The effects of extremely low-frequency magnetic fields on melatonin and cortisol, two marker rhythms of the circadian system

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Introduction

We are continuously exposed in our environment to electromagnetic fields (EMF) which are either of natural origin (geomagnetic field, intense solar activity, thunderstorms) or manmade (factories, transmission lines, electric appliances at work and home), magnetic resonance imaging, medical treatment, etc. Electric and magnetic fields which exist wherever electricity is generated, transmitted, or distributed correspond to three frequency ranges: the extremely low frequency (ELF)

In the past 30 years the concern that daily exposure to extremely low-frequency magnetic fields (ELF-EMF) (1 to 300 Hz) might be harmful to human health (cancer, neurobehavioral disturbances, etc) has been the object of debate, and has become a public health concern. This has resulted in the classification of ELF-EMF into category 2B, ie, agents that are "possibly carcinogenic to humans" by the International Agency for Research on Cancer. Since melatonin, a neurohormone secreted by the pineal gland, has been shown to possess oncostatic properties, a "melatonin hypothesis" has been raised, stating that exposure to EMF might decrease melatonin production and therefore might promote the development of breast cancer in humans. Data from the literature reviewed here are contradictory. In addition, we have demonstrated a lack of effect of ELF-EMF on melatonin secretion in humans exposed to EMF (up to 20 years' exposure) which rebuts the melatonin hypothesis. Currently, the debate concerns the effects of ELF-EMF on the risk of childhood leukemia in children chronically exposed to more than 0.4 μT. Further research is thus needed to obtain more definite answers regarding the potential deleterious effects of ELF-EMF.

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range includes the frequencies (50 Hz in Europe, 60 Hz in North America) of the electric power supply and of electric and magnetic fields (EMF) generated by electricity power lines and electric/electronic appliances; intermediate frequency (IF, 300 Hz to <10 MHz) is used in computer monitors, industrial processes, and security systems; and finally, radiofrequency range (RF, 10 MHz to 300 GHz) includes radars, and radio and television broadcasts and telecommunications.

Biological effects of ELF-EMF and their consequences on human health have become the subject of important and recurrent public debate. The growth of electric power use in industrialized countries and the parallel increase of environmental exposure to ELF-EMF resulted in a widespread concern that ELF-EMF may have harmful effects in humans, a concern stimulated in the past decades by a number of epidemiologic studies reporting deleterious effects of ELF-EMF on human health. Wertheimer and Leeper[1,2] published the first report, conducted in the Denver area, on the association between childhood cancer and exposure to ELF-EMF, with the conclusion of a higher risk of childhood leukemia at higher residential ELF-EMF exposure. Savitz et al[3] gave support to this assertion with the publication of similar results in the same area (Denver). From then, several epidemiologic papers have reported a possible link, without any experimental evidence, however, between exposure of humans to ELF-EMF and diseases such as leukemia and other cancers,[4-6] depression, and suicide,[7] and neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis.[8-11] All these results, though some of them were conflicting, resulted in a "melatonin hypothesis" as a tentative explanation, with the idea that those potential ELF-EMF deleterious effects might be a consequence of an inhibitory effect of ELF-EMF on the production of melatonin,[12] a hormone whose secretion has been shown to be altered (concentration decline and/or alteration of its circadian rhythm) in some diseases including cancers (review in Hill et al, ref 13), depressive disorders,[14-16] and disorders of the circadian time structure.[17,18]

The concern regarding public health resulted in reports on this matter of official organizations, the most recent reports being those of the International Agency for Research on Cancer (IARC) in 2002 and the World Health Organization in 2007.[19] Of special interest, the IARC published in 2002 an evaluation of the carcinogenic risks of ELF to humans.[20] The agency classified ELF electric fields into category 3, which in the classification corresponds to "inadequate evidence" of deleterious effects, and classified ELF magnetic fields into category 2B, corresponding to the category of agents that are "possibly carcinogenic to humans." A classification into group 2B is "usually based on evidence in humans which is considered credible, but for which other explanations could not be ruled out." It has to be noted that these extremely-low-frequency electric and magnetic fields are separate entities.

Whether or not ELF magnetic field exposure is causally related to increased health risks has led many scientists to examine the potential mechanisms by which ELF magnetic fields might affect human health. It is known that cancer and neurobehavioral alterations may be associated with circadian rhythm disruption and/or effect on melatonin secretion.[21-24] Theoretically, melatonin could be a good mechanistic candidate to explain potentially deleterious effects of EMF since: i) its secretion is dramatically inhibited by light,[25-28] which is the visible part of EMF; ii) the circadian pattern of the hormone is phase-advanced or -delayed by light according to the time of exposure, which is known as the phase response curve or PRC,[29] and this property might occur with exposure to EMF; iii) the oncostatic properties of melatonin have been described,[30-32] which resulted in the hypothesis that a decrease in the secretion of melatonin by the pineal gland might promote the development of breast cancer in humans[12]; iv) and last, its association with depressive disorders has been put forward.[14-16]

Since both melatonin and cortisol are major markers of the circadian system, we reviewed data from the literature on these two marker rhythms, in search of deleterious effects of EMF on both their blood levels and abnormalities in their circadian profiles, eg, a phase-advance or a phase-delay which would point out a rhythm desynchronization of the organism, ie, a situation that occurs when the biological clock is no longer in step with its environment.[17,33]

Rationale for studying the effects of ELF-EMF on melatonin and cortisol secretions

Melatonin (N-acetyl 5- methoxytryptamine), a neurohormone produced by the pineal gland, is characterized by a prominent circadian rhythm with high levels at night and very low levels during the daytime, whatever the age.[34,35] Its secretory pattern has a strong endogenous

component and is physiologically controlled by light. Melatonin is therefore considered as a marker rhythm of the circadian temporal structure. A marker rhythm is a physiological rhythmic variable, whose circadian pattern is highly reproducible on an individual basis and as a group phenomenon, which thus allows characterization of the timing of the endogenous rhythmic time structure and provides information on the synchronization of individuals *(Figure 1)*.[36] Besides melatonin, the most frequent marker rhythms used both in humans and animals are the core body temperature circadian pattern[37] and the cortisol circadian rhythm, since they are also highly reproducible.[36,17]

Cortisol also displays a robust and highly reproducible circadian rhythm that does not respond rapidly to minor and transient environmental changes, as they are part of daily life, which also makes it a good candidate as a marker rhythm.[36] Since a relationship between the pineal gland and the adrenal gland has been documented in vitro,[38] and considering the hypothesis of the alteration of melatonin by EMF, it can be useful to look at their potential effects on cortisol, another rhythm marker of the circadian system, and to obtain an additional argument for a circadian desynchronization of the organism.

ELF-EMF effects on melatonin

Animal studies

For the sake of clarity, we present in two different tables the reports on ELF-EMF effects on melatonin. *Table Ia* displays the reports showing an alteration of melatonin secretion in different animal species, mainly rodents, after exposure to ELF-EMF. *Table Ib* deals with all of the studies reporting no effect of ELF-EMF on melatonin secretion in the different species under study.

