6 NEUROENDOCRINE SYSTEM

The pineal and pituitary neuroendocrine glands, both situated in the brain and intimately connected with and controlled by the nervous system, release hormones into the blood stream which exert a profound influence on body metabolism and physiology, particularly during development and reproduction, partly via their influence on the release of hormones from other endocrine glands situated elsewhere in the body. These studies have been reviewed by NIEHS (1998), IARC (2002), McKinlay et al. (2004) and recently by AGNIR (2006).

The hypothesis, first suggested by Stevens (1987), that exposure to EMFs might reduce melatonin secretion and thereby increase the risk of breast cancer has stimulated a number of human laboratory studies and investigations of circulating melatonin levels in people exposed to EMFs in domestic or occupational situations.

6.1 Volunteer studies

The majority of studies have investigated the effects of EMF exposure, mostly to power frequencies, on circulating levels of the pineal hormone melatonin (or on the urinary excretion of a metabolite of melatonin). Fewer studies have been carried out on circulating levels of pituitary hormones or other hormones released from other endocrine glands such as the thyroid gland, adrenal cortex and reproductive organs.

6.1.1 The pineal hormone: melatonin

Melatonin is produced by the pineal gland in the brain in a distinct daily or circadian rhythm which is governed by day length. It is implicated in the control of daily activities such as the sleep/wake cycle and in seasonal rhythms such as those of reproduction in animals that show annual cycles of fertility and infertility. Maximum serum levels occur during the night, and minimum levels during the day, even in nocturnally active animals. Night-time peak values of serum melatonin in humans, however, can vary up to ten-fold between individuals (Graham et al., 1996). It has been suggested that melatonin has a negative impact on human reproductive physiology, but that any changes are slight compared to those seen in experimental animals (Reiter, 1997). However, the overall evidence suggests that human melatonin rhythms are not significantly delayed or suppressed by exposure to magnetic fields (AGNIR, 2001b; IARC 2002; ICNIRP, 2003; NIEHS, 1998; although see Karasek & Lerchl, 2002).

6.1.1.1 Laboratory studies

Several laboratory studies have been carried out in which volunteers, screened for various factors which might have influenced melatonin levels, were exposed or sham exposed overnight to circularly or horizontally polarized intermittent or continuous power-frequency magnetic fields. No significant effects of exposure on night-time serum melatonin levels were found (Crasson et al., 2001; Graham et al., 1996; Graham, Cook & Riffle, 1997; Kurokawa et al., 2003a; Selmaoui, Lambrozo & Touitou, 1996; Warman et al., 2003a). Other studies, using the excretion of the major urinary metabolite of melatonin as a surrogate measures of serum melatonin, also found no effect (Åkerstedt et al., 1999; Crasson et al., 2001; Graham et al., 2001a; Graham et al., 2001b; Selmaoui, Lambrozo & Touitou, 1996). The use of the urinary excretion data complicates interpretation, however, since information regarding any possible phase shift in melatonin production is lost. Griefahn (2001; 2002) found no effect of exposure to 16.7 Hz magnetic fields on hourly saliva melatonin concentration.

Some positive effects have been reported, but these have generally not proved consistent. An initial report (Graham et al., 1996) of a magnetic field-induced reduction of night-time serum melatonin levels in volunteers with low basal melatonin levels was not confirmed using a larger number of volunteers. It is possible that the initial positive findings were due to chance with a relatively small number of subjects. However, the results of a study investigating the effects of night-time exposure to 60 Hz fields for four nights (Graham et al., 2000b) suggested a weak cumulative effect of exposure. Exposed subjects showed more intra-individual variability in the overnight levels of excretion of melatonin or its major metabolite on night 4, although there was no overall effect on levels of melatonin.

Wood et al. (1998) exposed or sham exposed male subjects to an intermittent, circularly-polarised, power-frequency magnetic field at various times during the dusk or night and measured the effect on night-time serum melatonin levels. The results indicated that exposure prior to the night-time rise in serum melatonin may have delayed the onset of the rise by about half an hour and may have reduced peak levels, possibly in a sensitive sub-group of the study population. However, exposure categorisation was made post-hoc (Wood et al., 1998) and the result can only be considered to be exploratory.

6.1.1.2 Residential and occupational studies

Several studies of responses have been carried out in people in residential or occupational situations. These are naturally more realistic than laboratory studies but suffer from diminished control of possible confounding factors, such as differences in lifestyle (Warman et al., 2003b). With regard to domestic exposure, one study (Wilson et al., 1990) has examined the possible effects on volunteers exposed at home to pulsed EMFs generated by mains or DC-powered electric blankets over a 6–10 week period. Overall, no effect of exposure was seen on the urinary excretion of the major urinary metabolite of melatonin (aMT6s). However, transient increases in night-time excretion were seen in the periods following the onset of a period of electric blanket use and following the cessation of the period of electric blanket use in seven of 28 users of one type of electric blanket. This observation may, however, be rather weak given the lack of correspondence of the effect with field condition and the fact that responsiveness was only identified following the separate analysis of the excretion data from each of 42 volunteers, of which some analyses may have turned out positive by chance (Hong et al., 2001). In contrast, Hong et al. (2001) found no significant field dependent effects on melatonin rhythms in nine men following 11 weeks of night-time exposure. In this study, the urinary excretion of aMT6s was followed in five urine samples collected each day. This study too, however, exercised very little control over possible confounding by environmental and lifestyle factors.

Several more recent studies relating to residential exposure have been carried out. Davis et al. (2001) reported lower nocturnal levels of melatonin, measured as the excretion of aMT6s, in women with a history of breast cancer to be associated with higher bedroom magnetic field levels, once adjustment had been made for hours of daylight, age, body mass index, current alcohol consumption and the use of certain medications. Levallois et al. (2001) found no relation of night-time excretion of aMT6s to proximity of the residence to power lines or to EMF exposure. There were, however, significantly stronger relations to age and obesity (out of five variables for which the authors investigated effect modification) in women who lived close to power lines than in those who lived more distantly. In a general review of all these studies, IARC (2002) concluded that it was difficult to distinguish between the effects of magnetic fields and those of other environmental factors. In a later study, Youngstedt et al. (2002) found no significant associations between several measures of magnetic field exposure in bed (but not elsewhere) and various measures of the urinary excretion of aMT6s in 242 adults, mostly women, aged 50–81.

