EFFECTS OF POWER FREQUENCY ALTERNATING MAGNETIC FIELDS ON REPRODUCTION AND PRE-NATAL DEVELOPMENT OF MICE

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ABSTRACT — Three groups of ICR male and female mice were exposed to 50-Hz, sinusoidal, alternating, horizontal magnetic fields of 0.0 mT (sham), 0.5 mT and 5.0 mT (rms) for 9 and 2 weeks prior to mating for males and females, respectively, through fertilization and until cesarean sectioning. Fetuses were collected by cesarean section on the 18th day of gestation. Approximately half were randomly selected for skeletal examination and the remainder used for visceral examination. No significant differences were found between the field- and the sham-exposed groups in pre-, post- and total implantation losses; number of live fetuses; sex ratio; live fetal weight; number of externally abnormal fetuses; and numbers of fetuses with skeletal and visceral anomalies. These results suggest that exposure to power-frequency magnetic fields has no major effects on reproduction and development in mice, and do not support the association of EMF exposure with adverse reproductive effects suggested by epidemiology.

KEY WORDS: Reproduction, Mouse, Magnetic field, Power-frequency, Teratology, Reproductive performance

INTRODUCTION

Debate on the adverse effect on health of a non-ionizing electromagnetic field (EMF) was triggered by epidemiology in 1970s in the U.S. The debate concentrated on the extremely low frequency (ELF, <300 Hz) region, and especially power frequency, because of social impact. In the ELF region, electric and magnetic fields can be separated, and the former faded away from debate in the early stage owing to its poor environmental transmission.

A large number of studies was performed on the bioeffects of the ELF magnetic field, for the most part related to cancer and reproduction. We undertook our experiment under such circumstances.

Some epidemiological studies have reported potential effects on human reproduction from exposure to power-frequency (50- or 60-Hz) electromagnetic fields, including both parental occupational exposure to

electric and magnetic fields and domestic and occupational use of electric appliances by pregnant women (Meyers *et al.*, 1989). Since Wertheimer and Leeper, 1988, reported a significant increase in spontaneous abortion during the season in which electric blankets, waterbeds and ceiling heaters were used, several additional reports have been published concerning abortion incidence. Some of them (Sanjose *et al.*, 1991; Juutilainen *et al.*, 1993) supported the positive association, but others (Klaunenberg, 1991; Hatch, 1992) did not. Some other reproductive outcomes were studied in epidemiology, including birth weight, congenital anomalies, sex ratio, etc. Wertheimer and Leeper, 1986, reported a slightly elevated risk of low birth weight. Bracken *et al.*, 1995, supported them using dosimeters, but Savitz and Ananth, 1994, did not. As for congenital anomalies, Olsham *et al.*, 1991, reported an increased risk of atrial septal defect in the offspring of electricians, electric and electronic workers. However,

Dlugosz *et al.*, 1992, and Robert, 1993, reported slightly decreased risks of some types of malformations in the exposed groups.

Reproduction tests using animals exposed to power-frequency, sinusoidal magnetic fields are less numerous, and the results generally did not show an adverse effect. Kowalczyk *et al.*, 1994, observed a significant increase in litter size and a decrease in frequency of external anomaly, and no significant effect on pre-implantation survival in CD1 mice exposed to a 50-Hz, 20 mT magnetic field. In another study, they observed no significant effect on pregnancy rate, pre- and post-implantation survivals in a dominant lethal test using CD1 male mice exposed to a field of 10 mT. Martin, 1992, reported no effect of 60-Hz, 3 μ T (PTP, Peak-to-peak) sinusoidal and DC-biased, sinusoidal magnetic field exposure on chick embryos in the most sensitive development period, the first 48 hr after fertilization. Huuskonen *et al.*, 1993, however, reported significant increases in both numbers of implantation and live fetuses and in incidence of fetuses with minor skeletal anomalies in Wistar rats exposed continuously to a 50-Hz, 35.6 μ T (PTP) (13 μ Trms), sinusoidal magnetic field. These authors (Juutilainen *et al.*, 1997; Huuskonen *et al.*, 1998) performed another reproduction study using CBA/Ca mice exposed to magnetic fields, including the same field as in the previous study, and observed no significant effects on any endpoints, although insignificant increases in incidences of skeletal variations were reproduced.