The very first data on the topic deal with electric fields (not magnetic fields), and date back to 1981, with the report on the reduction of pineal melatonin and N-acetyltransferase (NAT), the key enzyme for melatonin synthesis, in rats exposed to electric fields 20 h/day for 30 days.[39,40] Other reports, however, failed to find any effect, or were inconclusive or contradictory.[41,42] Then the interest shifted from electric to magnetic fields, with a large number of studies devoted to the effects of ELF-EMF on melatonin levels in different animal species.[43,44]

Yellon[45,46] and Wilson et al,[47] documenting the effects of magnetic fields, were the first to report a reduction of both pineal and plasma melatonin in Djungarian hamsters with a short exposure to a sinusoidal 100-µT magnetic field. In addition, Wilson et al[47] also reported an increase in the concentration of norepinephrine in the suprachiasmatic nuclei, the central rhythm-generating system.

The majority of laboratory studies were then carried out on rats. Kato et al,[48] in exposing male Wistar-King rats for 6 weeks to a 50-Hz circularly polarized sinusoidal magnetic field using increasing intensities, showed a decrease

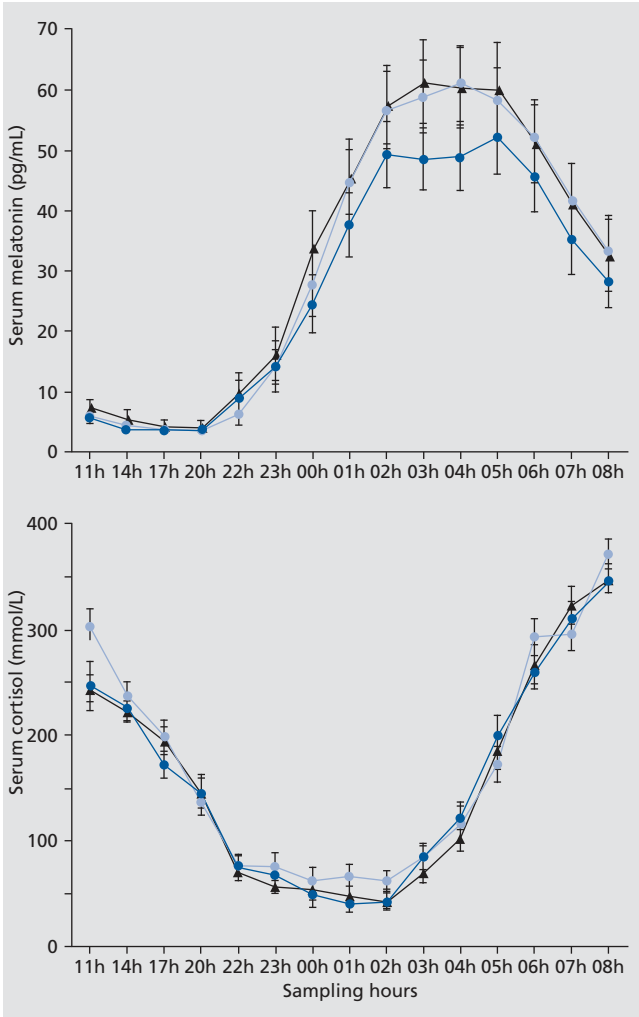

Figure 1. Reproducibility of the circadian patterns of plasma cortisol and melatonin in young healthy men. The circadian rhythms of the two hormones are highly reproducible from a day to another. Both are useful circadian markers of the time structure.
Reproduced from ref 36: Selmaoui B, Touitou Y. Reproducibility of the circadian rhythms of serum cortisol and melatonin in healthy subjects. A study of three different 24-h cycles over six weeks. *Life Sci*. 2003;73:3339-3349. Copyright © Pergamon Press 2003

Reference of the study	Species	Exposure characteristics	Timing of exposure	Fluid or pineal	Sampling time	Effect on melatonin secretion
Wilson et al, 1981[39]	Adult rats	60 Hz- 1.7–1.9 kV/m	20 h/day for 30 days	Pineal Mel and NAT activity	Day/night	Decrease in pineal Mel and NAT activity
Wilson et al, 1986[40]	Adult rats	60 Hz- 65 kV/m (39 kV/m effective)	20 h/day for 3 weeks	Pineal Mel and NAT activity	Day/night	Decrease in pineal Mel and NAT activity within 3 weeks
Reiter et al, 1988[41]	Adult rats	50 Hz- 10, 65 or 130 kV/m	During gestation and 23 days postnatally	Pineal Mel	Nighttime	Decreased and delayed nighttime peak
Martinez Soriano et al, 1992[52]	Adult rats	50 Hz- 5 mT	30 min during the morning for 1, 3, 7, 15 and 21 days	Ser Mel	Nighttime	Decrease in Ser Mel on day 15
Kato et al, 1993[48]	Adult rats	50 Hz- 1, 5, 50 or 250 µT	6 weeks	Pineal and Pl Mel	Nighttime	Decrease in serum and pineal melatonin
Yellon, 1992, 1994[46]	Djungarian hamsters	60 Hz- 100 µT	18 h/ day for one week	Pineal and Ser Mel	Nighttime	Decreased and delayed nighttime peak
Grota et al, 1994[42]	Adult rats	60 Hz- 10 or 65 kV/m	20 h/day for 30 days	Pineal Mel and NAT activity, Ser Mel	Nighttime	Decrease in Ser Mel after exposure to 65 kV/m but no effect on nighttime pineal Mel and NAT
Kato et al, 1994[51]	Adult albino rats	50 Hz- 1 µT, circularly polarized	6 weeks	Pineal and Ser Mel	Day/night	Decrease in nighttime pineal and Ser Mel Recovery 1 week after cessation of exposure
Kato et al, 1994[50]	Adult pigmented rats	50 Hz- 1 µT, circularly polarized	6 weeks	Ser Mel	12 h and 24 h	Decrease at night
Löscher et al, 1994[53]	Adult rats	50 Hz- 0.3-1 µT	24 h/day, 7 days/ week 91 days	Ser Mel	Nighttime	Decrease in nocturnal Ser Mel
Rogers et al, 1995[76]	Baboons	60 Hz- 6 kV/m and 50 µT or 30 kV/m and 100 µT irregular and intermittent sequence	6 weeks	Ser Mel	Nighttime	Decrease in Ser Mel
Selmaoui and Touitou, 1995[62]	Adult rats	50 Hz- 1, 10 or 100 µT	12 h, or 18 h per day for 30 days	Ser Mel and pineal NAT activity	Nighttime	Decrease in Mel and NAT activity after 100 µT (acute) and 10 and 100 µT (chronic)
Truong et al, 1996[57]	Young Djungarian hamsters	60 Hz- 100 µT	15 min, 2 h before dark; over 3-weeks	Pineal and Ser Mel	Nighttime	Decreased and delayed nighttime peak though not replicated in the same paper = inconclusive
Yellon, 1996[58]	Djungarian hamsters	60 Hz- 100 µT	15 min, 2 h before dark; over 3-weeks	Pineal and Ser Mel	Nighttime	Decreased and delayed nighttime peak though not replicated in the second part of the paper = inconclusive