A number of other studies have examined urinary metabolite excretion in occupationally exposed workers. For railway workers, Pfluger & Minder (1996) reported that early evening aMT6s excretion (taken as an index of daytime serum melatonin levels) but not early morning excretion was decreased in exposed workers. However, the authors noted that the effects of differences in daylight exposure, which suppresses night-time melatonin, could not be excluded. In a study of electric utility workers, Burch et al. (1998; 1999) found no overall effect of exposure on night-time aMT6s excretion (taken as an index of night-time melatonin levels) when considering mean levels of exposure. The authors did find lower levels of night-time excretion in individuals exposed to temporally more stable magnetic fields, raising some questions as to the interpretation of these data. A reduction in melatonin levels was found to be associated with working near 3-phase conductors and not near 1-phase conductors, indicating a possible role of field polarisation (Burch et al., 2000). Burch, Reif & Jost (1999) also found that reduction of aMT6s excretion was associated with high geomagnetic activity. Juutilainen et al. (2000) found that occupational exposure to magnetic fields produced by sewing machines did not affect the ratio of Friday morning/Monday morning levels of aMT6s excretion, suggesting that weekends without workplace exposure did not change melatonin response. Average Thursday night excretion (Friday morning sample) was lower in exposed compared to control workers.

In a study of a further group of male electrical utility workers, Burch et al. (2002) investigated nocturnal excretion of aMT6s in men with high compared with low or medium workplace 60-Hz exposure. After adjusting for light exposure at work, reduced melatonin levels were found within men with high cellular phone use; the effect was not present in those with medium or no such phone use. Touitou et al. (2003) found no effect on serum melatonin levels or the overnight excretion of urinary aMT6s in workers at a high voltage substations chronically exposed to 50 Hz magnetic fields compared to white collar workers from the same company.

A preliminary study by Arnetz & Berg (1996) of daytime serum melatonin levels in visual display units (VDU) workers (sex not given) exposed to ELF and other frequency electromagnetic fields (values not given) reported a slightly larger decrease during VDU work compared to leisure time. The biological significance of this small daytime effect is not at all clear, given that serum melatonin peaks during the night.

In a study by Lonne-Rahm et al. (2000), 24 patients with electromagnetic hypersensitivity and 12 controls were exposed to a combination of stress situations and electric and magnetic fields from a VDU. Blood samples were drawn for circulating levels of stress-related hormones (melatonin, prolactin, adrenocorticotrophic hormone, neuropeptide Y and growth hormone). In double-blind tests, none of these parameters responded to the fields, neither alone nor in combination with stress levels.

Table 46 summarizes the human melatonin studies.

6.1.2 Pituitary and other hormones

Few studies of EMF effects on hormones of the pituitary and other endocrine glands have been carried out. Principal pituitary hormones investigated in EMF studies include several hormones involved in growth and body physiology, particularly thyroid-stimulating hormone (TSH) which controls the function of the thyroid gland and the release of thyroxin; adrenocorticotropic hormone (ACTH), which regulates the function of the adrenal cortex and particularly the release of cortisol; and growth hormone (GH), which affects body growth. Hormones released by the pituitary which have important sexual and reproductive functions have also been studied, particularly follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin. Both FSH and LH influence the function of the testis and the release of testosterone.

Three laboratory studies have investigated the possible effects of acute exposure to power-frequency magnetic fields and power-frequency electric and magnetic fields on TSH, thyroxin, GH, cortisol, FSH, LH and testosterone in men (Maresh et al., 1988; Selmaoui, Lambrozo & Touitou, 1997) and GH, cortisol and prolactin in men and women (Åkerstedt et al., 1999). Overall, no effects were found.

An occupational study (Gamberale et al., 1989) of linesmen working on “live” or “dead” 400-kV power lines found no effect of combined

Table 46. Human melatonin studies

Endpoint	Exposure	Response	Comment	Authors
ELF magnetic fields				
Laboratory studies				
Night-time serum melatonin levels	60 Hz 1 or 20 µT, intermittent 8 h at night	No effect. Possible effect on low melatonin subjects not replicated in larger study.	Well described and well planned double blind study.	Graham et al., 1996
Night-time serum melatonin levels	60 Hz 20 µT, continuous 8 h at night	No effect.	Well described and well planned double blind study.	Graham, Cook & Riffle, 1997
Night-time serum melatonin levels and excretion of its major urinary metabolite (aMT6s).	50 Hz 10 µT, continuous or intermittent 9 h at night	No effect.	Well described and well planned double blind study.	Selmaoui, Lambrozo & Touitou, 1996
Night-time serum melatonin levels	50 Hz 20 µT, sinusoidal or square wave field, intermittent 1.5–4 h at night	Possible delay and reduction of night-time melatonin levels in sub-group.	Double blind study; incomplete volunteer participation.	Wood et al., 1998
Night-time serum melatonin levels	50 Hz 1 µT during sleep (24.00 to 08.00 h)	No effect.	Double blind study.	Åkerstedt et al., 1999
Night-time serum melatonin levels and excretion of aMT6s.	60 Hz 28.3 µT, continuous 8 h at night	No effect.	Well described and well planned double blind study.	Graham et al., 2000b
Night-time serum melatonin levels and excretion of aMT6s	50 Hz 100 µT, continuous or intermittent 30 min	No effect.	Well described and well planned double blind study.	Crasson et al., 2001

Table 46. Continued

Night-time serum melatonin levels in women	60 Hz 28.3 μT, intermittent 8 h at night	No effect.	Well described and well planned double blind study.	Graham et al., 2001a
Night-time serum melatonin levels and excretion of aMT6s	60 Hz 127 μT, continuous or intermittent 8 h at night	No effect.	Well described and well planned double blind study.	Graham et al., 2001b
Night-time serum melatonin levels and excretion of aMT6s	60 Hz 28.3 μT, continuous 8 h at night	No effect.	Well described and well planned double blind study.	Graham et al., 2001c
Salivary melatonin levels	16.7 Hz 200 μT 6 h at night	No effect.	Well described and well planned double blind study.	Griefahn et al., 2001
Salivary melatonin levels	16.7 Hz 200 μT 6 h at night	No effect.	Well described and well planned double blind study.	Griefahn et al., 2002
Night-time serum melatonin levels	50 Hz 20 μT, linearly polarised 8 h at night	No effect.	Well described and well planned double blind study.	Kurokawa et al., 2003a
Night-time serum melatonin levels	50 Hz 200 or 300 μT 2 h at night across rising phase of melatonin secretion	No effect.	Well described and well planned double blind study.	Warman et al., 2003a
ELF electric and magnetic fields				
Domestic occupational studies				
Early morning excretion of urinary aMT6s	60 Hz EMFs generated by pulsed AC or DC current supply to electric blankets 7–10 weeks at night	No overall effect; transient increases in 7/28 users of one type of blanket.	Realistic, but concomitant lack of control over lifestyle etc.	Wilson et al., 1990

