

10 REPRODUCTION AND DEVELOPMENT

The effects of exposure to low frequency EMFs on fertility, reproduction, prenatal and postnatal growth and development have been investigated in epidemiological and laboratory studies for a number of years. Epidemiological studies have examined reproductive outcome in relation to visual display terminal use, and to residential exposure, especially in relation to electrically heated beds. Experimentally, this issue has been addressed in studies of effects on mammalian and non-mammalian species, particularly birds. Several comprehensive reviews are available (e.g. AGNIR, 1994; Brent et al., 1993; Brent, 1999; Huuskonen, Lindbohm & Juutilainen, 1998; IARC, 2002; ICNIRP, 2003; Juutilainen, 2003; Juutilainen & Lang, 1997; McKinlay et al., 2004; NIEHS, 1998).

10.1 Epidemiology

10.1.1 Maternal exposure

10.1.1.1 Video display terminals

A number of epidemiological studies have investigated possible association of adverse pregnancy outcome with the use of video display terminals during pregnancy (for reviews, see Brent et al., 1993; Delpizzo, 1994; IARC, 2002; Juutilainen, 1991; Parazzini et al., 1993; Shaw, 2001; Shaw & Croen, 1993). The electromagnetic fields emitted by video display terminals include ELF as well as higher frequencies up to 100 kHz. In general, these studies have not suggested increased risks for spontaneous abortion, low birth weight, pre-term delivery, intrauterine growth retardation, or congenital abnormalities. However, most of the studies did not include any measurements of ELF field exposure. The average exposure of a video display operator is typically low (around 0.1 μT), so these studies are not informative for assessing possible effects associated with higher exposures. Lindbohm et al. (1992) carried out measurements of the field emissions of displays used by the study subjects, and observed an increased odds ratio (3.4; 95% CI: 1.4–8.6) for spontaneous abortions among women who used the few video display terminal types that had unusually high ELF magnetic field emissions ($> 0.9 \mu\text{T}$ peak-to-peak value). Another study that included ELF field measurements (Schnorr et al., 1991) did not report any association with field exposure. The strongest fields to which subjects were exposed in this study were weaker than those in the Lindbohm study.

10.1.1.2 Electrically heated beds

Electric blankets and electrically heated waterbeds can significantly increase exposure to ELF magnetic and electric fields, because 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 waterbeds are exposed to flux densities of 0.3–0.5 μT (Bracken et al., 1995; Florig & Hoburg, 1990; Kaune et al., 1987). The use of these devices may also result in increased maternal heat stress.

The first suggestion of harmful effects of electric blankets and heated waterbeds came from the study by Wertheimer & Leeper (1986). They examined seasonal patterns of foetal growth and spontaneous abortion rate among the users of heated beds, and reported that these outcomes were associated with conception in the winter months, and hence with use of bed heating. This study, however, has been criticized for several methodological shortcomings (Chernoff, Rogers & Kavet, 1992; Hatch, 1992). The findings of the studies on electrically heated beds and birth defects have been mostly negative. The use of electric blankets or heated waterbeds was not related to neural tube defects, oral cleft defects, or urinary tract defects (Dlugosz et al., 1992; Milunsky et al., 1992; Shaw et al., 1999). In the study of Li, Checkoway & Mueller (1995) electric blanket use was not associated with an increased risk of urinary tract anomalies. However, in a subgroup of women (37 cases, 85 controls) with a history of sub-fertility, an odds ratio of 4.4 was observed (95% CI: 0.9-23).

All the above studies were retrospective and assessment of exposure was usually based on self-reported data on the use of heated beds. Thus, incomplete information of exposure level (which varies between different types of electric blankets and waterbeds) and biased reporting of exposure may have influenced the findings. These difficulties were partly overcome in a prospective study (Bracken et al., 1995). In this study, exposure was estimated by measurements of magnetic fields produced by electric blankets and waterbeds and using interview data on hours of daily use. Low birth weight and intrauterine growth retardation were not related to use of electrically heated beds during pregnancy. The same group also examined the occurrence of spontaneous abortion in women who used electric blankets or electrically heated waterbeds (Belanger et al., 1998). The use of electric blankets did result in an increased risk ratio (1.8; 95% CI: 1.1–3.1), whereas the use of waterbeds or wire codes indicating elevated ELF field exposure were not associated with increased risk. In another prospective study (Lee et al., 2000), no increased risks of spontaneous abortions were found for users of electric blankets (OR = 0.8; 95% CI: 0.6–1.2) or waterbeds (OR = 1.0; 95% CI 0.7–1.3). No increase of risk with increasing setting-duration combination of electrically heated bed use was observed. The adjusted odds ratio for the twenty women who used electric blankets at high setting for 1 hour or less was 3.0 (95% CI: 1.1–8.3), but there were no spontaneous abortions among the women (n = 13) who used a high setting for 2 hours or more.