Table Ia. Magnetic field reports on the modification of melatonin secretion in different animal species. Mel, melatonin; Pl, plasma; Ser, serum; aMT6s, 6 sulfatoxymelatonin; MF, magnetic field; NAT: serotonin N-acetyl transferase

Reference of the study	Species	Exposure characteristics	Timing of exposure	Fluid or pineal	Sampling time	Effect on melatonin secretion
Mevissen et al, 1996[71]	Adult rats	50 Hz- 10 µT	24 h/day, 7 days/wk, for 91 days	Ser Mel	Nighttime	Decreased Mel levels
Niehaus et al, 1997[59]	Djungarian hamsters	50 Hz- 450 µT sinusoidal or 360 µT rectangular	56 days	Pineal and Ser Mel	Nighttime	Increased nighttime serum melatonin levels after rectangular field exposure
Reiter et al, 1998[83]	Adult rats	0 Hz- Pulsed Magnetic field (1s off and on intervals) of 50 to 500 µT	15 to 120 min	Pineal Mel and NAT activity, Ser Mel	Nighttime	Inconsistent results from 15 experiments
Lerchl et al, 1998[60]	teleost fish, the brook trout (Salvelinus fontinalis)	1 Hz- maximum 40 µT (200 ms on, 800 ms off)	45min : exposure started at 22 h45	Pineal and Ser Mel	At 23:30	Increase
Selmaoui and Touitou, 1999[63]	Aged rats	50 Hz- 100 µT	18 h per day for one week	Ser Mel and pineal NAT	Nighttime	Decrease of Mel and NAT activity in young but not aged rats
Wilson et al, 1999[52]	Siberian hamsters	50 Hz- 100 or 500 T, continuous and/or intermittent	30 min or 2 h before onset of darkness and for up to 3 h up to 42 days	Pineal Mel	Nighttime	Decrease of pineal Mel and NAT activity in short photoperiod
Fernie et al, 1999[81]	Kestrel	60 Hz- current created a magnetic field of 30 µT and an electric field of 10 kV/m.	For one or two breeding season	Pl Mel	08 h-11 h (Males) and 13-15 h (females)	Effect in adult males but not females. Long-term, but not short-term, MF exposure of adults suppressed in their fledglings. Seasonal shift
Huuskonen et al, 2001[54]	Female adult rats	50 Hz- 13 or 130 µT	24 h/day from day 0 of pregnancy; and killed during light and dark periods between 70 h and 176 h after ovulation	Ser Mel	Nighttime	Decrease of Ser Mel concentration by 34 and 38% at 13 and 130 µT
Burchard et al, 2004[84]	Holstein heifers	60 Hz- 10kV/m	22h/day for 4 weeks	Ser Mel	9 h, 10 h, 11 h, and 12 h	Inconsistent results between 2 replicates
Kumlin et al, 2005[55]	Female mice	50 Hz- at 100 µT	52 days	Urinary aMT6s	Nocturnal urine was collected 1, 3, 7, 14, 16 and 23 days after beginning of exposure	Significant day-night difference in the aMT6s levels. No effect on the total 24 h

Table Ia. Continued

Reference of the study	Species	Exposure characteristics	Timing of exposure	Fluid or pineal	Sampling time	Effect on melatonin secretion
Dyche et al, 2012[61]	Adult rats	60 Hz- 1000 mG	1 month	Urinary aMT6s	Urine collected for the last 3 days of the exposure period	Mild increase of nighttime aMT6s

Table Ia. Continued

Reference of the study	Species	Exposure characteristics	Timing of exposure	Fluid or pineal	Sampling time	Effect on melatonin secretion
Kato et al, 1994[49]	Adult rats	50 Hz- 1 µT, horizontally or vertically oriented MF	6 weeks	Pineal and Pl Mel	12 h and 24 h	No effect
Lee et al, 1993, 1995[74,75]	Suffolk sheep	60 Hz- 6 kV/m and 4 µT	Overhead power lines (10 months)	Ser Mel	8 x 48 h periods	No effect
Rogers et al, 1995[56]	Baboons	60 Hz- 6 kV/m and 50 µT	6 weeks 30 kV/m and 100 µT, 3 weeks	Ser Mel	Nighttime	No effect
Kroeker et al, 1996[68]	Rats	0 Hz- 800 gauss	between 12 hours and 8 days	Pineal and Ser Mel	Nighttime	No effect
Yellon, 1996[58]	Adult Djungarian hamsters	60 Hz- 100 µT	15 min, 2 h before dark	Pineal and Ser Mel	Nighttime	No effect
Mevissen et al, 1996[72]	Adult rats	50 Hz- 50 µT	24 h/day, 7 days/week, for 91 days	Ser Mel	Nighttime	No effect on DMBA-treated rats
Bakos et al, 1995; 1997[64,65]	Adult rats	50 Hz- 1, 5, 100 or 500 µT	24 h	Urinary aMT6s	Day/night	No effect
Löscher et al, 1998[69]	Adult rats	50 Hz- 100 µT	18 h per day for one week	Ser Mel	Nighttime (3 samples)	No effect
Yellon and Truong, 1998[77]	Adult Siberian hamster	60 Hz- 100 µT 15 min per day	Up to 21 days	Pineal and Ser Mel	Nighttime	No effect
Burchard et al, 1998[78]	Holstein cows	60 Hz- 10 kV/m and a uniform horizontal magnetic field of 30 µT	Up to 56 days of exposure	Pl Mel	every 0.5 h for 14 h starting at 17 h	No effect
John et al, 1998[70]	Adult rats	60 Hz, 1 mT	20 h/day for 6 weeks	Urinary aMT6s	Circadian pattern	No effect in 3 experiments out of 4
de Bruyn et al, 2001[73]	Mice	50 Hz- between 0.5 and 77 µT wit h an average of 2.75 µT	24 h/day from conception until adult age	Pl Mel	23 h-01 h30	No effect
Fedrowitz et al, 2002[67]	Adult rats	50 Hz- 100 µT	24 h/day for 2 weeks	Pineal Mel	at 9 h30, 10h30, 12h30, 1h30	No effect

Table Ib. Reports on the lack of effect of magnetic field on melatonin secretion in different animal species. Mel, melatonin; Pl, plasma; Ser, serum; aMT6s, 6 sulfatoxymelatonin; MF, magnetic field; NAT, serotonin N-acetyl transferase; NG, not given