Table 46. Continued

Urinary excretion of aMT6s collected 5 times per day	50 Hz ~1–8 μT, electric ‘sheet’ over the body 11 weeks at night	No effect.	The only restriction on each subject’s usual daily activities were avoiding overeating and strenuous exercise.	Hong et al., 2001
Morning and evening urinary excretion of aMT6s in railway workers.	16.7 Hz approximately 20 μT mean value in engine drivers	Decreased evening 6-aMT6s levels but no effect on morning levels. No dose-response effect.	Subjects acted as own controls; samples collected early autumn; fully described protocol.	Pfluger & Minder, 1996
Night-time and early morning urinary excretion of aMT6s in electric utility workers	60 Hz ~0.1–0.2 μT 24 hr at work, home and during sleep	No overall effect with exposure. Temporally more stable fields at home (using calculated index) associated with reduced nocturnal melatonin.	Well described study; some adjustment for age, month of participation and light exposure.	Burch et al., 1998
Post work urinary excretion of aMT6s electric utility workers	60 Hz occupational exposure over a week	No overall effect. Reduction in aMT6s excretion in workers exposed to more stable fields during work.	Significant interaction with occupational light exposure.	Burch et al., 1999
Night-time urinary excretion of aMT6s in electric utility workers	60 Hz occupational exposure to magnetic fields	Exposure-related reduction in aMT6s excretion in workers exposed in substations or 3 phase environments for > 2 h.	Adjusted for workplace light exposure.	Burch et al., 2000
Night-time urinary excretion of aMT6s in garment workers	50 Hz occupational exposure to magnetic fields	Average aMT6s excretion lower in exposed workers compared to office workers.	No difference in Friday to Monday levels	Juutilainen et al., 2000
Night-time urinary excretion of aMT6s	50 Hz proximity to power lines and/or exposure to domestic EMFs	No overall effect. Significantly stronger association with age and obesity in women living closer to power lines.	Adjusted for confounders.	Levallois et al., 2001

Table 46. Continued

Night-time urinary excretion of aMT6s	60 Hz domestic exposure to magnetic fields	Borderline association with one measure of exposure in a subgroup of women.	Significant association with day length.	Davis et al., 2001
Night-time urinary excretion of aMT6s in electric utility workers	60 Hz occupational exposure to magnetic fields	Exposure-related reduction in aMT6s excretion in highly exposed workers associated with mobile phone use.	Not present in workers with low or medium phone use.	Burch et al., 2002
24 hr urinary excretion of aMT6s	60 Hz domestic exposure to magnetic fields measured in the bedroom only	No significant associations between exposure and excretion.	Potential confounders such as lighting, age and medication taken into account.	Youngstedt et al., 2002
Serum melatonin levels and urinary excretion of aMT6s in high-voltage sub-station workers	geometric mean fields of 0.1–2.6 µT chronic occupational exposure (1–20 y)	No effect compared to levels in white-collar workers.	Considerable care taken to avoid some confounders, e.g. study participants all non-smokers.	Touitou et al., 2003
ELF and VLF electric and magnetic fields				
Occupational studies				
Morning and afternoon serum melatonin levels in VDU workers during one working and one leisure day.	Exposure details not given	Decrease in serum melatonin during the day was statistically significant at work (-0.9 ng/l) but not leisure (-0.8 ng/l).	Samples collected Oct – Feb. Experimental protocol briefly described. No measured fields; no control over lifestyle etc.	Arnetz & Berg, 1996
Circulating levels of stress-related hormones (melatonin, prolactin, ACTH, neuropeptide Y and growth hormone)	24 patients with electromagnetic hypersensitivity and 12 controls electric and magnetic fields from a VDU	No effect.	Double blind study.	Lonne-Rahm et al., 2000

electric and magnetic field exposure over a working day on daytime levels of serum TSH, cortisol, FSH, prolactin, LH and testosterone. A preliminary study (Arnetz & Berg, 1996) of VDU workers (sex not specified) exposed to ELF electric and magnetic fields (exposure not given) reported elevated ACTH levels at work compared to leisure time; an effect, as the authors note, which is probably attributable to work-related factors other than EMFs.

The studies on the effects of ELF on the human pituitary and endocrine system are summarized in Table 47.

Table 47. Human pituitary and other endocrine studies

Endpoint	Exposure	Response	Comment	Authors
ELF magnetic fields				
Laboratory studies				
Night-time serum levels of TSH, thyroxin, cortisol, FSH and LH in young men	50 Hz 10 μT, continuous or intermittent overnight from 23.00 to 08.00 h	No differences between exposed and sham-exposed.	Well designed, double-blind study.	Selmaoui, Lambrozo & Touitou, 1997
Night-time levels of GH, cortisol and prolactin in men and women	50 Hz 1 μT during sleep (24.00 to 08.00 h)	No effect.	Double blind study.	Åkerstedt et al., 1999
ELF electric and magnetic fields				
Laboratory study				
GH, cortisol and testosterone in young men	60 Hz 9 kV m^{-1} and 20 μT 2 h following 45 min rest	No effect.	Double-blind study.	Maresh et al., 1988
Occupational studies				
Day-time serum TSH, cortisol, FSH, prolactin, LH, and testosterone in linesmen working on “live” and “dead” 400 kV power lines	50 Hz 2.8 kV m^{-1} and 23.3 μT 4.5 h during working day	No effect.	Counterbalanced presentation of “live” and “dead” power lines.	Gamberale et al., 1989
Morning and afternoon serum ACTH levels in VDU workers during one working and one leisure day	Exposure details not given.	Increase in serum ACTH during the day was statistically significant at work (0.6 pmol/l). but not leisure (0.1 pmol/l)	Samples collected Oct – Feb. Experimental protocol briefly described. No measured fields; no control over lifestyle etc.	Arnetz & Berg, 1996

6.2 Animal studies

A large number of studies have been carried out investigating the effects of EMF on circulating melatonin levels in animals, because of the possible links between EMF and breast cancer. The impact of melatonin on reproduction is particularly pronounced in seasonally breeding animals, where the effect varies depending on the length of gestation in order to ensure that the offspring are born in late spring when food is plentiful. Thus, for melatonin, the studies have been subdivided into those on laboratory rodents, which have short gestational periods and seasonally breeding animals and primates, which are more closely related to humans.