Overall, the studies on electrically heated beds have not provided convincing evidence for an association with adverse pregnancy outcomes. This view is supported by reviews from the UK Advisory Group on Non-ionising Radiation (AGNIR, 1994) and more recently from the Health Council of the Netherlands (HCN, 2004). There is some indication of different patterns of results for waterbeds and electric blankets. For use of waterbeds during pregnancy, the risk estimates have generally been close to 1.0, while higher (and in some cases statistically significant) risk estimates have been reported for electric blankets, particularly among those women who used the high power setting of electric blankets. This pattern of results could be inter-

puted to reflect the higher magnetic fields produced by electric blankets (compared to waterbeds), or higher thermal stress experienced by the users of electric blankets.

Table 67 summarizes the results of epidemiological studies investigating various reproductive outcomes in humans exposed to different ELF sources.

Table 67. Epidemiological studies on reproductive outcome

Endpoint	Study population	Exposure (EB: electric blankets; WB: electrically heated water beds)	Relative risk (95% CI)	Authors
Miscarriage Low birth weight	673 cases, 583 controls	EB WB	not determined	Wertheimer & Leeper, 1986
Miscarriage	Prospective study, n = 2967	EB, use at conception	1.74 (1.0–3.2)	Belanger et al., 1998
		EB, use at interview	1.61 (0.8–3.2)	
		EB, high setting at conception	1.65 (0.6–4.9)	
		EB, high setting at interview	2.05 (0.7–4.7)	
		WB, use at conception	0.59 (0.3–1.1)	
		WB, use at interview	0.63 (0.4–1.1)	
		WB, high setting at conception	0.59 (0.3–1.1)	
	WB, high setting at interview	0.49 (0.2–1.1)		
Miscarriage	Prospective study, n = 5144	EB	0.8 (0.6–1.2)	Lee et al., 2000
		EB, high setting	1.6 (0.6–3.3)	
		WB	1.0 (0.7–1.3)	
		WB, high setting	1.0 (0.7–1.5)	
Low birth weight Intrauterine growth retardation	Prospective study, n = 2967	EB or WB, low setting ^a	1.2 (0.5–2.8)	Bracken et al., 1995
		EB or WB, high setting ^a	1.2 (0.6–2.5)	
		EB or WB, low setting ^a	0.8 (0.4–1.7)	
		EB or WB, high setting ^a	1.6 (1.0–2.6)	
Neural tube defects Oral cleft defects	535 cases, 535 controls	EB	0.9 (0.5–1.6)	Dlugosz et al., 1992

Table 67. Continued

		WB	1.1 (0.6–1.9)	
		EB	0.7 (0.4–1.2)	
		WB	0.7 (0.4–1.1)	
Neural tube defects	Cohort, n = 23491	EB	1.2 (0.5–2.6)	Milunsky et al., 1992
Neural tube defects	Two studies, 1455 cases, 1754 controls in total	EB (study 1)	1.8 (1.2–2.6)	Shaw et al., 1999
		EB (study 2)	1.2 (0.6–2.3)	
		WB (study 1)	1.2 (0.8–1.8)	
		WB (study 2)	1.2 (0.8–1.9)	
CLP, isolated ^b		EB	0.8 (0.5–1.5)	
		WB	1.0 (0.7–1.5)	
CLP, multiple ^c		EB	1.3 (0.5–3.4)	
		WB	1.8 (1.0–3.2)	
Urinary tract anomalies (UTA)	118 cases, 369 controls	EB	1.1 (0.5–2.3)	Li, Checkoway & Mueller, 1995
UTA, subfertile women	37 cases, 85 controls			
		WB	0.8 (0.3–2.7)	
		EB	4.4 (0.9–23)	

^a Exposure during 3rd trimester. Odds ratios were lower for exposures estimated for earlier periods of pregnancy.

^b Cleft lip with/without cleft palate, no other (or only minor) anomalies.

^c Cleft lip with/without cleft palate with at least one accompanying major anomaly.

10.1.1.3 Other residential and occupational exposure

Several studies have investigated residential ELF exposures other than heated beds. Wertheimer & Leeper (1989), using an approach similar to their earlier study on electric blankets and waterbeds (Wertheimer & Leeper, 1989), reported that monthly rate of foetal loss was correlated with monthly increase of heating degree days (= need of heating) in homes with ceiling cable heat (which was reported to expose the occupants to magnetic fields of about 1 μ T), but not in homes without such heating. No association with pregnancy outcome has been seen in studies that have assessed magnetic field exposure using wire codes (a method of classifying dwellings based on proximity to visible electrical installations, widely used in epidemiological studies on childhood cancer – see chapter 11) or proximity to power lines.