Reference of the study	Species	Exposure characteristics	Timing of exposure	Fluid or pineal	Sampling time	Effect on melatonin secretion
Bakos et al, 2002[66]	Adult rats	50 Hz- 100 or 50 microT	8 h/day for 1 week	Urinary aMT6s	Nighttime	No effect
Rodriguez et al, 2004[80]	Holstein cows	60 Hz- vertical electric field of 10 kV/m and a horizontal magnetic field of 30 µT	for 16 h/day for 4 weeks	Pl Mel	Over 24 h	No effect during dark period. Daytime mel low
Burchard et al, 2007[79]	Holstein heifers	60 Hz- 30 µT	20 h/day for 4 weeks	Ser Mel	09 h, 10 h, 11 h	No effect
Dell'omo et al, 2009[82]	Eurasian kestrels	50 Hz-power lines hig h voltage : 4-8 µT	Breeding season	Ser Mel	NG	No effect

Table Ib. Continued

in pineal and plasma melatonin concentrations without any dose–response relationship. With the same protocol of exposure and species, but with a horizontal or vertical magnetic field, the same authors failed to find any effect on melatonin levels.[49] Suspecting a possible interference of pigmentation, Kato et al[50,51] then documented in Long–Evans rats the same intensities of a circularly polarized magnetic field and did indeed show a reduction of pineal and plasma melatonin concentrations. Other studies on rats or mice,[52-55] baboons,[56] and hamsters[57,58] also showed a reduction in the nighttime peak of melatonin. The same team reported a phase delay in the nocturnal peak time of melatonin in hamsters,[46,57,58] though they acknowledged in one paper that they were unable to replicate these findings, which make them inconclusive.[58] Some authors have reported an increase in nighttime melatonin levels.[59-61]

With the aim of comparing short-term and long-term exposure effects, Selmaoui and Touitou[62] used male Wistar rats housed in a 12:12 light:dark schedule and submitted to a 50-Hz sinusoidal magnetic field of 1, 10, or 100 µT intensity, either once for 12 h or repeatedly 18 h per day for 30 days. While a single 12-h exposure to a 1- or 10-µT magnetic field had no effect on plasma melatonin levels or NAT and hydroxyindole-O-methyltransferase (HIOMT) pineal activities, a 100-µT exposure significantly decreased 30% plasma concentrations of melatonin and depressed 23% pineal NAT activity (HIOMT activity unchanged) when compared with sham-exposed rats. In turn, the 30 days' repeated exposure showed that while the 1-µT intensity showed no effects on pineal function, both the 10- and 100-µT intensities resulted in an approximately 42% decrease of plasma melatonin levels. NAT activity was also decreased, and HIOMT activity remained unchanged. This study showed that a sinusoidal magnetic field alters plasma melatonin levels and pineal NAT activity, and that the sensitivity threshold varies with the duration of exposure, thus suggesting that magnetic fields may have a cumulative effect upon pineal function. This melatonin and NAT activity decrease was able to be replicated in adult rats in another study by Selmaoui and Touitou,[63] while they also reported that aged rats were not affected by ELF-EMF.

Löscher et al[53] studied the effects of a 24 h/day, 7 days/week, and 3-month exposure to magnetic fields on female rats bearing DMBA-induced mammary tumors; the field intensities were similar to the domestic exposures recorded close to electric power facilities. Whereas a significant decrease of blood melatonin concentrations was observed with 1 µT, no influence on the development of the mammary tumors could be put in evidence.

Table Ib presents data on different animal species reporting the lack of effect of ELF-EMF on the concentrations of pineal or blood melatonin and on the urinary concentration of 6-sulphatoxymelatonin, the main metabolite of the hormone. These reports were either inconsistent or failed to show any effect of ELF-EMF in species as different as rats or mice,[64-73] sheep,[74,75] baboons,[76] Djungarian hamsters,[58,77] cows or heifers,[78-80] and kestrels.[81,82]

The comparison of *Table Ia* (effects on melatonin) and *Table Ib* (lack of effects on melatonin) clearly shows that a number of these studies resulted in inconsistent data, even when the data were replicated by the same team with the same protocol and characteristics of exposure.[48,49,57,58,83,84]

Last, some authors studying the effects of exposure to ELF-EMF of various biological systems such as isolated pineal glands[85-90] or MCF-7 cells[91-96] were unable to arrive at definite conclusions *(Table II)*.

Reference of the study	Exposure characteristics	End point	Effect of MF on melatonin
Studies on rat and hamster isolated pineal glands			
Lerchl et al, 1991[85]	33.7 Hz - 44 µT for 2.5 h	NE stimulation of Mel production in rat	Decreased production and release
Richardson et al, 1992[86]	0 Hz- 1 h to a pulsed 0.4-G static MF	NAT activity and Mel in rat	Decrease of NAT activity and Mel content
Rosen et al, 1998[87]	60 Hz- 50 µT	NE stimulation of Mel release in rat	Decreased release
Brendel et al, 2000[88]	50 Hz or 16.7 Hz- 86 µT for 8 h	Isoproterenol stimulation of Mel production in Djungarian hamster	Decrease in Mel concentration
Lewy et al, 2003[89]	50 Hz- 1 mT for 4 h	NE stimulation of Mel production in rat	Increased release
Tripp et al 2003[90]	50 Hz- 500 microT for 4 h	Mel release in rat pineal glands	No effect
Studies on MCF-7 cell growth			
Liburdy et al, 1993[91]	60 Hz- 1.2 µT for 7 days	Mel inhibition of MCF-7 cell growth	Decrease in growth inhibition
Harland and Liburdy, 1997[92]	60 Hz- 1.2 µT for 7 days	Tamoxifen and Mel inhibition of MCF-7 cell growth	Decrease of Mel and Tamoxifen's inhibitory action
Blackman et al, 2001[93]	60 Hz- 1.2 µT for 7 days	Tamoxifen and Mel inhibition of MCF-7 cell growth	Decrease of Mel and Tamoxifen's inhibitory action
Ishido, 2001[94]	50 Hz- 1.2 or 100 µT for up to 7 days	Mel inhibition of cAMP and DNA synthesis in MCF-7 cells	Decrease of inhibition induced by Mel
Leman et al, 2001[95]	2 Hz- 0.3 mT, 1h/day for 3 days	Mel inhibition of breast cancer cells	No effect
Girgert et al 2010[96]	50 Hz-1.2 mT for 48 h	Signal transduction of the Mel receptor MT1 in MCF-7	Signal transduction involving MT1 was disrupted in MCF-7

Table II. Effects of magnetic fields on various biological systems in vitro. NE, norepinephrine; Mel: melatonin