6.2.1 Melatonin

As indicated above, Stevens (1987) first suggested that chronic exposure to electric fields may reduce melatonin secretion by the pineal gland and increase the risk of breast cancer. This followed reports particularly by Wilson et al. (1981) of a significant overall reduction in pineal melatonin in rats chronically exposed to 60 Hz electric fields and by Tamarkin et al. (1981) and Shah, Mhatre & Kothari (1984) of increased DMBA-induced mammary carcinogenesis in rats with reduced melatonin levels. However, the significance of these observations for humans is not clearly established.

6.2.1.1 Laboratory rodents

Few studies have been carried out using mice. In a study by Picazo et al. (1998) a significant reduction in the night-time serum melatonin levels of mice exposed up to sexual maturity for four generations to power frequency magnetic fields was observed.

A great many more studies have been carried out using rats. The effects of electric fields were investigated before interest turned predominantly to magnetic fields. Several studies by one group of authors (Reiter et al., 1988; Wilson et al., 1981; Wilson et al., 1983; Wilson, Chess & Anderson, 1986) reported that the exposure to electric fields significantly suppressed pineal melatonin and the activity of the N-acetyl-transferase enzyme (NAT) important in the synthesis of melatonin in the pineal gland. This effect was transient, appearing within three weeks of exposure but recovered within three days following the cessation of exposure. Subsequently, however, the same laboratory (Sasser et al., 1991) reported in an abstract that it was unable to reproduce the E-field-induced reduction in pineal melatonin. Another laboratory (Grota et al., 1994) also reported that exposure to power-frequency electric fields had no effect on pineal melatonin levels or NAT activity, although serum melatonin levels were significantly depressed.

Further work used rats to investigate the effect of exposure to power-frequency magnetic fields. An early study by Martínez-Soriano et al. (1992) was inconclusive because of technical difficulties. A more extensive series of tests has been carried out by Kato et al. (1993; 1994a; 1994b; 1994c; 1994d, summarized in Kato & Shigemitsu, 1997). They studied the effects of exposure to circularly- or linearly-polarised power-frequency magnetic fields of up to 250 μT for up to 6 weeks on pineal and serum melatonin levels in male rats. These authors reported that exposure to circularly polarised but not linearly polarised field reduced night-time serum and pineal melatonin levels. However, a major difficulty with the interpretation of many of the studies by this group was that the sham-exposed groups were sometimes treated as a "low dose" exposed groups because they were exposed to stray magnetic fields (of less than 2%) generated by the exposure system. Thus, statistical comparison was sometimes made with historical controls. Such procedures fail to allow for the inter-experimental variability that was reported in replicate studies by Kato & Shigemitsu (1997). Results from four further groups who have investigated magnetic-field effects on serum and pineal melatonin levels in rats (Bakos et al., 1995; Bakos et al., 1997; Bakos et al., 1999; John, Liu & Brown, 1998; Löscher, Mevissen & Lerchl, 1998; Mevissen, Lerchl & Löscher, 1996; Selmaoui & Touitou, 1995; Selmaoui & Touitou, 1999) were inconsistent but mostly negative.

Table 48 summarizes the studies into effects of ELF fields on melatonin in experimental animals.

6.2.1.2 Seasonal breeders

Four different laboratories have investigated the effects of EMF exposure on pineal activity, serum melatonin levels and reproductive development in animals which breed seasonally. A series of studies by Yellon and colleagues (Truong, Smith & Yellon, 1996; Truong & Yellon, 1997; Yellon, 1994; Yellon, 1996; Yellon & Truong, 1998) investigated magnetic field exposure of Djungarian hamsters in which the duration of melatonin secretion during the shortening days of autumn and winter inhibit reproductive activity. These authors reported that a brief exposure to a power-frequency magnetic field 2 h before the onset of darkness reduced and delayed the night-time rise in serum and pineal melatonin. In expanded replicate studies no reduction in melatonin was observed and no effect was seen on reproductive development. In contrast to this work, Niehaus et al. (1997) reported that the chronic exposure of Djungarian hamsters to "rectangular" power-frequency magnetic fields resulted in increased testis cell numbers and night-time levels of serum melatonin. However, the results are not easy to interpret: increased melatonin levels in the Djungarian hamster are usually accompanied by decreased testicular activity. Wilson et al. (1999) investigated the effect of exposure to power-frequency magnetic fields on pineal melatonin levels, serum prolactin levels and testicular and seminal vesicle weights in Djungarian hamsters moved to a "short day" light regime in order to induce sexual regression. Night-time pineal melatonin levels were reduced following acute exposure but this effect diminished with prolonged exposure. In contrast, induced sexual regression, as indicated by the testicular and seminal vesicle weights, seemed to be enhanced rather than diminished by prolonged magnetic field exposure, suggesting a possible stress response.

Table 48. Melatonin studies in laboratory rodents

Endpoint	Exposure	Response	Comment	Authors
ELF electric fields				
Rats				
Night-time pineal melatonin levels and NAT enzyme activity in adult rats	60 Hz 1.7–1.9 kV m^{-1} (not 65 kV m^{-1} due to equipment failure) 20 h per day for 30 days	Reduced pineal melatonin and NAT activity.	Data combined in one experiment because of variability.	Wilson et al., 1981
Night-time pineal melatonin levels and NAT enzyme activity in adult rats	60 Hz 65 kV m^{-1} (39 kV m^{-1} effective) up to 4 weeks	Pineal melatonin and NAT activity reduced within 3 weeks exposure; recovered 3 days after exposure.		Wilson, Chess & Anderson, 1986
Night-time pineal melatonin levels in adult rats	60 Hz 10, 65 or 130 kV m^{-1} during gestation and 23 days postnatally	Night-time peak reduced and delayed in exposed animals.	No simple dose-response relationship.	Reiter et al., 1988
Night-time pineal melatonin levels in adult rats	60 Hz 65 kV m^{-1} 20 h per day for 30 days	No effect on night-time peak pineal melatonin.	Meeting abstract, but included because it attempted to replicate earlier studies from this group.	Sasser et al., 1991
Night-time pineal melatonin and NAT activity and serum melatonin in adult rats	60 Hz 10 or 65 kV m^{-1} 20 h per day for 30 days	No effect on night-time melatonin and NAT; serum melatonin down after 65 kV m^{-1}.	Similar to Wilson et al. 1986.	Grota et al., 1994