Measurement-based exposure assessment has been used in five studies. One study showed a suggestive association (OR = 5.1; 95% CI: 1.0–26) between early pregnancy loss and magnetic fields above 0.63 μT measured at the front door (Juutilainen et al., 1993). The preclinical miscarriages studied by Juutilainen et al. may be etiologically different from the clinically observed miscarriages investigated in the other studies. Fields above 0.2 μT measured in residences were not associated with miscarriages, low birth weight or pre-term delivery (Savitz & Ananth, 1994). These two studies had small numbers of exposed women, and used spot measurements to characterize the magnetic field levels of the subjects' homes. Spot measurements have been shown to be correlated with personal exposure, but their use may result in significant misclassification (Eskelinen et al., 2002). A prospective study (Bracken et al., 1995) used a wrist-worn meter to assess personal average exposure during seven days. Exposure to fields above 0.2 μT was not statistically significantly associated with low birth weight or intrauterine growth retardation.

Another prospective cohort study assessed the association of personal measured ELF magnetic field exposure with spontaneous abortion (Li et al., 2001). The association with time-weighted average (TWA) magnetic field exposure was not significant. However, a significantly increased risk (OR = 1.8; 95% CI: 1.2–2.7) was found when the exposure metric used was maximum exposure above 1.6 μT . The association was stronger for early miscarriages (<10 weeks of gestation). Analysis of dose-response showed weakly rising risk with magnetic field “dose”, measured as the product of field level and duration above 1.6 μT (in μT s). The association was more pronounced (OR = 2.9; 95% CI: 1.6–5.3) among those women who indicated that the measurement (by body-worn meter) had been taken on a “typical day”, possibly reflecting lower exposure misclassification among these subjects. The risk was further increased for subjects who had a history of difficulties during pregnancy.

A nested case-control study with personal exposure measurements (Lee et al., 2002) reported findings that were in certain respects similar to those of Li et al. (2001). In the study by Lee et al. miscarriages did not show a significant association with TWA magnetic fields (although a suggestive step function response was seen with higher TWA quartiles). Statistically significant associations, and dose response trends with increasing exposure quartiles, were found for two personal exposure metrics – maximum exposure and rate-of-change of the magnetic field – but the value of these metrics has not yet been established.

Lee et al. (2002) also conducted a prospective substudy of 219 participants of the same parent cohort. The results of the prospective substudy were consistent with those of the case-control study, suggesting increased miscarriage risk associated with high rate-of-change and maximum field values. Unlike the nested study results, the personal TWA exposure at home (but not total 24-h TWA exposure) showed a significantly increased risk for fields above 0.2 μT (OR = 3.0; 95% CI: 1.1–8.4).

Savitz (2002) hypothesized that the apparent association with peak exposures and magnetic field variability might be explained by lower mobility of subjects who experience nausea, which is known to be less common among women who will miscarry. In their response, Li & Neutra (2002) provided evidence against this hypothesis using data from the prospective study by Li et al. (2001). However, McKinlay et al. (2004) noted that the parameter that provided evidence of a risk – namely maximum magnetic fields – was not chosen *a priori* on the basis of aetiological plausibility (Li & Neutra, 2002). In addition, the results were sensitive to the choice of breakpoint, which was made on the basis of the observations; and the study was not a standard prospective study as more than half of the miscarriages (and all those at all strongly related to maximum field exposure) occurred before the measurements were made. McKinlay et al. (2004) also note that the compliance rate was low and the possibility of selection bias was not excluded. Analyses of four data sets from the Li et al. (2001) study indicate that the magnitude of the maximum, but not the 95th or 99th percentile, is affected by the sampling rate of the meter and the mobility of the wearer (Mezei et al., 2006). This supports the hypothesis proposed by Savitz that the differential mobility of cases and controls could affect the maximum magnetic field measured.

Finally, in a case-control study in France, Robert et al. (1996) looked at congenital abnormalities in relation to distance from power lines. For distance < 50 m the odds ratios was 1.3 (95% CI: 0.5–3.2) and for distance < 100 m it was 1.0 (95% CI: 0.5–2.0). However, this was based on only two cases and since the entire study involved only 11 cases and 22 controls, its statistical power was limited.

Overall, the studies on residential ELF magnetic field exposure have provided some limited evidence for increased miscarriage risk associated with magnetic field exposure. This association is stronger for maximum value and variability of the magnetic field than for time-weighted average field level, but risk estimates above 1.0 were also reported for high TWA magnetic fields. One study provided evidence that the effect might be stronger for early miscarriages, and one study suggested effects on very early (pre-clinical) foetal loss. There is no evidence (but also very few data) of increased risks of adverse pregnancy outcomes other than miscarriage.

