by Zusman et al. are not known due to inadequate data given in the article.

In vitro development of CBA/S mouse embryos was not affected by exposure to a 50-Hz magnetic field at 13 μT [72].

3.7. Summary of animal studies

The results of animal studies are inconsistent. Different studies have found effects on different endpoints, while many studies have reported no effects on any endpoint evaluated. A possible explanation for these inconsistencies is that there are no biological effects of weak low-frequency MFs. Another possibility is that MFs affect animal reproduction, but the results vary because of differences in experimental conditions. The studies have used different durations of daily exposure, and the timing of exposure has varied in relation to stage of embryonal development [22]. Animal strain is an important variable. It is common in teratological evaluations that a certain strain may respond to a given chemical or physical agent, while no effects are found in another species or another strain of the same species. The type of effect seen also varies between strains. Studies on low-frequency MFs are further complicated by the fact that the interaction mechanisms are not known. Because of the unknown mechanisms, it is not known which aspects of MF exposure are essential for the biological effects. In addition to the frequency, waveform, intensity, duration and timing of MF exposure, there are various other exposure parameters that may be of importance, such as direction of the field or the strength and direction of the static MF of the earth. These and several other exposure parameters [73] have generally not been controlled in the experiments, which may explain part of the inconsistencies between studies.

Overall, animal studies indicate that the possible teratogenic or reproductive effects of low-frequency MFs are not strong. The proportion of affected fetuses has been low in all studies, and only minor alterations have been seen in the indices of postnatal development and behavior. Subtle effects cannot be ruled out, however.

4. Discussion

Both epidemiological and animal studies indicate that low-frequency magnetic fields do not exert strong effects on embryonal development. No gross malformations have been found in animal studies, and epidemiological studies have not shown evidence of an excess of birth defects. There is some epidemiological evidence of an increased risk of spontaneous abortion, and experimental studies have also provided suggestive evidence of increased fetal loss (resorptions) in one animal strain. However, the epidemiological results have involved populations exposed to ELF magnetic fields, but the animal studies were conducted using VLF fields.

There is no direct epidemiological evidence to support the minor skeleton changes seen in animal studies, but the successful medical use of MFs in bone healing [61] indicates that MF exposure might affect bone formation in humans.

It has been suggested that deficits in body weight are sensitive indicators of developmental toxicity [74]. Some animal studies have indicated decreased fetal weight or size, but most studies have shown no changes, and one study reported increased weight and length of fetuses. The epidemiological data available on low birth weight or intrauterine growth retardation are very limited, but no statistically significant effects have been reported.

Postnatal effects similar to the behavioral and developmental changes seen in prenatally exposed animals have not been evaluated in any epidemiological study. The epidemiological results on childhood cancer are inconsistent, and there are no experimental results that would support such effects in animals.

Only slight increases have been reported in any parameters used for measuring embryonal damage, suggesting that maternal MF exposure might affect only a small portion of the embryos. This may indicate that MFs are embryotoxic only together with other environmental or genetic risk factors, consistently with the co-teratogenic effects of MF exposure reported by Chiang et al. [62].

The epidemiological studies on the effects of paternal exposure are contradictory and inconclusive. The results of the multigeneration animal studies do not suggest any major effects of MF on male reproduction.

In epidemiological studies, some effects have been reported at ELF magnetic flux densities below 1 μT. In animal studies, however, the weakest fields that have produced any effects have been 13 μT (50 Hz) or 15 μT (20 kHz). The field intensities, however, should not be directly compared without considering the interaction mechanisms. Direct comparison of the intensities (at the same frequency) is possible only if it is assumed that the biological effects of MFs are based on direct magnetic interaction. If the bioeffects are caused by the electric currents induced by MF, then body size and orientation should also be taken into account. The eddy currents induced by alternating magnetic fields increase with increasing body size [e.g. [75]].

There is very little data on exposure–response relationships. Most of the experimental studies have not tested the effects of different magnetic field intensities. Of the three field strengths used by Stuchly et al. [52], only the highest (66 μT) was associated with significantly increased minor skeleton anomalies. Other studies with different magnetic field intensities reported negative results [56–59]. Most epidemiological studies have used dichotomous exposure classifications and provide therefore no information about the exposure–response relationship. The data of Lindbohm et al. [28] suggests a relationship between spontaneous abortions and magnetic field intensity, with the increased risk seen only for those VDTs emitting ELF fields above 0.3 μT. In the study by Juutilainen et al. [16], the increased risk of early pregnancy loss was associated with fields above 0.6 μT, but not with those between 0.1 and 0.6 μT. In a reanalysis, the data were more consistent with a threshold at 0.5–1 μT than a linearly increasing risk [76]. A threshold-type exposure–response relationship, with a threshold at about 1.3 μT was previously reported in chicken embryos [43]. The possible existence of a threshold should be considered in the interpretation of epidemiological results. Many epidemiological studies have had very little power to detect possible risks associated with fields above 1 μT; the highest exposures have typically been relatively low.

There are more animal studies reporting effects at VLF than at ELF frequencies. However, comparing the effects of different frequencies is difficult because each study has typically used only one frequency. Huuskonen et al. [53] found increased minor skeleton anomalies at both 50 Hz and 20 kHz. All epidemiological studies have involved exposure to ELF (50 or 60 Hz) MFs. VDT workers are exposed to both ELF and VLF frequencies, but epidemiological studies have not provided evidence for an association between pregnancy outcome and the weak VLF emissions of VDTs.

The biophysical and biological mechanisms by which low-frequency MFs could affect reproduction and development are not known. Several hypothetical mechanisms have been proposed, and ELF magnetic fields have been reported to affect many cellular processes, including, e.g. signal transduction, gene expression, cell proliferation and intercellular communication (Löscher and Liburdy, this issue). Such effects could theoretically disturb embryonal development and/or implantation process. Suppressed melatonin production caused by maternal MF exposure could also lead to altered reproductive functions. The pineal hormone melatonin has a regulatory action on hormones, including estrogen. MF exposure has been reported to decrease the nocturnal serum and pineal melatonin levels in animals, although not consistently in all studies ([77,78]; see also Löscher and Liburdy, this issue), and recent epidemiological studies indicate that occupational MF exposure may suppress melatonin production also in humans [79,80].

5. Conclusions

The epidemiologic evidence does not, taken as a whole, suggest strong associations between exposure to ELF magnetic fields and adverse reproductive outcome. An effect at high levels of exposure cannot be excluded, however. Further research is needed with improved study design and particularly with improved exposure assessment. In these studies, it would be important to ensure the inclusion of a sufficient number of subjects exposed to high levels of ELF magnetic fields. There is also a need for descriptive data on exposure to magnetic fields in various occupational and environmental settings. These data would be valuable for the assessment of exposure and reasonable restriction of the study population to exposed groups in future epidemiologic investigations.

Animal studies do not suggest strong effects on embryonal development or reproduction. If effects exist, only a small percentage of the embryos is affected. The apparently weak embryonal effects of MF exposure might express themselves as early deaths (resorptions), minor skeleton changes, or slight changes detectable only by postnatal observations, depending on the presence of other external or internal (genetic) factors that interact with the MF. Further studies should address effects on early embryonal development, postnatal effects of prenatal exposure and interactions of magnetic fields with known teratogens.

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