Table 48. Continued

ELF magnetic Fields				
Mice				
Serum melatonin levels in 4th gen. male mice	50 Hz 15 µT for 4 generations	Reduced night-time levels.	Experimental procedures not fully described.	Picazo et al., 1998
Rats				
Serum melatonin levels in adult rats	50 Hz 5 mT 30 min during the morning for 1, 3, 7, 15 and 21 days	Serum melatonin reduced on day 15; no values for days 1, 7 or 21.	Technical difficulties; brief description of method.	Martinez et al., 1992
Pineal and serum melatonin levels in adult rats	50 Hz 1, 5, 50 or 250 µT, circularly polarised 6 weeks	Night-time and some daytime reductions in serum and pineal melatonin.	Questionable comparisons to historical controls.	Kato et al., 1993
Serum melatonin levels in adult rats	50 Hz 1 µT, circularly polarised 6 weeks	Night-time melatonin levels reduced, returning to normal within one week.	Comparison to sham exposed.	Kato et al., 1994d
Pineal and serum melatonin levels in adult rats	50 Hz 1 µT, circularly polarised 6 weeks	Night-time pineal and serum levels reduced.	Comparison to sham exposed and historical controls.	Kato et al., 1994c
Serum melatonin levels in adult rats	50 Hz 1 µT, horizontally or vertically polarised 6 weeks	No effect.	Comparison to sham exposed and historical controls.	Kato et al., 1994b

Table 48. Continued

‘Antigonadotrophic’ effect of melatonin on serum testosterone in adult rats	50 Hz circularly polarised 1, 5, or 50 µT for 6 weeks	No effect.	Comparison with sham exposed.	Kato et al., 1994a
Night-time serum melatonin levels and pineal NAT activity in adult rats	50 Hz 1, 10 or 100 µT 12 h once, or 18 h per day for 30 days	Reduced melatonin and NAT activity after 100 µT (acute) and 10 and 100 µT (chronic).		Selmaoui & Touitou, 1995
Night-time serum melatonin levels and pineal NAT activity in young (9 wks) and aged (23 mos) rats	50 Hz 100 µT 18 h per day for one week	Reduced melatonin and NAT activity in young rats but not old rats.		Selmaoui & Touitou, 1999
Night-time excretion of melatonin urinary metabolite in adult rats	50 Hz 1, 5, 100 or 500 µT 24 h	No significant effects compared to base-line pre-exposure controls.		Bakos et al., 1995; 1997; 1999
Night-time pineal melatonin levels in non-DMBA treated adult rats	50 Hz 10 µT 13 weeks	No effect.	A small part of a larger, well planned mammary tumour study.	Mevissen, Lerchl & Löscher, 1996
Night-time serum melatonin, levels in SD rats	50 Hz 100 µT 1 day, 1, 2, 4, 8 or 13 weeks	No consistent effects on melatonin.	The few positive effects could not be replicated.	Löscher, Mevissen & Lerchl, 1998
Night-time excretion of melatonin urinary metabolite in adult rats	60 Hz 1 mT continuous for 10 days or 6 weeks intermittent for 2 days	No effect.		John, Liu & Brown, 1998

Table 49. Melatonin levels in seasonally breeding animals

Endpoint	Exposure	Response	Comment	Authors
ELF magnetic fields				
Djungarian hamsters				
Night-time pineal and serum melatonin levels	60 Hz 100 μT 15 min, 2 h before dark	Reduced and delayed night-time peak; diminished and absent in 2nd and 3rd replicates.	Considerable variability between replicate studies.	Yellon, 1994
Night-time pineal and serum melatonin levels; adult male reproductive status	60 Hz 100 μT 15 min, 2 h before dark; second study over 3-week period	Reduced and delayed night-time peak; diminished in 2nd replicate study; no effect on melatonin-induced sexual atrophy.	Considerable variability between replicate studies.	Yellon, 1996
Night-time pineal and serum melatonin levels; adult male reproductive status	60 Hz 100 μT 15 min, 2 h before dark for 3 weeks	No effect on pineal or serum melatonin; no effect on melatonin-induced sexual atrophy.	Second part of above paper.	Yellon, 1996
Night-time pineal and serum melatonin levels; male puberty, assessed by testes weight	60 Hz 100 μT 15 min, 2 h before dark from 16–25 days of age	Reduced and delayed night-time peak; absent in 2nd replicate study. No effect on development of puberty.	Considerable variability in melatonin levels between replicate studies.	Truong, Smith & Yellon, 1996
Night-time pineal and serum melatonin levels	60 Hz 10 or 100 μT (continuous) or 100 μT (intermittent) 15 or 60 min before or after onset of dark period	No effect.		Truong & Yellon, 1997
Night-time rise in pineal and serum melatonin levels; testes weight	60 Hz 100 μT 15 min per day, in complete darkness, for up to 21 days	No effect, even in absence of photoperiodic cue.		Yellon & Truong, 1998
Night-time pineal and serum melatonin levels; testis cell numbers	50 Hz 450 μT (peak) sinusoidal or 360 μT (peak) rectangular 56 days	Increased cell number and night-time serum melatonin levels after rectangular field exposure.	Animals on long day schedule; difficult interpretation.	Niehaus et al., 1997

Table 49. Continued

Night-time pineal melatonin levels, and testis and seminal vesicle weights in short day (regressed) animals	60 Hz 100 or 500 T, continuous and/or intermittent starting 30 min or 2 h before onset of darkness; for up to 3 h up to 42 days	Reduced pineal melatonin after 15 min exposure; reduced gonad weight but not melatonin after 42 day exposure.	Authors suggest a stress-like effect.	Wilson et al., 1999
ELF electric and magnetic fields				
Suffolk sheep				
Night-time serum melatonin levels and female puberty, detected by rise in serum progesterone	60 Hz 6 kV m^{-1} and 4 µT, generated by overhead power lines 10 months	No effect of EMFs; strong seasonal effects.	Two replicate studies; open air conditions.	Lee et al., 1993; 1995

The third set of studies of EMF effects on seasonal breeders concerned Suffolk sheep; these have a long gestational period and become reproductively active in the autumn, as day length shortens. In two replicate studies (Lee et al., 1993; 1995), Suffolk lambs were exposed outdoors to the magnetic fields generated by overhead transmission lines for about 10 months. The authors reported no effect of exposure on serum melatonin levels or on the onset of puberty.

Table 49 summarizes the studies into effects of ELF fields on melatonin in seasonal breeders.