The results of epidemiological studies on reproductive outcomes in people exposed to ELF fields in their homes are summarized in Table 68.

Table 68. Epidemiological studies on reproductive outcome and exposure to residential ELF magnetic fields assessed by measurements, wire codes or distance to power line

Study population	Outcome	Exposure ^a	Risk estimate and 95% CI	Authors
257-396 pregnancies	Miscarriage	Home spot measurement 0.2 μ T	0.8 (0.3–2.3)	Savitz & Ananth, 1994
		High wire code	0.7 (0.3–1.9)	
	Low birth weight	High wire code	0.7 (0.2–2.3)	
	Preterm delivery	Home spot measurement 0.2 μ T	0.7 (0.1–4.0)	
High wire code		0.2 (0.0–1.5)		
Prospective study, n = 2967	Miscarriage	Very high wire code	0.37 (0.2–1.1)	Belanger et al., 1998
Prospective study, n = 969	Miscarriage (MC)	Personal TWA 0.3 μ T	1.2 (0.7–2.2)	Li et al., 2001
		Personal 24-h maximum 1.6 μ T	1.8 (1.2–2.7)	
		Total sum above 1.6 μ T 476 μ Ts	2.0 (1.2–3.1)	
	MC before 10 weeks	Personal 24-h maximum 1.6 μ T	2.2 (1.2–4.0)	
	MC after 10 weeks	Personal maximum 1.6 μ T	1.4 (0.8–2.5)	
155 cases, 509 controls	Miscarriage	Very high wire code	1.2 (0.7–2.1)	Lee et al., 2002
		Home spot measurement 0.2 μ T	1.1 (0.5–2.2)	
		Personal TWA 0.128 μ T	1.7 (0.9–3.2)	
		Personal 24-h maximum 3.51 μ T	2.3 (1.2–4.4)	
		Personal rate-of-change 0.094 μ T	3.1 (1.6–6.0)	
Prospective study, n = 219	Miscarriage	Home spot measurement 0.2 μ T	3.1 (1.0–9.7)	
		Personal TWA 0.2 μ T	1.9 (0.6–6.1)	
		Personal 24-h maximum 2.69 μ T	2.6 (0.9–7.6)	

Table 68. Continued

		Personal rate-of-change 0.069 μ T	2.4 (0.9–6.6)	
89 cases, 102 controls	Early pregnancy loss	Home spot measurement 0.25 μ T	1.1 (0.6–2.3)	Juutilainen et al., 1993
		Home spot measurement 0.63 μ T	5.1 (1.0–26)	
Prospective study, n = 2967	Low birth weight	Very high wire code	0.83 (0.3–2.1)	Bracken et al., 1995
		Personal TWA 0.2 μ T	1.35 (0.3–6.1)	
	Intrauterine growth retardation	Very high wire code	0.75 (0.4–1.6)	
		Personal TWA 0.2 μ T	1.16 (0.4–3.1)	
11 cases, 22 controls	All abnormalities	Distance to power line 100 m	0.95 (0.5–2.0)	Robert et al., 1996
		Distance to power line 50 m	1.25 (0.5–3.2)	

^a In many studies, the results were reported for several different exposure levels. The highest exposure levels were selected for this table.

10.1.2 Paternal exposure

Reproductive outcomes have also been occasionally related to paternal magnetic field exposure. Buiatti et al. (1984) reported that cases with infertility reported radioelectric work as their usual occupation more often than the controls. No association was observed between semen abnormalities and job titles linked to magnetic field exposure (Lundberg, Bracken & Belanger, 1995). Schnitzer, Olshan & Erickson (1995) reported an excess of birth defects in the children of electronic equipment operators. Increased frequency of abnormal pregnancy outcome (congenital malformations and fertility difficulties) was observed among high-voltage switchyard workers (Nordström, Birk & Gustavsson, 1983). No significant increase of abnormal birth outcome was found for offspring of power-industry workers (Tornqvist, 1998). Two studies suggested an association between magnetic field exposure and decreased male/female ratio in the offspring (Irgens et al., 1997; Mubarak, 1996).

The results of the studies on paternal exposure are inconclusive and share the methodological limitation that occupation is used as a surrogate for electromagnetic field exposure. While some studies indicated increased risks associated with electrical occupations, there is very little evidence for a causal role of ELF fields in these associations.

10.2 Effects on laboratory mammals

10.2.1 Electric fields

Several studies have addressed effects of 60 Hz electric fields on reproduction and development in rats, using field strengths from 10 kV m⁻¹ to 150 kV m⁻¹ (for review, see IARC, 2002). The studies involved large group sizes and exposure over multiple generations. In general, the studies did not report any consistent adverse effects. For example, malformations were increased and fertility was decreased in one experiment (Rommereim et al., 1987). These effects were not confirmed in further studies by the same group (Rommereim et al., 1990; 1996).