Given both the importance of the question that power-frequency magnetic fields could influence reproduction and pre-natal development and the limited number of experiments available, we completed a reproduction and teratology test using ICR mice exposed to strong magnetic fields.

MATERIALS AND METHODS

Animals

ICR male (5 weeks of age, weighing 27 g to 30 g) and female (10 weeks of age, weighing 27 g to 30 g) mice in SPF condition were obtained from CLEA Japan Co. (Fujinomiya, Japan). This strain, which also is referred to as CD1, is often used in ionizing radiation studies. The mice were kept in the SPF condition at 22 $\pm$ 2°C and 40%-70% RH throughout the experiment. They had access to mouse diet CRF-1 (Oriental Yeast Co., Tokyo, Japan) and to microfiltered and UV sterilized tap water *ad libitum*. It was confirmed by a preliminary test that animals did not hesitate to eat and to

drink from the stainless steelware in the field. The lighting schedule was lights-on from 06:00-18:00.

Magnetic field

The International Radiation Protection Association (IRPA), 1990, recommended 0.5 mT as the occupational continuous exposure limit in its interim guideline. We adopted this as the lower level of exposure, and we used a field intensity 10 times higher (5.0 mT). Animals were exposed to the fields using an exposure facility with structure and performance reported elsewhere in detail (Yasui and Otaka, 1993). Performance is shown in Table 1. The magnetic field is automatically switched off when a person enters the exposure room to avoid exposing workers to the field. Average exposure time was 23.0 hr/day for males and 22.7 hr/day for females.

Although a higher flux density is preferable in order to enhance the exposure effect, 5.0 mT is almost the technically attainable limit for a large-scale animal exposure system. Magnetic field from an electric blanket was estimated as 1 μ T (IEC 61000-2-7) and those in occupational and residential environments as 4-0.2 μ T. 5.0 mT was regarded as strong enough compared with actual human exposure.

Treatment

The procedure (Fig.1) was based on OECD guidelines 414, 1981, and 415, 1983, for chemical testing. Thirty-five male mice were exposed to a sham (0.0 mT), 0.5 mT or 5.0 mT(rms) magnetic field for 9 weeks, long enough to cover at least one complete spermatogenic cycle. In order to detect a subtle effect, a large-scale experiment was preferable, but there was a limit imposed by the exposure system capacity. At 15 weeks of age, each male was mated with a female 13 weeks of age exposed to a sham (0.0 mT), 0.5 mT or

Table 1. Performance of exposure facility. Details of the facility are described elsewhere, together with the building for maintenance of SPF condition.

Frequency	50 Hz
Flux density	Sham(0.1-1 μ T), 0.5 mT and 5.0 mT
Exposure space	2.64W $\times$ 0.18H $\times$ 0.56D $\times$ 2 $\times$ 3 sets
Flux uniformity	$\pm$ 10%
Flux direction	Horizontal
Acoustic noise	Lower than 60dB(A)
Stability of current	Within $\pm$ 0.4%
Distortion of wave form	Lower than 3%

Table 2. Observations on external anomalies. Club foot is expected to recover with growth. Exencephaly and cleft palate were considered to be fatal.

Dependent variable	Number of animals (%)			Historical Control (S.D.)	Reference*
	Sham	0.5 mT	5.0 mT		
No. of dams	28	32	34	40	
No. of abnormal fetuses/ Total live fetuses	7/368 (1.9%)	7/412 (1.7%)	7/447 (1.6%)	1/261 (0.3%)	
No. of dams with abnormal fetuses	7 (1.7%)	5 (1.6%)	7 (1.5%)	2.5%	0-0.58%
Open eyelid	1 (0.3%)	3 (0.7%)	3 (0.7%) †	0.3 (1.4)	0.09
Club foot	3 (0.8%)	4 (1.0%)	3 (0.7%)	0	0.09-0.18
Kink tail	1 (0.3%)	0 (0%)	0 (0%)	0	NA
Cleft palate	1 (0.3%)	0 (0%)	1 (0.2%)	0	0.13-0.35
Exencephaly	0 (0%)	0 (0%)	1 (0.2%) †	0.3 (1.4)	0.06
Polydactyly	1 (0.3%)	0 (0%)	0 (0%)	0	NA
Dwarf	3 (0.8%)	1 (0.2%)	2 (0.4%)	NA	NA

† : A fetus with open eyelid and exencephaly.