6.2.1.3 Non-human primates

Non-human primates are close, in evolutionary terms, to humans and share many similar characteristics. Rogers et al. (1995b; 1995a) studied responses in male baboons. Generally, no effect on night-time serum melatonin levels was seen (Rogers et al., 1995a). However, a preliminary study (Rogers et al., 1995b), based on data from only two baboons, reported that exposure to an irregular, intermittent sequence of combined electric and magnetic fields in which switching transients were generated, resulted in a marked suppression of the night-time rise in melatonin. These studies are summarized in Table 50.

Table 50. Melatonin levels in non-human primates

Endpoint	Exposure	Response	Comment	Authors
ELF electric and magnetic fields				
Night-time serum melatonin level in baboons	60 Hz 6 kV m^{-1} and 50 μT, 6 weeks 30 kV m^{-1} and 100 μT, 3 weeks	No effect.		Rogers et al., 1995a
Night-time serum melatonin level in baboons	60 Hz 6 kV m^{-1} and 50 μT or 30 kV m^{-1} and 100 μT irregular and intermittent sequence for 3 weeks	Reduced serum melatonin levels.	Preliminary study on two baboons.	Rogers et al., 1995b

6.2.2 *The pituitary and other hormones*

The pituitary gland, like the pineal gland, is intimately connected to the nervous system. It releases hormones into the blood stream either from specialised neurosecretory cells originating in the hypothalamus region of the brain, or from the cells in the pituitary whose function is under the control of such neurosecretory cells via factors released into a specialised hypothalamic-pituitary portal system. The main pituitary hormones investigated in EMF studies include several involved in growth and body physiology, particularly thyroid-stimulating hormone (TSH), which controls the function of the thyroid gland, adrenocorticotrophic hormone (ACTH), which regulates the function of the adrenal cortex, and growth hormone (GH), which affects body growth, and hormones which have important sexual and reproductive functions, particularly follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin (or luteotrophic hormone).

6.2.2.1 Pituitary-adrenal effects

The possibility that EMF might act as a stressor has been investigated in a number of studies that have examined possible effects of EMF exposure on the release of hormones involved in stress responses, particularly ACTH and cortisol and/or corticosterone released from the adrenal cortex. For ELF electric fields, Hackman & Graves (1981) reported a transient (minutes) increase in serum corticosterone levels in young rats immediately following the onset of exposure to levels greatly in excess of the electric field perception threshold; however, exposure for longer durations had no effect. A lack of effect of prolonged exposure to ELF fields has been reported by other authors on ACTH levels (Portet & Cabanes, 1988) and on cortisol/corticosterone levels (Burchard et al., 1996; Free et al., 1981; Portet & Cabanes, 1988; Quinlan et al., 1985; Thompson et al., 1995). Two studies, both limited by small numbers of animals, reported positive effects of exposure to power frequency electric (de Bruyn & de Jager, 1994) and magnetic (Picazo et al.,

1996) fields on the diurnal rhythmicity of cortisol/corticosterone levels in mice.

6.2.2.2 Other endocrine studies

Studies of TSH levels and of the thyroid hormones (T3 and T4), which have a major influence on metabolic functions, have been carried out in three studies. No effect on serum TSH levels was found (Free et al., 1981; Portet & Cabanes, 1988; Quinlan et al., 1985); in addition, no effects were reported on serum thyroxin (T3 and T4) levels in rabbits (Portet & Cabanes, 1988), but T3 levels were reduced in rats (Portet and Cabanes, 1988). Growth hormone levels were reported to increase in rats intermittently exposed for 3 h (Quinlan et al., 1985), but were reported to be unaffected following prolonged (3–18 weeks) electric-field exposure at the same level (Free et al., 1981).

Similarly negative or inconsistent data exist concerning possible effects of ELF field exposure on hormones associated with reproduction and sexual development. Prolactin, FSH, LH and testosterone levels in rats were reported unaffected by exposure to power-frequency electric fields (Margonato et al., 1993; Quinlan et al., 1985); similar results for prolactin were reported by Free et al. (1981), but variable effects on FSH levels were seen during development and serum testosterone levels were reported to be decreased in adults. In contrast, an increase in serum prolactin levels was reported in Djungarian hamsters briefly exposed to ELF magnetic fields (Wilson et al., 1999), and an increase in serum progesterone in cattle exposed to combined electric and magnetic fields (Burchard et al., 1996). In a subsequent study, Burchard et al. (2004) found that continuous exposure to an electric field for 4 weeks had no effect on circulating levels of progesterone, prolactin and insulin-like growth factor.

Table 51 summarizes the studies investigating the effects of ELF fields on hormone levels in experimental animals.

6.3 In vitro studies

In vitro studies of exposure to EMFs divide into two types of investigation: effects on the production of melatonin by cells from the pineal gland; and effects on the action of melatonin on cells. Some studies have investigated the effects of static magnetic fields, but these have not been reviewed here.

Table 51. The pituitary and other hormones

Endpoint	Exposure	Response	Comment	Authors
ELF electric fields				
Mice				
Serum levels of corticosterone in adult male mice	60 Hz 10 kV m^{-1} 22 h per day for 6 generations	Elevated daytime but not night-time levels compared to controls.	Small numbers and variable daytime data.	de Bruyn & de Jager, 1994
Rats				
Serum levels of TSH, GH, FSH, prolactin, LH, corticosterone and testosterone in young and adult male rats	60 Hz 100 kV m^{-1} (unadjusted) 20 h per day for 30 and/or 120 days (adults) or from 20–56 days of age (young)	Testosterone levels significantly decreased after 120 days; no other consistent effects in adults; significant changes in FSH levels in young rats.	Variable changes in hormone plasma concentration during development.	Free et al., 1981
Serum corticosterone levels in adult male mice.	60 Hz 25 or 50 kV m^{-1} 5 min per day up to 42 days	Transient increase in serum levels at onset of exposure.	Positive control group; incomplete presentation of data.	Hackman & Graves, 1981
Serum levels of TSH, GH, prolactin and corticosterone in adult male rats	60 Hz 100 kV m^{-1}, continuous or intermittent 1 or 3 h	Increase in GH levels in rats exposed intermittent for 3 h, but not 1 h; no other effects.	Care taken to avoid extraneous confounding factors.	Quinlan et al., 1985
Serum levels of TSH, ACTH, thyroxin ($T_3 + T_4$) and corticosterone in young male rats	50 Hz 50 kV m^{-1} 8 h per day for 28 days	No significant effects except T_3 (but not T_4) reduced.		Portet & Cabanes, 1988
Serum levels of FSH, LH and testosterone in adult male rats	50 Hz 25 or 100 kV m^{-1} 8 h per day for up to 38 weeks	No significant effects.	Variable data.	Margonato et al., 1993
Rabbits				
Serum levels of GH, ACTH, thyroxin ($T_3 + T_4$) and corticosterone (and cortisol) in 6 week old rabbits	50 Hz 50 kV m^{-1} 16 h per day from last 2 weeks of gestation to 6 weeks after birth	No significant effects.		Portet & Cabanes, 1988