Human studies

Much of the evidence for the melatonin hypothesis is based on data obtained in rodents with a 25% to 40% reduction in the hormonal concentration, though, as shown above, results on the effects of ELF-EMF in rodents and higher mammals provided controversial results. Since the 1990s several research papers have documented the effects of ELF-EMF on the secretion of melatonin in humans. Most research published has involved an acute exposure (from 30 min to 4 days on average) of healthy volunteers to ELF-EMF with different exposure characteristics *(Tables IIIa* and *IIIb)*. The data on humans are controversial, since of the papers published about one third reported a decrease in melatonin secretion[97-107] with, however, some comments to be mentioned such as the lack of evidence for a dose-response,[97] or a decrease not exclusively related to ELF-EMF and found in some particular subgroups[98-107] *(Table IIIa)*. In contrast to the previous ones, two thirds of the reports failed to find any effect of ELF-EMF on melatonin secretion in humans *(Table IIIb)*.[108-130] Most work published on humans dealt with short-term exposure for evident ethical reasons. Taking into account the data we have shown on rats of potentially cumulative effects of ELF-EMF,[62] we performed a study in workers chronically exposed daily for 1 to 20 years, both in the workplace and at home, since the workers were housed near the substations. We showed no alteration in their melatonin secretion (plasma level or circadian profiles) which strongly suggests that ELF-EMF do not have cumulative effects on melatonin secretion in humans, and thus clearly rebuts the melatonin hypothesis that a decrease in blood melatonin concentration (or a disruption in its secretory pattern) explains the occurrence of clinical disorders or cancers possibly related to ELF-EMF.[125]

ELF-EMF effects on cortisol and corticosterone

In contrast to the number of studies on the effects of ELF-EMF on melatonin secretion, few data are available in the literature on the pituitary adrenal axis. The hormones

under study (corticosterone for rats, cortisol for other mammals), exposure characteristics (short- and long-term), and timing and duration of exposure (1 to 6 months) in different animal species are detailed in *Table IV*.

Reference of the study	Subjects (N)	Sex	Age (years)	Exposure characteristics	Timing of exposure	Fluid or pineal	Sampling time	Effect on melatonin secretion
Pfluger and Minder, 1996[97]	108	M	NG	16 Hz- ~20 µT mean value in engine drivers	30 min – 4 h	Urinary aMT6s	Morning and evening samples	Decrease of aMT6s in evening; No evidence for a dose-response
Arnetz and Berg, 1996[98]	47	NG	NG	1 day exposure to video display unit (VDU)	1 day	Ser Mel	Morning and afternoon samples	Decrease but exposure not exclusively related to 50/60 Hz
Wood et al,1998[99]	44	M	18-49	50 Hz- 20 µT, sinusoidal or square wave field, intermittent	19 h-21 h	Pl Mel	20 min, 30 min, or hourly at night	Delay and decrease of Mel in subgroup
Burch et al, 1998[100]	142	M	20–60	60 Hz- 0.1–0.2 µT	Occupational exposure	Urinary aMT6s	Morning urine samples	No effect at work. urinary aMT6s decreased at home
Burch et al, 1999[101]	142	M	20-60	60 Hz- occupational exposure	Occupational exposure over a week	Urinary aMT6s	Overnight urine samples	Decrease in aMT6s excretion in workers exposed to more stable fields during work.
Burch et al, 2000[102]		M	NG	60 Hz- occupational exposure (electric utility workers), from 950 nT to 1.05 µT (exposure for < 2 h/day or > 2 h day)	3 consecutive days monitored	Urinary aMT6s	Overnight aMT6s	Decrease in aMT6s excretion in workers exposed for >2 h
Juutilainen et al, 2000[103]	60	F	mean age: ~44	50 Hz- 0.3–1 µT and > 1 µT and 0.15 µT	Occupational exposure	Urinary aMT6s	Nighttime and morning urine collection	aMT6s excretion lower in exposed workers compared with office workers
Davis et al, 2001[104]	203	F	20-74	60 Hz- domestic exposure. Half of the subjects had mean levels of <0.04 µT	residential 72 h	Urinary aMT6s	Nighttime samples	Decrease, primarily in subgroup using medication
Burch et al, 2002[105]	226 electric utility workers	M	**18-60**	60 Hz- occupational exposure	occupational exposure: measures on 3 consecutive work days	Urinary aMT6s	Overnight aMT6s	Decrease in aMT6s associated with mobile phone use
Davis et al. 2006[106]	115	F	20-40	60 Hz- 5 to 10 mG	At night for 5 consecutive nights	Urinary aMT6s	Overnight samples	Decrease
Burch et al, 2008[107]	153	M	Mean age = 44	0 Hz- 15 nT to 30 nT + 60 Hz	3 h, 24 h, 36 h	Urinary aMT6s	Overnight aMT6s	Decrease in aMT6s associated with elevated geomagnetic activity

Table IIIa. Magnetic field reports on a melatonin secretion decrease in humans. Mel, melatonin; aMT6s, 6 sulfatoxymelatonin; M, male; F: female; MF, magnetic field; NG, not given

Reference of the study	Subjects (N)	Sex	Age (years)	Exposure characteristics	Timing of exposure	Fluid	Sampling time	Effect of MF on melatonin secretion
Wilson et al, 1990[108]	42	F, M	NG	CPW electric blanket. 0.2-0.6 μT	8 weeks	Urinary aMT6s	Urine voidings	No effect
Schiffman et al, 1994[109]	9	M	22-34	0 Hz- Magnetic resonance imaging. 1.5 T	01 h	Pl Mel	Nighttime (2 samples)	No effect
Selmaoui et al, 1996[110]	32	M	20-30	50 Hz- 10 μT, to continuous or intermittent MF	23 h-08 h	Ser Mel and urinary aMT6s	Every 2 h during the daytime, hourly during the nighttime	No effect
Graham et al,1996[111]	33	M	19-34	60 Hz- 1 or 20 μT, intermittent	23 h-07 h	Pl Mel	Hourly at night	No effect
Graham et al, 1997[112]	40	M	18-35	60 Hz- 20 μT, continuous	23 h-07 h	Pl Mel	Hourly at night	No effect
Åkerstedt et al, 1999[113]	18	F, M	18-50	50 Hz- 1 μT	23 h-08 h	Pl Mel	At 23 h 02h30 h, 05 h, and 08 h	No effect
Graham et al,2000[114]	30	M	18–35	60 Hz- 28.3 μT	4 consecutive nights from 23 h – 07 h	Urinary aMT6s	Overnight urine samples	No effect
Crasson et al, 2001[115]	21	M	20-27	50 Hz- 100 μT, continuous or intermittent	30 min at 13 h30 and 16 h30	Ser Mel and Urinary aMT6s	Hourly from 20 h to 07 h	No effect
Graham et al, 2001[116]	24	M	19–34	60 Hz- 127 μT, continuous or intermittent	23 h – 07h	Ser Mel and Urinary aMT6s	Hourly from 24 to 07 h	No effect
Graham et al, 2001[117]	46	F, M	40-60	60 Hz-28.3 μT	23 h – 07 h	Urinary aMT6s	Morning urine samples	No effect
Griefahn et al, 2001[118]	7	M	16-22	16.7 Hz- 200 μT	18h – 02 h	Sal Mel	Hourly for 24 h	No effect
Haugsdal et al. 2001[119]	11	M	23-43	0 Hz- 2-7 mT, 9 h	22 h – 07 h	Urinary aMT6s	4 samples / 24 h	No effect
Hong et al, 2001[120]	9	M	23-37	50 Hz- 1–8 μT, electric 'sheet' over the body	11 weeks at night	Urinary aMT6s	5 times a day	No effect
Levallois et al, 2001[121]	416	F	20–74	50 Hz- between 0.1 and 0.3 μT	Residential exposure	Urinary aMT6s	Overnight urine samples	No effect except in subgroup of women with high BMI
Griefahn et al, 2002[122]	7	M	16–22	16.7 Hz, 0.2 mT	17 h-01 h	Sal Mel	Hourly for 24 h	No effect
Youngstedt et al, 2002[123]	242	F, M	50-81	60 Hz- Mean of one week exposure = 0.1 μT	Residential exposure within bed	Urinary aMT6s	Fractional urine	No Effect
Kurokawa et al, 2003[124]	10	M	20–37	50 Hz- 20 μT	20 h-08 h	Ser Mel	Hourly from 20 h to 08 h	No effect