Exposure to 50 Hz electric fields at 50 kV m⁻¹ did not induce significant effects on growth and development in eight-week-old male rats exposed 8 h per day for 4 weeks, or rabbits exposed 16 h per day from the last two weeks of gestation to six weeks after birth (Portet & Cabanes, 1988).

Sikov et al. (1987) conducted a three-generation study on Hanford Miniature swine. The exposed group was kept in a 60 Hz, 30 kV m⁻¹ electric field for 20 h per day, 7 days per week. Two teratological evaluations were performed on the offspring of the F₀ generation. Malformations were decreased in the first teratological evaluation (significant only if analysed by foetus), but increased in the second evaluation. Increased malformations were also found among offspring of the F₁ generation at 18 months, but not in another offspring 10 months later. The inconsistency of the results makes it impossible to conclude that there is a causal relationship between ELF electric field exposure and developmental effects in swine.

10.2.2 Magnetic fields

10.2.2.1 Effects on prenatal development

Several studies have investigated effects of low frequency magnetic fields on prenatal development of rodents, and have been reviewed previously (Huuskonen, Lindbohm & Juutilainen, 1998; IARC, 2002). The magnetic flux densities varied from 2 µT to 30 mT. In general, the results do not show any consistent effects on gross external or visceral malformations or increase of foetal loss. The only findings that show some consistency are increases in minor skeletal alterations in several experiments in rats (Huuskonen, Juutilainen & Komulainen, 1993; Mevissen, Buntenkotter & Löscher, 1994; Ryan et al., 2000; Stuchly et al., 1988) and mice (Huuskonen et al., 1998b; Kowalczuk et al., 1994). However, in many other studies in rats (Chung et al., 2003; Negishi et al., 2002; Rommereim et al., 1996) and mice (Chiang et al., 1995; Frolen, Svedenstal & Paulsson, 1993; Ohnishi et al., 2002; Wiley et al., 1992) this effect was not observed. The lowest flux density reported to induce this kind of effect was 13 µT (Huuskonen, Juutilainen & Komulainen, 1993; Huuskonen et al., 1998b). Skeletal variations are relatively common findings in teratological studies and often considered biologically insignificant. Some of the groups concluded that the increased skeletal changes observed in their studies resulted from statistical fluctuation rather

than effects of the magnetic field exposure. Another possible explanation is that these findings indicate subtle developmental effects similar to the developmental instability reported by Graham et al. (2000c) in *Drosophila* (see 3.2). The use of low frequency magnetic fields for facilitating bone healing (for review, see IARC, 2002) may imply effects on growth and development of bone tissue.

Table 69 summarizes the results of ELF studies on prenatal development in mammals.

Table 69. Low frequency magnetic fields and prenatal development in mammals						
Animal strain	Frequency waveform	Flux density (μT)	Exposure time (days)	Findings^a	Other findings, notes	Authors
CBA/Ca mouse	50 Hz sinusoidal	12.6, 126	0–18	M- S+ R-		Huuskonen et al., 1998b
CD-1 mouse	50 Hz sinusoidal	20 000	0–17	M- S- R-	Body weight and length increased.	Kowalczyk et al., 1994
Swiss Webster mouse	15.6 kHz sawtooth	40 (p-p)	5–16	M+ S- R-	Combined exposure with cytosine arabinoside.	Chiang et al., 1995
CBA/S mouse	20 kHz sawtooth	15 (p-p)	0–18 1–18 4–18 6–18	M- S- R+		Frolen, Svedenstål & Paulsson, 1993
CBA/S mouse	20 kHz sawtooth	15 (p-p)	0–4.5 0–6	M- R-	Number of dead fetuses increased, weight and length decreased.	Svedenstål & Johanson, 1995
CBA/S mouse	20 kHz sawtooth	15 (p-p)	0–18	M- S- R-		Huuskonen et al., 1998a
CBA/Ca mouse	20 kHz sawtooth	15 (p-p)	0–18	M- S+ R-		Huuskonen et al., 1998b
CD-1 mouse	20 kHz sawtooth	3.6, 17, 200 (p-p)	0–17	M- S- R-		Wiley et al., 1992
Wistar rat	50 Hz sinusoidal	12.6	0–20	M- S+ R-		Huuskonen, Juutilainen & Komulainen, 1993