Table 51. Continued

ELF magnetic fields				
Mice				
Serum cortisol levels in adult male mice	50 Hz 15 µT 14 weeks prior to conception, gestation and 10 weeks post gestation	Loss of diurnal rhythmicity; daytime levels fell and night-time levels rose.	Small numbers per group.	Picazo et al., 1996
Djungarian hamsters				
Serum levels of prolactin in adult male Djungarian hamsters on long or short days	60 Hz 100 µT 15 min before dark 100 µT, intermittent / continuous 45 min per day before dark for 16–42 days	Prolactin levels elevated 4 h after dark following acute but not chronic exposure.	Incomplete presentation of prolactin data.	Wilson et al., 1999

6.3.1 *Effects on melatonin production in vitro*

There are only a few studies that have investigated the effect of magnetic fields on melatonin production in vitro. All used rodents as the source of pineal gland cells but there are marked differences in their methodology. Most used power frequencies (50 or 60 Hz), but the field strength (50 µT–1 mT) and duration (1–12 h) differ between the studies. Direct measures include melatonin content or melatonin release from cells. Indirect measures can be made from the activity of N-acetyltransferase (NAT), an enzyme involved in the synthesis of melatonin, or of hydroxyindole-O-methyltransferase (HIOMT), an enzyme responsible for methylation and hence release of melatonin from the cells. Most of the studies have stimulated pharmacologically the production of melatonin in the isolated glands by the addition of noradrenaline (NA) or isoproterenol.

Lerchl et al. (1991) exposed pineal glands from young rats, removed during the day light period, to a combination of a static field (44 µT) and a low frequency magnetic field (44 µT at 33.7 Hz), the theoretical conditions for cyclotron resonance of the calcium ion. Exposure caused a reduction in NAT activity, melatonin production and melatonin release into the culture medium. Rosen, Barber & Lyle (1998) also used pineal glands from the rat, but this study was different to the other studies in that the pineal gland was separated into individual cells. The overall result was that magnetic field exposure caused a statistically significant 46% reduction in stimulated melatonin release. Chacon (2000) used rat pineal glands to study NAT activity. The enzyme activity decreased by approximately 20% after 1 h exposure to the highest field strength tested (1000 µT) but was not significantly altered by field strengths of 10 or 100 µT. The interpretation of the result may be complicated by the removal of the pineal gland during the rats' dark period, which may have had an effect on melatonin synthesis and a confounding effect on the result.

A study by Brendel, Niehaus & Lerchl (2000) used pineal glands from the Djungarian hamster. It also differed from the previous studies in that the glands were maintained in a flow-system, so that changes of melatonin released from the glands could be monitored throughout the duration of the experiment. The experimental protocol appears to have been well-designed with random allocation of exposure or sham to identical exposure systems and the experiments run blind. The authors concluded that EMF inhibited melatonin production in both the 50 Hz and 16.67 Hz experiments. However there is only one time point in one of four experiments that the melatonin released is statistically different from the sham exposed. Similarly, a study by Tripp, Warman & Arendt (2003) used a flow system to detect changes of melatonin release during the course of the exposure. The exposure was for 4 h to a circularly polarised magnetic fields at 500 µT, 50 Hz. Samples were taken every 30 min; the process used remote collection to avoid potential artefacts involved in manual collection. The glands were not stimulated pharmacologically and no field-dependent changes in melatonin release were detected.

Lewy, Massot & Touitou (2003) used rat pineal glands isolated in the morning and hence during the 12 h light period. The glands were exposed for 4 h to a 50 Hz magnetic field at 1 mT. The activity of enzymes NAT and HIOMT was measured, as well as the release of melatonin into the incubation liquid. In contrast to many other studies, field exposure given simultaneously with NA or 30 min prior to NA administration caused a significant increase (approximately 50%) in melatonin release. There was no change in melatonin release due to field exposure in glands that had not been stimulated by NA.

6.3.2 Effects on the action of melatonin in vitro

The main interest in this area was caused by the claim that exposure to magnetic fields can block the inhibitory effect of melatonin on growth of breast cancer cells. The original work was reported by Liburdy et al. (1993) in a study using a human oestrogen-responsive breast cancer cell line (MCF-7). They found that the proliferation of MCF-7 cells can be slowed by the addition of physiological concentrations of melatonin (1 nM). However, if the cells are simultaneously exposed to a 60 Hz, 1.2 µT magnetic field, then the effect of melatonin on the rate of proliferation is reduced. The effects are fairly small and can only been seen after 7 days in culture. They suggested that the magnetic field disrupted either the ligand/receptor interaction or the subsequent signalling pathway. The authors found no effect at a magnetic field strength of 0.2 µT and suggested a threshold between 0.2 µT and 1.2 µT. No effect was seen using field exposure alone. A similar effect of a 60 Hz field was reported by Harland & Liburdy (1997) but using tamoxifen (100 nM) rather than melatonin to bring about the initial inhibition. The effect has been reported in other cell lines, namely a second breast cancer cell line, T47D, (Harland, Levine & Liburdy, 1998) and a human glioma cell line 5F757 (Afzal, Levine & Liburdy, 1998). However, as previously noted (AGNIR, 2001b; NIEHS, 1998), the effect seen in the initial study (Liburdy et al., 1993) was small (10–20 % growth over 7 days) and some concern was noted regarding the robustness of the effect.

Blackman, Benane & House (2001) set out to replicate these findings, using the MCF-7 cells supplied by Liburdy, but with a modified and improved experimental protocol. Melatonin caused a significant 17% inhibition of MCF-7 growth ($p < 0.001$), even though the standard errors of the estimated growth statistics showed considerable overlap. This reported effect was abolished by exposure to a 60 Hz magnetic field at 1.2 μT, confirming the results of Liburdy et al. (1993). In addition, tamoxifen caused a 25% inhibition in cell numbers, which was reduced to a 13% inhibition by exposure to a 60 Hz magnetic field at 1.2 μT. This result confirmed the results reported by Harland & Liburdy (1997), in which a 40% inhibition was reduced to 25% by EMF exposure. A later study by Ishido (2001) exposed MCF-7 cells (supplied by Liburdy) to 0, 1.2 or 100 μT at 50 Hz for 7 days. Melatonin at concentrations of 10^{-9} M or higher induced inhibition of intracellular cyclic AMP which was blocked by exposure to a 50 Hz field at 100 μT. Similarly DNA synthesis, which was inhibited by 10^{-11} M melatonin levels, was partially released by exposure at 1.2 μT.