Table IIIb. Magnetic field reports on the lack of effect on melatonin secretion in humans. Mel, melatonin; Pl, plasma; Ser, serum; Sal, saliva; aMT6s, 6 sulfatoxymelatonin; M, male; F, female; BMI, body mass index; MF, magnetic field; RF, radio frequency; NG, not given

Reference of the study	Subjects (N)	Sex	Age (years)	Exposure characteristics	Timing of exposure	Fluid	Sampling time	Effect of MF on melatonin secretion
Touitou et al, 2003[125]	30	M	31.5–46	50 Hz- mean fields of 0.1–2.6 μT	Occupational and residential exposure (1 to 20 years)	Ser Mel and urinary aMT6s	Hourly from 20 h to 08 h	No effect
Warman et al, 2003[126]	19	M	18-35	50 Hz- 200 or 300 μT	2- h exposure between 17 h and 23 h	Ser Mel	17 h and 10 h	No effect
Cocco et al, 2005[127]	51	F, M	Mean age 56.6	50 Hz- from 0.0045 μT to 0.148 μT	Residential	Urinary aMT6s	At 22 h and 08 h	No effect
Gobba et al. 2006[128]	59	F, M	Mean age 42 and 46	60 Hz- low exposed (≤0.2 μT) or higher exposed (>0.2 μT)	3 consecutive days recorded for workers	Urinary aMT6s	Morning urine	No effect
Juutilainen and Kumlin, 2006[129]	60	F	Mean age 40 to 53	50 Hz- from 0.1 to 2.5 μT	3 consecutive weeks	Urinary aMT6s	Morning urine	No effect Inconclusive results with light exposure
Clark et al, 2007[130]	127	F	12 to 81	60 Hz- 20 nT to 130 nT and RF 0.04 μW/cm² to 1.4 μW/cm²	Residential for 2.5 days	Urinary aMT6s	Overnight	No effect

Table IIIb. Continued

While the majority of papers failed to find any effect,[131-137] others have reported either an increase in the hormonal concentrations[138-144] or a decreased concentration.[145] The results of these studies are thus inconsistent and contradictory. Comparison between studies revealed that the discrepancy in the results might be due in part to the difference in the animal species used (rabbit, ewe lambs, cows, rats, or mice), class of age, and duration and intensity of exposure. Another factor that should be taken into account is that glucorticoids (ie, cortisol or corticosterone) levels are sensitive to many stressors that might affect hormone levels. It is well known that handling or bleeding animals increase corticosterone, a stress marker, and it is thus important to ensure that any external confounding stressor has to be controlled.

Overall, these data suggest that no consistent effects have been seen in the stress-related hormones of the pituitary-adrenal axis in a variety of mammalian species. Data on ELF-EMF effects on cortisol in humans are scarce. We have found 7 papers on the matter *(Table V)*.[109,124,146-149] All of these papers report only on short exposure of adult volunteers to ELF-EMF, and all failed to find any effect.

Conclusion

We are all exposed to electric and magnetic fields of weak intensity. The levels of exposure of the general population range from 5 to 50 V/m for electric fields and from 0.01 to 0.2 μT for magnetic fields. The possible risk on health with exposure to electromagnetic fields became a concern to the public, which led to numerous studies by scientists on the topic. We have shown in this review that the reported studies are largely contradictory with regard to epidemiologic studies (about half of the studies found a relationship and the other half failed to find any), to the potential biological effects of ELF-EMF, and to the potentially mechanisms put forward; no clear explanations exist for these contradictory results. The relative risk (RR) which establishes the relation between exposure to ELF-EMF and cancer, is approximately 2 to 3. In the absence of clear explanation(s) a number of hypotheses have been raised. The characteristics of the magnetic field (linear or circular polarization, duration, timing), the animal species and, within a species, the strain appears to have a role in determining the biologic response obtained. Therefore, great care

Reference of the study	Species	Exposure characteristics	Timing of exposure	Fluid or pineal	Sampling time	Effect of MF on melatonin secretion
Papers reporting no effect						
Free et al, 1981[131]	Rats	60 Hz- 100 kV/m	20 h/day for 30 or 120 days (adults) or from 20 to 56 days of age (young)	Ser corticosterone	08 h30-12 h30	No effect
Quinlan et al, 1985[132]	Rats	60 Hz- 100 kV/m; continuous or intermittent	1 or 3 h	Ser corticosterone	11 h or 13 h	No effect
Portet and Cabanes, 1988[133]	Rabbits and rats	50 Hz- 50 kV/m	*Rabbit*: 16 h/day from last 2 weeks of gestation to 6 weeks after birth. *Rat*: 8 h/day for 4 weeks	Ser cortisol (rabbits) and corticosterone (rats)	Nighttime	No effect
Thompson et al, 1995[134]	Ewe lambs	60 Hz- 500-kV transmission line (mean electric field 6 kV/m, mean magnetic field 40 mG)	Up to 43 weeks	Ser cortisol	48 h sampling (3-h intervals at daylight and hourly at night)	No effect
Burchard et al, 1996[135]	Dairy cows (Holstein)	60 Hz- 10 kV/m and 30 µT	Up to 56 days of exposure	Pl cortisol	Twice weekly	No effect
Szemerszky et al, 2010[136]	Rats	50 Hz-0.5 mT	for 5 days, 8 h daily (short) or for 4-6 weeks, 24 h daily (long)	Ser corticosterone	NG	No effect
Martinez-Samano et al, 2012[137]	Rats	60 Hz - 2.4 mT	2 hours (12 h-14 h)	Pl corticosterone	NG	No effect
Papers reporting an effect						
Hackman and Graves, 1981[138]	Rats	60 Hz- 25 or 50 kV/m	15 min per day up to 42 days	Ser corticosterone	Before and after exposure	Increase in serum levels at onset of exposure
Gorczynska and Wegrzynowicz, 1991[139,140]	Rats	1 and 10 mT	1 h daily for 10 days	Ser cortisol	Nighttime	Increase
de Bruyn and de Jager, 1994[141]	Mice	60 Hz- 10 kV m-1	22 h per day for 6 generations	Ser corticosterone	Day/night	Elevated daytime but no effect on night-time levels
Picazo et al, 1996[142]	Mice	50 Hz- 15 µT	14 weeks prior to gestation and 10 weeks post-gestation	Ser cortisol	Circadian	Circadian rhythm Altered
Bonhomme-Faivre et al, 1998[145]	Mice	50 Hz- 5 µT	after 90 and 190 days	Ser cortisol	Morning	On day 190, exposed animals showed a decrease in the cortisol
Marino et al, 2001[143]	Mice	60 Hz- 500 µT	for 1–175 days	Ser corticosterone	Nighttime	Changes in Ser corticosterone
Mostafa et al, 2002[144]	Rats	50 HZ-200 µT	Up to 2 weeks	Pl corticosterone	NG	Increase of plasma corticosterone