*: Nakatsuka *et al.*, 1997, in Crj: CD-1 and Slc: ICR.

NA: Not available.

Skeletal anomaly

Table 3 summarizes the results of skeletal examination of the fetuses. No increase was observed in the incidence of skeletal malformations. Some increases in the incidence of variations, *i.e.*, splitting of the ossification center in the cervical vertebral arches, cervical ribs, accessory sternebra, and 14th ribs (extra thoracic rib), were observed in the 0.5 mT group, but no trend with field strength was apparent. Table 4 shows degree of ossification.

Anomaly of internal organs

Table 5 summarizes the results of visceral examination of the fetuses. Two fetuses, from two dams, with localized ventricular septal defect were found in the 5.0 mT group. Abnormal origin of the right subclavian artery, a rare malformation in this laboratory, was seen in the 5.0 mT group. As for variation, incidences of supernumerary coronary orifice were 2, 4, and 5 in the sham, 0.5 mT, and 5.0 mT groups, respectively.

Dead embryo and implantation loss

Table 6 summarizes the results of examining of uterine contents in dams. Spontaneous abortion was a main issue of epidemiological studies on EMF. Dead embryos and implantation loss are related to it. Pre-implantation loss was 8.1% in the 5.0 mT group versus 4.8% in the sham group, and the number of dead embryos in the early stage was 0.8 in the 0.5 mT group versus 0.4 in the sham group. Although statistically

insignificant, both are 5% marginal. Compared with historical control data, 13.5%, the former can be regarded as within the fluctuation. Numbers of dead embryos in the late stage of gestation were almost equal between the exposure levels.

Lack of a change in the sex ratio is consistent with the results of Kowalczyk *et al.*, 1994, and inconsistent with the result of Huuskonen *et al.*, 1993, who reported increases in total implants and live fetuses in the exposed groups.

Total implants and total live fetuses were consistent with the reference data. Insignificant increases in number of total dead embryos and total implantation losses were observed in the exposed groups, which seem to compensate for the insignificant increase in total implants to yield equal numbers of total live fetuses.

DISCUSSION

Spontaneous abortion was the main concern of the epidemiological studies on EMF in human reproductive outcomes, and the elevated risks were found in most of the epidemiological studies, although the lower limits of the 95% confidence intervals were below 1. The results of the present study did not support elevated risk. The results on dead embryos in Table 6 alone did not support a causal relation of 50-Hz magnetic field and spontaneous abortions.

Effects of magnetic fields on reproduction in mice.

Table 3. Results of skeletal examinations of fetuses. Variation is a minor anomaly, mostly expected to recover with growth, and never affects viability. Some litters had many fetuses with skeletal anomalies; for example, accessory sternebra. Skeletal development was anticipated to be affected by EMF even if sinusoidal, but the possible effect is not large enough to be detectable.

	Sham	0.5 mT	5.0 mT	Reference
No. of dams	28	32	34	
No. of fetuses examined	190	214	234	
No. of fetuses and litter mean % with				
Bifurcation of the cervical vertebral arches	30 (14.9%)	28 (13.0%)	44 (17.9%)	0.80
Splitting of ossification center of the cervical vertebral arches	10 (5.2%)	18 (8.2%)	16 (7.3%)	0.27-0.53
Fusion of the cervical vertebral arches †	0 (0%)	0 (0%)	1 (0.5%)	0.23
Cervical ribs	25 (12.4%)	38 (18.6%)	33 (13.4%)	NA
Fusion of the sternebrae †	1 (0.5%)	0 (0%)	0 (0%)	0.26-1.23
Accessory sternera	16 (8.5%)	33 (15.3%)	12 (4.7%)	NA
Splitting of the sternebrae	1 (0.5%)	0 (0%)	0 (0%)	NA
Asymmetry of the sternebrae	1 (0.4%)	0 (0%)	2 (0.8%)	NA
Splitting of ossification centers of the 14th ribs	1 (0.5%)	0 (0%)	1 (0.3%)	NA
14th ribs	37 (20.5%)	58 (27.0%)	50 (20.8%)	NA
Lumbarization of the sacral vertebrae	2 (1.2%)	0 (0%)	0 (0%)	NA
Sacralization of the lumbar vertebrae	5 (2.6%)	2 (0.9%)	1 (0.4%)	0.08
Total	100 (52.3%)	124 (57.8%)	116 (47.4%)	