However, although the MCF-7 cell line has undoubtedly provided a useful model to investigate effects on isolated breast cancer cells it is only one possible model in cells that have been separated from their natural environment and therefore its implication for breast cancer in general is limited. The cell line is rather heterogeneous; different subclones show different growth characteristics (e.g. Luben & Morgan, 1998; Morris et al., 1998) raising the possibility that the effects were specific to individual subclone phenotypes. The effects of stronger magnetic fields were studied by Leman et al. (2001) in three breast cancer cell lines that were reported to have different metastatic capabilities: MDA-MB-435 cells, which were considered to be highly metastatic, MDA-MB-231 cells which were considered to be weakly metastatic, and MCF-7 cells, which were considered as non-metastatic. Only the weakly and non-metastatic cells responded to melatonin and optimum inhibition was achieved at 1mM concentration of melatonin (a million-fold higher than used in the Liburdy study). Exposure for 1 h to a pulsed field at 300 μT repeated for 3 days had no effect on growth in either cell line.

The in vitro studies into the effects of ELF magnetic fields on melatonin are summarized in Table 52.

Table 52. Magnetic field effects on melatonin

Endpoint	Exposure	Response	Comment	Authors
Effects on melatonin production in vitro				
NA stimulation of melatonin production and release from rat pineal gland	Static field and 33.7 Hz, 44 µT 2.5 h	Reduced production and release.	Opposite to expected effect of calcium ions.	Lerchl et al., 1991
NA stimulation of melatonin release from rat pineal cells	60 Hz 50 µT 12 h	Reduced release.		Rosen, Barber & Lyle, 1998
NAT activity in rat pineal glands	50 Hz 10, 100 µT or 1 mT 1 h	Decreased NAT activity at the highest exposure level only.		Chacon, 2000
Isoproterenol stimulation of melatonin production in Djungarian hamster pineal gland	50 Hz or 16.7 Hz 86 µT 8 h	Melatonin production reduced.	Continuous flow system used allowing temporal resolution of any effect.	Brendel, Niehaus & Lerchl, 2000
Melatonin release from rat pineal gland	50 Hz 0.5 mT 4 h	No effect on melatonin release.	Continuous flow system used allowing temporal resolution of any effect.	Tripp, Warman & Arendt, 2003
NA stimulated melatonin release from rat pineal gland.	50 Hz 1 mT 4 h	Melatonin release increase.		Lewy, Massot & Touitou, 2003
Effects on cell responses to melatonin or tamoxifen in vitro				
Melatonin inhibition of MCF-7 cell growth	60 Hz 1.2 µT 7 days	EMF exposure reduced growth inhibition.	Small (10–20%) effect.	Liburdy et al., 1993
Tamoxifen inhibition of MCF-7 cell growth	60 Hz 1.2 µT 7 days	EMF exposure reduced growth inhibition.		Harland & Liburdy, 1997
Melatonin or Tamoxifen inhibition of MCF-7 cell growth	60 Hz 1.2 µT 7 days	EMF exposure reduced growth inhibition by melatonin and tamoxifen.	Standard errors on growth statistics show considerable overlap.	Blackman, Benane & House, 2001
Melatonin inhibition of cAMP and DNA synthesis in MCF-7 cells	50 Hz 1.2 or 100 µT 7 days	Reduction of melatonin induced inhibition.		Ishido, 2001

Table 52. Continued

Melatonin inhibition of growth of 3 breast cancer cell lines including MCF-7	2 Hz pulsed field; pulse width 20 ms 0.3 mT 1 h per day for 3 days	No effect on cell growth.	Leman et al., 2001

6.4 Conclusions

The results of volunteer studies as well as residential and occupational studies suggests that the neuroendocrine system is not adversely affected by exposure to power-frequency electric and/or magnetic fields. This applies particularly to the circulating levels of specific hormones of the neuroendocrine system, including melatonin, released by the pineal gland, and a number of hormones involved in the control of body metabolism and physiology, released by the pituitary gland. Subtle differences were sometimes observed in the timing of melatonin release or associated with certain characteristics of exposure, but these results were not consistent. It is very difficult to eliminate possible confounding by a variety of environmental and lifestyle factors that might also affect hormone levels. Most laboratory studies of the effects of ELF exposure on night-time melatonin levels in volunteers found no effect when care was taken to control possible confounding.

From the large number of animal studies investigating power-frequency EMF effects on rat pineal and serum melatonin levels, some reported that exposure resulted in night-time suppression of melatonin. The changes in melatonin levels first observed in early studies of electric-field exposures up to 100 kV m^{-1} could not be replicated. The findings from a series of more recent studies which showed that circularly-polarised magnetic fields suppressed night-time melatonin levels were weakened by inappropriate comparisons between exposed animals and historical controls. The data from other magnetic fields experiments in laboratory rodents, covering intensity levels over three orders of magnitude from a few microtesla to 5 mT, were equivocal, with some results showing depression of melatonin but others showing no change. In seasonally breeding animals, the evidence for an effect of exposure to power-frequency fields on melatonin levels and melatonin-dependent reproductive status is predominantly negative. No convincing effect on melatonin levels has been seen in a study of non-human primates chronically exposed to power-frequency fields, although a preliminary study using two animals reported melatonin suppression in response to an irregular and intermittent exposure.

The effects of ELF exposure on melatonin production or release in isolated pineal glands was variable, although relatively few in vitro studies have been undertaken. The evidence that ELF exposure interferes with the action of melatonin on breast cancer cells in vitro is intriguing and there appears to be some supporting evidence in terms of independent replication using MCF-7 cells. However this system suffers from the disadvantage that the cell lines frequenctly show genotypic and phenotypic drift in culture that can hinder transferability between laboratories.

With the possible exception of transient (minutes duration) stress following the onset of ELF electric field exposure at levels significantly above perception thresholds, no consistent effects have been seen in the stress-related hormones of the pituitary-adrenal axis in a variety of mammalian species. Similarly, mostly negative or inconsistent effects have been observed in amounts of growth hormone, levels of hormones involved in controlling metabolic activity or associated with the control of reproduction and sexual development, but few studies have been carried out.

Overall, these data do not indicate that ELF electric and/or magnetic fields affect the neuroendocrine system in a way that would have an adverse impact on human health and the evidence is thus considered inadequate.