Table IV. Effects of EMF on cortisol or corticosterone secretion in different animal species. Pl, plasma; Se, serum; NG, not given

Reference of the study	Subjects (N)	Sex	Age (years)	Exposure characteristics	Timing of exposure	Fluid	Sampling time	Effect of MF on melatonin secretion
Maresh et al, 1988[146]	11	M	21-29	60 Hz-9 kV/m and 20 µT	2 hours of exposure	Pl cortisol	10, 30, 60, 90 and 120 min after exercise	No effect
Gamberale et al, 1989[147]	26	M	25-52	50 Hz- 2.8 kV/m and 23.3 µT 4.5 h during working day	10 h-12 h, 12 h30-14 h30	Ser cortisol	06 h45-07 h, 12 h-12 h10, 16 h30-17 h10	No effect
Selmaoui et al, 1997[148]	32	M	20-30	50 Hz- 10 µT, continuous or intermittent	23 h -08 h	Ser cortisol	Every 2 h during the daytime, hourly during the nighttime	No effect
Åkerstedt et al, 1999[113]	18	F, M	18-50	50 Hz- 1 µT	23 h-0 8h	Pl cortisol	At 23 h 02 h30, 05 h, and 08 h	No effect
Kurokawa et al, 2003[124]	10	M	20–37	50 Hz- 20 µT	20 h-08 h	Ser cortisol	Hourly from 20 h to 08 h	No effect
Ghione et al, 2004[149]	10	M	Mean age: 41	3 7Hz- 80 µT	1 hour of exposure between 9 h and 12h	Pl cortisol	2 samples: one 15 min befor the start of the study and one after the end of exposure period	No effect

Table V. Magnetic field reports on cortisol secretion in humans. Ser, serum; Pl, plasma; M, male; F, female; MF, magnetic field

must be given when comparing data obtained in different animal species, even within a group as rodents, since differences have been described between rodent species and even between pigmented and albino breeds.

A possible change in the spatial structure of the photoreceptor pigment rhodopsin due to the electric field induced by the magnetic field has been proposed. Magnetic fields might also change either the electrical activity of the pinealocytes or their ability to produce melatonin, or both. With regard to the numerous studies performed on the effects of ELF-EMF on melatonin, the differences observed in animals and humans in these effects may be due to the differences in anatomical location and configuration of the pineal gland, and also the difference in the rest-activity cycle between rodents and humans. A different sensitivity to ELF-EMF could also be part of the explanation. Some human subjects may have greater sensitivity to ELF-EMF, but this is difficult to demonstrate because of the important interindividual variability in plasma concentration of melatonin. As far as melatonin is concerned, we have shown a lack of effect of ELF-EMF on melatonin (concentration and circadian rhythm) in workers exposed daily for up to 20 years in their workplace and at home, which strongly suggests that chronic ELF-EMF exposure appears to have no cumulative effects in human adults; this rebuts the "melatonin hypothesis" raised as an explanation for the deleterious sanitary effects of ELF-EMF.[125]

In the same way, the application of high-throughput omics technologies to investigate the influences of ELF-EMF is confronted with the heterogeneity among the biological materials investigated, which are as different as blood cells/vessels, tissue cells, nerves, and bacteria, and this makes it difficult to compare data and to arrive at firm conclusions on the potential effects of ELF-EMF on biological systems.[150] As an example, most breast tumors become resistant to tamoxifen, and it has been shown that ELF-EMF reduce the efficacy of tamoxifen in a manner similar to tamoxifen resistance. By exposing cells of the breast cancer line MCF-7 to ELF-EMF, it has been found that ELF-EMF alter the expression of estrogen receptor cofactors, which in the authors' view may contribute to the induction of tamoxifen resistance in vivo.[151]

Currently, the debate concerns the effects of ELF-EMF on children, with some data published in the literature pointing out the risk of childhood leukemia in relation to residential exposure, and underlining that this risk (the RR is around 2) can exist when children are chronically exposed to more than 0.4 µT.10 Large-scale collaborative studies are still needed to fill the gaps in our knowledge and provide answers to these numerous questions not yet resolved. Last, the deleterious risk of ELF-EMF on frail populations such as children and aged people may be greater and should be documented, at least for their residential exposure. ❑

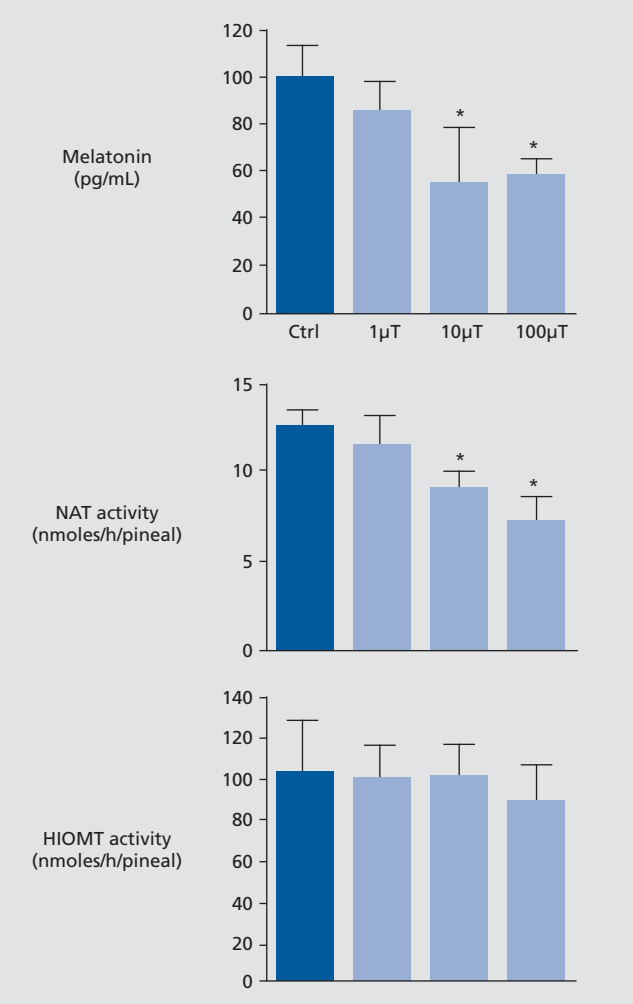

Figure 2. Effects of chronic exposure of male rats to a sinusoidal 50-Hz magnetic field (from 1 to 100 μT) on nocturnal pineal activity. The rats were exposed every day from 14:00 to 08:00 for 30 days at three different intensities. Only 10 and 100 μT were able to depress serum melatonin and pineal activity. No effect was observed on HIOMT activity. The asterisks indicate a significant difference ($P<0.05$) with the control group (Ctrl).
Reproduced from ref 62: Selmaoui B, Touitou Y. Sinusoidal 50-Hz magnetic fields depress rat pineal NAT activity and serum melatonin. Role of duration and intensity of exposure. *Life Sci*. 1995;57:1351-1358. Copyright © Pergamon Press 1995