† : Malformation, No mark: Variation, * is affixed if significantly different from sham.

Reference: Nakatsuka *et al.*, 1998. In Crj: CD-1 and Slc: ICR.**Table 4.** Degree of ossification. An ossified bone is observed as a stained spot with Alizarine red S in the skeleton of the fetus under an optical microscope.

			Sham	0.5 mT	5.0 mT
No. of dams			28	32	34
No. of fetuses examined			190	214	234
Vertebrae	Cervical centra		6.90 (0.32)	6.98 (0.07)	6.71 (1.17)
	Caudal centra		10.38 (1.36)	10.71 (0.98)	9.99 (1.73)
Hyoid			1.00 (0.00)	0.98 (0.09)	1.00 (0.00)
Incisor	Upper		0	0	0
	Lower		2.00 (0.00)	2.00 (0.00)	1.99 (0.06)
Sternebra			5.99 (0.03)	6.00 (0.00)	6.00 (0.00)
Metacarpus		Left	4.00 (0.00)	4.00 (0.00)	3.98 (0.09)
		Right	4.00 (0.00)	4.00 (0.00)	3.98 (0.09)
Manus	Proximal	Left	3.99 (0.05)	4.00 (0.00)	3.88 (0.48)
		Right	3.98 (0.05)	4.00 (0.00)	3.88 (0.48)
	Medial	Left	2.70 (0.47)	2.91 (0.44)	2.66 (0.72)
		Right	2.76 (0.48)	2.94 (0.38)	2.73 (0.70)
	Distal	Left	4.93 (0.26)	5.00 (0.00)	4.88 (0.51)
		Right	4.92 (0.26)	5.00 (0.00)	4.88 (0.51)
	Metatarsus	Left	4.99 (0.03)	4.99 (0.04)	4.98 (0.10)
		Right	4.99 (0.03)	4.99 (0.04)	4.98 (0.10)
Pes	Proximal	Left	4.95 (0.20)	4.99 (0.04)	4.82 (0.68)
		Right	4.95 (0.20)	4.99 (0.04)	4.82 (0.68)
	Medial	Left	1.79 (1.04)	2.13 (0.97)	2.01 (1.04)
		Right	1.76 (1.05)	2.19 (0.95)	2.03 (1.06)
	Distal	Left	5.00 (0.00)	5.00 (0.00)	4.85 (0.66)
		Right	5.00 (0.00)	5.00 (0.00)	4.85 (0.66)

Litter mean of number of ossified bones (standard deviation).

* is affixed if significantly different from sham.

Table 5. Observations of internal organs of fetuses. Left umbilical artery is a very slight variation. The malformations are fatal.

Dependent variable	Sham	0.5 mT	5.0 mT	Reference
No. of dams	28	32	34	NA
No. of fetuses examined	178	198	213	NA
No. of fetuses (litter mean % with)				
Abnormal origin, r't subclavian artery †	0 (0%)	0 (0%)	1 (0.5%)	NA
Deformity of the heart †	1 (0.6%)	0 (0%)	0 (0%)	NA
Localized ventricular septal defect †	0 (0%)	0 (0%)	2 (1.1%)	NA
Supernumerary coronary orifice	2 (0.8%)	4 (2.0%)	5 (2.0%)	0.11
Congenital diaphragmatic hernia †	0 (0%)	0 (0%)	1 (0.4%)	NA
Left umbilical artery	35 (18.8%)	26 (13.1%)	35 (15.3%)	NA
Total	38 (19.4%)	30 (15.1%)	43 (18.9%)	

† : Malformation; No mark: variation.