Table 69. Continued

Wistar rat	50 Hz sinusoidal	30 000	0–19	M- S+ R-		Mevisson, Buntenkotter & Löscher, 1994
SD rat	60 Hz sinusoidal	0.6, 1000	0–20	M- S- R-		Rommereim et al., 1996
SD rat	60 Hz sinusoidal	2, 200, 1000	6–19	M- S- R-		Ryan et al., 1996
SD rat	60, 180 or 60+180 Hz sinusoidal	200	6–19	M- S+ R-		Ryan et al., 2000
SD rat	50 Hz sinusoidal	7, 70, 350	0–7 8–15	M- S- R-		Negishi et al., 2002
ICR mouse	50 Hz sinusoidal	500, 5000	0–18	M- S-	Exposure before mating.	Ohnishi et al., 2002
SD rat	60 Hz sinusoidal	5, 83.3, 500	6–20	M- S- R-	Visceral variations decreased, resorptions increased nonsignificantly .	Chung et al., 2003
Wistar rat	10 kHz sinusoidal	95, 240, 950	0–22	M- S- R-		Dawson et al., 1998
SD rat	18 kHz, sawtooth	5.7, 23, 66 (p-p)	0–21	M- S+ R-	Exposure before mating.	Stuchly et al., 1988
Wistar rat	20 kHz, sawtooth	15 (p-p)	0–20	M- S+ R-		Huuskonen, Juutilainen & Komulainen, 1993
ICR mouse	20 kHz, sawtooth	6.25 μ T (peak)	2.5–15.5	M- R-		Kim et al., 2004

^a M=major external or visceral malformations; S=minor skeleton anomalies; R=resorptions; + positive finding; - no statistically significant difference from controls.

Effects of a 50 Hz, 20 mT magnetic field on postnatal development and behaviour of prenatally exposed CD1 mice were studied by Sienkiewicz et al. (1994). 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 and the exposed animals remained on a Rota-rod for less time as juveniles. A reduction in run-

ning time on a Rota-rod which was found in juvenile mice may represent a magnetic field-induced impairment in motor coordination during adolescence.

Seven pregnant CD1 mice were exposed for the period of gestation to a vertical, sinusoidal, 50 Hz, magnetic field at 5 mT and eight control animals were sham-exposed. Ten males per group were tested at 82–84 days of age for deficits in spatial learning and memory in radial arm maze. No effects on performance were observed (Sienkiewicz, Larder & Saunders, 1996).

Chung, Kim & Myung (2004) exposed Sprague-Dawley rats (24 per group) for 21 h per day from gestational day 6 through lactational day 21 to 60 Hz magnetic fields at flux densities of 5, 83.3 or 500 μ T. Growth, physical development, behaviour, and reproductive performance of the offspring was evaluated. A fraction of the F₁ pups were evaluated for visceral and skeletal abnormalities, and the F₂ foetuses were evaluated for external visible malformations. The behavioural tests included righting reflex, negative geotaxis, traction test, papillary reflex, acoustic startle response, Rota-rod test, open field test and water-filled T-maze test. The statistically significant findings included decrease of anogenital distance in males of the 5 μ T group and females of the 5 and 500 μ T groups, performance in the open field test in males of the 5 μ T group, performance in one of the tests performed with the water maze with the females of the 5 μ T group, changes in some organ weights, and increased incidence of visceral variations in the 83.3 μ T group. However, as these findings showed no dose-response relationship and a high number of statistical comparisons were performed, they are most probably chance findings.

10.2.2.3 *Multi-generation studies*

A reproductive assessment by continuous breeding (RACB) study on the toxicity of 60 Hz magnetic fields was conducted by Ryan et al. (1999). The RACB protocol permits the evaluation of reproductive performance over multiple generations. Groups of Sprague-Dawley rats, 40 breeding pairs per group were exposed continuously for 18.5 hours per day to sinusoidal 60 Hz magnetic fields at field strengths of 0, 2, 200 or 1000 μ T or to an intermittent (1 hour on, 1 hour off) field at 1000 μ T. No exposure-related toxicity was observed in any of the three generations examined. Foetal viability and body weight were similar in all groups, and there were no differences in any measure of reproductive performance (litters per breeding pair, percent fertile pairs, latency to parturition, litter size, and sex ratio). Teratological examinations were not performed.

10.2.2.4 *Effects on mammalian embryos in vitro*

Huuskonen, Juutilainen & Kumolainen (2001) studied the effects of 13 μ T, 50 Hz magnetic fields on the development of preimplantation CBA/S mouse embryos. The development of the embryos was followed for eight days (up to the blastocyst stage). Significantly fewer embryos died at the 5–8-cell and >8-cell stages in the exposed group than in the control group, but no

differences were seen in other developmental stages. There was no overall difference in survival, and no abnormalities or effects on developmental rate were observed. In contrast, Beraldi et al. (2003) reported significantly decreased survival in cultured mouse embryos exposed to 50 Hz fields at 60, 120 or 220 μT . The effect (tested at 60 μT) was more pronounced in embryos obtained by in vitro fertilization than in those resulting from natural breeding. No effects were observed on the morphology or developmental rate of the embryos.