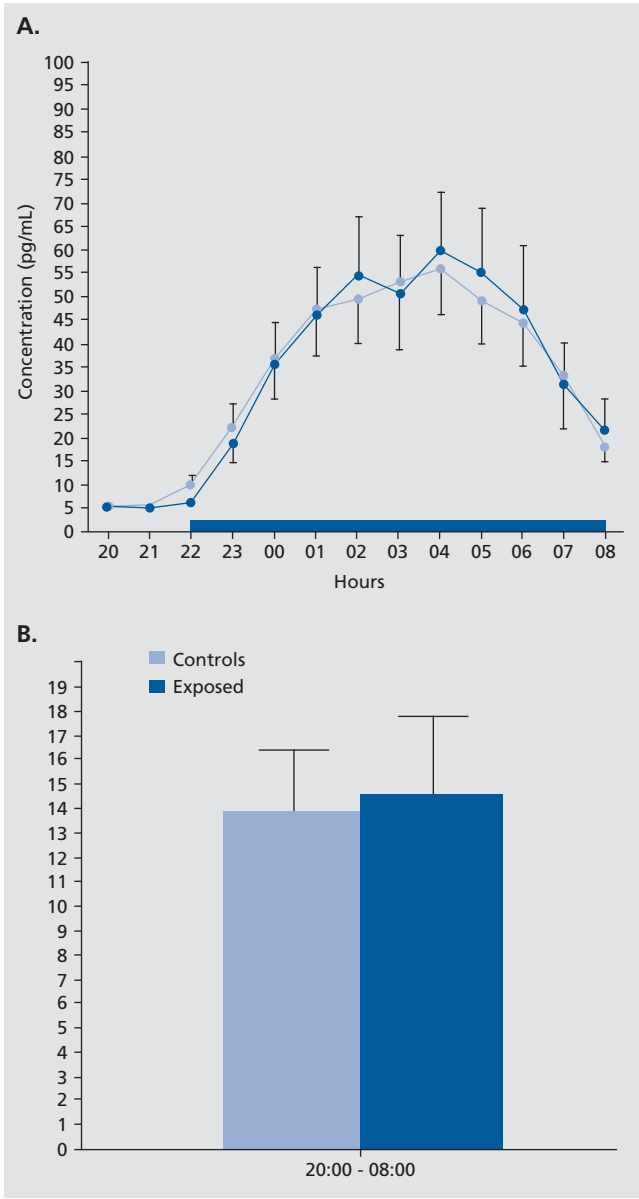

Figure 3. Nocturnal plasma melatonin patterns (A) and 6-sulfatoxymelatonin concentration (6SM; B) in the first-void morning urine (20:00 to 08:00). This study was carried out in 15 healthy chronically (in the workplace and at home) exposed men (daily and for 1 to 20 years) to a 50-Hz magnetic field in search of any cumulative effect from those chronic conditions of exposure. Fifteen healthy unexposed men served as controls. As shown here, the exposed subjects experienced no change in the hormone levels or circadian patterns of melatonin.
Reproduced from ref 125: Touitou Y, Lambrozo J, Camus F, Charbuy H. Magnetic fields and the melatonin hypothesis: a study of workers chronically exposed to 50-Hz magnetic fields. *Am J Physiol Regul Integr Comp Physiol*. 2003;284:R1529-535. Copyright © American Physiological Society 2003

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Los efectos de los campos magnéticos de frecuencias extremadamente bajas en la melatonina y el cortisol, dos ritmos marcadores del sistema circadiano

En los últimos 30 años la preocupación acerca de que la exposición diaria a campos magnéticos de frecuencias extremadamente bajas (ELF-EMF) (1 a 300 Hz) podría ser dañina para la salud humana (cáncer, trastornos neuroconductuales, etc.) ha sido objeto de debate y ha llegado a constituir un tema de preocupación para la salud pública. Esto ha llevado a que la Agencia Internacional para la Investigación del Cáncer haya clasificado a los ELF-EMF en la categoría 2B, es decir, agentes que son "posiblemente carcinogénicos para los humanos". Ya que se ha demostrado que la melatonina, neurohormona secretada por la glándula pineal, posee propiedades oncostáticas, ha surgido la "hipótesis melatoninérgica", la cual plantea que la exposición a EMF podría disminuir la producción de melatonina y así promover el desarrollo de cáncer de mama en humanos. Los datos de la literatura revisados aquí son contradictorios. Además, nosotros hemos demostrado una falta de efecto de ELF-EMF en la secreción de melatonina en humanos expuestos a EMF (por exposiciones de hasta 20 años) lo que refuta la hipótesis melatoninérgica. Actualmente el debate se centra en los efectos de ELF-EMF sobre el riesgo de leucemia infantil en niños crónicamente expuestos a más de 0,4 µT. Se requiere de futuras investigaciones para obtener respuestas más definitivas relacionadas con los efectos potencialmente deletéreos de ELF-EMF.

Les effets des champs magnétiques de très faible fréquence sur la mélatonine et le cortisol, deux rythmes-marqueurs du système circadien

L'exposition quotidienne aux champs électromagnétiques de basse fréquence (ELF-EMF) (1 à 300 Hz) a été l'objet dans les 30 dernières années de débats et de l'inquiétude du public sur la nocivité des ELF-EMF sur la santé (cancer, perturbations neurocomportementales) entraînant leur classification dans le groupe 2B du CIRC, groupe des agents "possiblement carcinogènes pour l'homme". Comme la mélatonine, une neurohormone sécrétée par la glande pinéale, possède des propriétés oncostatiques, "l'hypothèse de la mélatonine" a suggéré que les ELF-EMF diminuaient la synthèse de l'hormone et entraînaient ainsi le développement de cancers chez l'homme. Les articles que nous avons recensés dans la littérature sont très contradictoires. Nous avons pour notre part démontré l'absence d'effets des ELF-EMF sur la mélatonine chez des travailleurs exposés (jusqu'à 20 ans d'exposition) aux champs élecromagnétiques. Le débat porte actuellement sur le risque de leucémie chez l'enfant exposé de façon chronique à un champ supérieur à 0,4 µT. D'autres recherches sont nécessaires pour apporter une réponse définitive aux effets potentiellement dangereux des ELF-EMF sur l'homme.

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