Reference: Nakatsuka *et al.*, 1997.

NA: Not available.

Table 6. Observations on uterine contents. Early and late in the dead embryo were distinguished by existence of a placenta; pre-implantation loss is the difference between numbers of corpora lutea and total implants.

Dependent variable	Group mean (standard deviation)			Historical control	Reference
	Sham	0.5 mT	5.0 mT		
Number of dams	28	32	34	40	
Corpora lutea	14.6 (2.06)	14.7 (1.88)	15.1 (2.09)	15.4 (2.8)	13.9-17.4
Total implants	13.8 (2.10)	14.0 (1.94)	14.0 (2.92)	13.2 (2.7)	12.8-14.9
Dead embryos					
Early	0.4 (0.63)	0.8 (1.22)	0.7 (0.84)	0.5 (0.6)	NA
Late	0.2 (0.50)	0.3 (0.60)	0.2 (0.48)	0.3 (0.6)	NA
Total	0.6 (0.69)	1.1 (1.49)	0.9 (0.81)	0.8 (0.9)	8.0-10.4
Implantation loss (%)					
Pre-	4.8 (4.95)	4.7 (5.73)	8.1 (13.8)	13.5 (15.7)	NA
Post-	4.5 (5.13)	7.8 (10.3)	6.8 (8.01)	5.7 (7.1)	NA
Total	9.3 (6.08)	12.0 (12.4)	14.2 (15.2)	18.7 (15.3)	12.8-14.7
Live fetuses					
Male	6.2 (2.11)	6.1 (2.37)	6.1 (2.26)	6.4 (2.0)	NA
Female	6.9 (1.96)	6.8 (2.25)	7.1 (2.52)	6.1 (2.2)	NA
Total	13.1 (2.24)	12.9 (2.35)	13.1 (3.13)	12.5 (2.8)	11.7-13.1
Live fetal weight (g)					
Male	1.54 (0.10)	1.53 (0.08)	1.52 (0.12)	1.41 (0.11)	1.35-1.48
Female	1.47 (0.10)	1.47 (0.07)	1.46 (0.11)	1.37 (0.09)	1.32-1.43
Sex ratio (M/F)	174/194 (0.90)	194/217 (0.90)	206/241 (0.85)	254/245 (1.04)	NA

Reference: Nakatsuka *et al.*, 1997.

NA: Not available.

Table 7. Measures of reproductive performance. Unlike the human male, it was considered that male mice might be affected by EMF through contact of the testes with the cage wall possibly charged in the fields. The data shows the fields did not affect male mice.

Dependent variable	Sham	0.5 mT	5.0 mT	Historical control
Pre-coital days	2.5	3.0	2.4	2.3 (1.3)
Coital rate (%)	94	97	100	100*
Pregnancy rate (%)	91	94	97	93

*: 90.5% by the breeder's background data, Jcl Information 97-1030.

Jansson *et al.*, 1993, suggested in their epidemiological study that an increase in spontaneous abortion owing to exposure might cause a decrease in the number of anomalies, but the number of dead embryos in Table 6 is not consistent with this suggestion.

Some epidemiological studies were directed to low birth weight and growth retardation. Results on live fetal weight in Table 6 are far from showing significant differences between the exposure levels. Numbers of dwarfs in Table 2 were 3, 1, and 2 (from a dam) in the sham, 0.5 mT, and 5.0 mT groups, respectively, which did not support a possible adverse effect of the field on fetal development.

As for congenital anomaly, the results of the epidemiological studies were inconsistent, and increase in risk was small if any.

Insignificant increases were observed in (1) number of dead embryos in the early stage of gestation in the 0.5 mT group, (2) pre-implantation loss in the 5.0 mT group, (3) incidence of open eyelid in the exposed groups, and (4) incidence of cervical ribs and accessory sternebra in the 0.5 mT group, but they were not consistent with the results of Kowalczyk *et al.*, 1994.

CONCLUSION

No effects of 50-Hz, up to 5.0 mT magnetic fields were detected on reproduction in mice. This supports none of the associations between the field and human reproductive outcome suggested by epidemiological studies. Additional studies are needed to evaluate the possible effects with enhanced detection power.

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