10.2.2.5 Effects of paternal exposure

Possible effects of 50 Hz magnetic fields on the fertility of male Sprague-Dawley rats were investigated by Al-Akhras et al. (2001). Ten males per group (13 in the control group) were exposed to a sinusoidal, 50 Hz magnetic field at 25 μT for 90 days before they were mated with unexposed females (two females per male). The number of pregnancies decreased significantly from 24/26 (92%) in the control group to 10/20 (50%) in the exposed group. The effect persisted in a second mating after 45 days, but not at 90 days after removal from the magnetic field. Number of implantations per litter and viable foetuses per litter were not significantly affected. Effects on fertility in females (10 animals per group) were also evaluated in the same study. The 90-day exposure resulted in a statistically significant decrease of pregnancies, from 100% in the controls to 6/10 in the exposed females. The mean number of implantations per litter also decreased from 9.9 to 4.7 and the mean number of viable foetuses per litter from 9.6 to 4.3. These differences were statistically significant, but the numbers of animals in the groups were small.

In another study with similar design, the same investigators reported no adverse effects on fertility and reproduction in Swiss mice (Elbetieha, Al-Akhras & Darmani, 2002).

Picazo et al. (1995) exposed young male and female OF1 mice until adulthood to a sinusoidal 50 Hz, 15 μT magnetic field. The animals were then mated, and the offspring were kept under the same experimental conditions until they acquired sexual maturity. A significant increase of testis size and weight and of testosterone levels was observed in male offspring that had been exposed compared with a control group. However, complete spermatogenesis occurred in both control and exposed animals.

The effects of a 50 Hz, 1.7 mT sinusoidal magnetic field on mouse spermatogenesis (De Vita et al., 1995) was examined by flow cytometry. Groups of five male hybrid FI mice (C57Bl/Cne x C3H/Cne) were exposed for 2 or 4 hours, and measurements were performed at 7, 14, 21, 28, 35, and 42 days after exposure. The only statistically significant difference was a decrease in elongated spermatids at 28 days after treatment in the animals exposed for 4 h.

Kato et al. (1994b) reported no effects of circularly polarized 50 Hz magnetic fields at 1, 5 or 50 μT on plasma testosterone concentration in male Wistar-King rats.

10.3 Effects on non-mammalian species

10.3.1 Bird embryos

10.3.1.1 Development

Delgado et al. (1982) reported that weak pulsed ELF magnetic fields (0.12–12 μT ; 10, 1000 or 10000 Hz) affected the early development of chicken embryos examined after 48 h of incubation. After this initial finding, the same research group published several papers reporting similar effects (Leal et al., 1989; Ubeda et al., 1983; Ubeda et al., 1994; Ubeda, Trillo & Leal, 1987).

The initial results of Delgado were not replicated in an independent study (Maffeo, Miller & Carstensen, 1984). A large well-designed international study (“Henhouse project”) aimed at replicating Delgado's results has been carried out in six separate laboratories (Berman et al., 1990). Identical equipment and standardized experimental procedures were used. While the combined data showed a significant ($p < 0.001$) increase of abnormal embryos in the exposed group, the results were not consistently positive – only two laboratories found a statistically significant increase of abnormalities.

One of the laboratories that participated in the Henhouse project has reported a large additional investigation using pulsed waveforms and 50 Hz sinusoidal fields (Koch et al., 1993). Several different strains were tested to investigate possible strain-specific differences in sensitivity to magnetic fields. No significant magnetic field effects were observed.

Studies by Juutilainen and co-workers (1986) showed that the percentage of abnormalities was increased in chick embryos exposed during their first two days of development to 100 Hz magnetic fields with a pulsed, sinusoidal and rectangular waveforms. In another series of experiments with sinusoidal waveform, similar effects were found in a wide range of frequencies (Juutilainen & Saali, 1986). The effects of 100 Hz sinusoidal fields with a field strength of 1 A m^{-1} were confirmed in experiments with a large number of eggs (Juutilainen, 1986). Further experiments showed similar effects also at 50 Hz (sinusoidal), and indicated a threshold at 1.3 μT (Juutilainen, Läära & Saali, 1987).

Apart from the series of experiments by Juutilainen and colleagues, there have been few other studies on sinusoidal fields. Cox et al. (1993) attempted to partly replicate the findings of Juutilainen et al. No difference from control embryos was observed in 200 embryos exposed to a 10 μT , 50 Hz magnetic field.

Farrell et al. (1997) conducted an extensive series of experiments on the effects of pulsed and sinusoidal magnetic fields on chick embryo development, involving a total of more than 2500 embryos. Both 60 Hz, 4 μT sinusoidal fields and a 100 Hz field with 1 μT peak amplitude (similar to the field used in the Henhouse project) were used. Overall, the abnormality

rate was more than doubled by magnetic field exposure, and the effect was statistically significant for both 100 Hz and 60 Hz fields.

Quail embryo development has been reported to be affected by exposure to ELF magnetic fields (Terol & Panchon, 1995). The exposures were 50 or 100 Hz with rectangular waveform and intensities of 0.2, 1.2, 3.3 and 3.2 μT , and the embryos were examined at 48 h. There was a significant increase in embryonic deaths and abnormal development in the 100 Hz group, but not in the 50 Hz group.

10.3.1.2 Interaction with known teratogens

Pafkova & Jerabek (1994) reported that exposure to a 50 Hz, 10 mT magnetic field modified the embryotoxic effect of ionizing radiation on chick embryos examined at day 9 of development, although no effects of magnetic fields alone were detected. Embryotoxicity was expressed as the sum of embryonic deaths and malformations. Exposure to the magnetic field prior to the X-ray treatment seemed to protect the embryos from X-ray induced toxicity, while an enhancement of the embryotoxicity was seen when the magnetic field exposure followed the X-ray irradiation. The effects were seen consistently in several experiments and were statistically significant. The same group has also shown a similar protective effect of 50 Hz, 10 mT magnetic field exposure against subsequent exposures to the chemical teratogens insulin and tetracyclin (Pafkova et al., 1996).

Another research group has reported that the survival of chicken embryos exposed to UV-radiation is modified by exposure to a 60 Hz, 8 μT magnetic field (Dicarlo et al., 1999). Similarly to Pafkova's findings, the direction of the effect (enhancement or protection) depended on the exposure protocol. In this case magnetic field exposure always preceded UV exposure, but short exposure (2 h) seemed to protect the embryos, while longer exposure (96 h) increased the UV-induced mortality.

10.3.2 Other non-mammalian species

Exposure to sinusoidal magnetic fields has been reported to delay the development of fish embryos at 60 Hz, 0.1 mT (Cameron, Hunter & Winters, 1985), sea urchin embryos at 60 Hz, 0.1 mT (Zimmerman et al., 1990), and fish embryos at 50 Hz, 1 mT (Skauli, Reitan & Walther, 2000). No malformations were found in these studies.

Graham et al. (2000c) studied the effects of 60 Hz magnetic fields on "developmental stability" in *Drosophila melanogaster*. Developmental stability is a concept that describes the ability of an organism to maintain a consistent phenotype under given genetic and environmental conditions (this relatively new concept is potentially a useful tool for detecting weak environmental effects (Graham et al., 2000c). An individual with low developmental stability has reduced ability to correct disturbances in development. The standard measure of developmental instability is fluctuating asymmetry, random deviations from perfect bilateral symmetry. This measure has been shown to respond to environmental agents such as DDT, lead, and benzene.

Another measure of developmental instability is the frequency of phenodeviants in a population. Graham et al. exposed the fruit flies for their entire lives, egg to adult, to 60 Hz fields at 1.5 or 80 μT . The magnetic field exposures caused a significant reduction in body weight. The flies exposed to 80 μT showed reduced developmental stability measured both by fluctuating asymmetry (asymmetrical wing veins) and frequency of phenodeviants (fused abdominal segments). Mirabolghasemi & Azarnia (2002) have reported increased abnormalities in adult *D. melanogaster* flies after exposure of larvae to a 11 mT, 50 Hz field.

10.4 Conclusions

On the whole, epidemiological studies have not shown an association between adverse human reproductive outcomes and maternal or paternal exposure to ELF fields. There is some evidence for increased risk of miscarriage associated with measured maternal magnetic field exposure, but this evidence is inadequate.

ELF electric fields of up to 150 kV m^{-1} have been evaluated in several mammalian species, including studies with large group sizes and exposure over several generations. The results consistently show no adverse developmental effects.

The exposure of mammals to ELF magnetic fields of up to 20 mT does not result in gross external, visceral or skeletal malformations. Some studies show an increase in minor skeletal anomalies, in both rats and mice. Skeletal variations are relatively common findings in teratological studies and often considered biologically insignificant. However, subtle effects of magnetic fields on skeletal development cannot be ruled out. Very few studies have been published which address reproductive effects and no conclusions can be drawn from them.

Several studies on non-mammalian experimental models (chick embryos, fish, sea urchins and insects) have reported findings indicating that ELF magnetic fields at microtesla levels may disturb early development. However, the findings of non-mammalian experimental models generally carry less weight in the overall evaluation of developmental toxicity than those of corresponding mammalian studies.

Overall the evidence for developmental effects and for reproductive effects is inadequate.