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)
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,\(^4\)\(^5\) depression, and suicide,\(^6\) and neurodegenerative diseases such as Alzheimer’s disease and amyotrophic lateral sclerosis.\(^7\)\(^8\) 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,\(^9\) 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,\(^10\)\(^11\) and disorders of the circadian time structure.\(^12\)\(^13\) 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.\(^14\)\(^15\) Of special interest, the IARC published in 2002 an evaluation of the carcinogenic risks of ELF to humans.\(^16\) 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.\(^17\)\(^18\) Theoretically, melatonin could be a good mechanistic candidate to explain potentially deleterious effects of EMF since: i) its secretion is dramatically inhibited by light,\(^19\)\(^20\) 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,\(^21\) and this property might occur with exposure to EMF; iii) the oncostatic properties of melatonin have been described,\(^22\)\(^23\) 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\(^24\)\(^25\); iv) and last, its association with depressive disorders has been put forward.\(^26\)\(^27\)

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.\(^28\)\(^29\)

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.\(^30\)\(^31\) 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). Besides melatonin, the most frequent marker rhythms used both in humans and animals are the core body temperature circadian pattern and the cortisol circadian rhythm, since they are also highly reproducible. 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. Since a relationship between the pineal gland and the adrenal gland has been documented in vitro, 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. Other reports, however, failed to find any effect, or were inconclusive or contradictory. 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. Yellon and Wilson et al., 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 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., 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](image-url)
### 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 secretion                              | Sampling time | Effect on melatonin secretion                                  |
|--------------------------|--------------------------|-------------------------------------|-------------------------------------|------------------------------------------------------|---------------|---------------------------------------------------------------|
| Wilson et al, 1981       | 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       | 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       | 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 | 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         | Adult rats               | 50 Hz- 1, 5, 50 or 250 µT           | 6 weeks                             | Pineal and PI Mel                                   | Nighttime     | Decrease in serum and pineal melatonin                      |
| Yellon, 1992, 1994       | Djungarian hamsters      | 60 Hz- 100 µT                       | 18 h/day for one week               | Pineal and Ser Mel                                   | Nighttime     | Decreased and delayed nighttime peak                         |
| Grotta et al, 1994       | 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         | 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         | 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      | 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       | Baboons                  | 60 Hz- 6 kV/m and 50 µT or 30 kV/m and 100 µT irregu-lar and intermittent sequence | 6 weeks                             | Ser Mel                                              | Nighttime     | Decrease in Ser Mel                                           |
| Selmaoui and Touitou, 1995 | 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       | 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            | 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$^1$ | 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$^a$ | 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$^a$ | 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$^a$ | 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$^b$ | 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$^a$ | 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$^a$ | 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 | PI 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$^a$ | 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$^a$ | 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$^a$ | 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 1a. Continued
**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<sup>11</sup> | 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 |
| Kato et al, 1994<sup>44</sup> | Adult rats | 50 Hz- 1 μT, horizontally or vertically oriented MF | 6 weeks | Pineal and PI Mel | 12 h and 24 h | No effect |
| Lee et al, 1993, 1995<sup>41,45</sup> | 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<sup>44</sup> | 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<sup>40</sup> | Rats | 0 Hz- 800 gauss | between 12 hours and 8 days | Pineal and Ser Mel | Nighttime | No effect |
| Yellon, 1996<sup>9</sup> | Adult Djungarian hamsters | 60 Hz- 100 μT | 15 min, 2 h before dark | Pineal and Ser Mel | Nighttime | No effect |
| Mevissen et al, 1996<sup>3</sup> | 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<sup>14,43</sup> | Adult rats | 50 Hz- 1, 5, 100 or 500 μT | 24 h | Urinary aMT6s | Day/night | No effect |
| Löscher et al, 1998<sup>45</sup> | Adult rats | 50 Hz- 100 μT | 18 h per day for one week | Ser Mel | Nighttime (3 samples) | No effect |
| Yellon and Truong, 1998<sup>39</sup> | 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<sup>9</sup> | Holstein cows | 60 Hz- 10 kV/m and a uniform horizontal magnetic field of 30 μT | Up to 56 days of exposure | PI Mel | every 0.5 h for 14 h starting at 17 h | No effect |
| John et al, 1998<sup>40</sup> | 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<sup>13</sup> | Mice | 50 Hz- between 0.5 and 77 μT with an average of 2.75 μT | 24 h/day from conception until adult age | PI Mel | 23 h-01 h30 | No effect |
| Fedrowitz et al, 2002<sup>4</sup> | 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; PI, plasma; Ser, serum; aMT6s, 6 sulfatoxymelatonin; MF, magnetic field; NAT, serotonin N-acetyl transferase; NG, not given.
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,\(^{59,60}\) though they acknowledged in one paper that they were unable to replicate these findings, which make them inconclusive.\(^{58,59}\) Some authors have reported an increase in nightime melatonin levels.\(^{61-63}\)

With the aim of comparing short-term and long-term exposure effects, Selmaoui and Touitou\(^2\) 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,\(^3\) while they also reported that aged rats were not affected by ELF-EMF. Löscher et al\(^7\) 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.

\(Table \ I b\) 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,\(^44-75\) sheep,\(^74,75\) baboons,\(^76\) Djungarian hamsters,\(^55,72\) cows or heifers,\(^78-80\) and kestrels.\(^81,82\)

The comparison of \(Table \ I a\) (effects on melatonin) and \(Table \ I b\) (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.\(^46,49,57,58,83,84\)

Last, some authors studying the effects of exposure to ELF-EMF of various biological systems such as isolated pineal glands\(^55,80\) or MCF-7 cells\(^56,84\) were unable to arrive at definite conclusions (\(Table \ II\)).
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 human melatonin secretion (Table IIIb). 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, 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.

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

| 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<sup>85</sup> | 33.7 Hz - 44 µT for 2.5 h | NE stimulation of Mel production in rat | Decreased production and release |
| Richardson et al, 1992<sup>86</sup> | 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<sup>87</sup> | 60 Hz - 50 µT | NE stimulation of Mel release in rat | Decreased release |
| Brendel et al, 2000<sup>88</sup> | 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<sup>89</sup> | 50 Hz - 1 mT for 4 h | NE stimulation of Mel production in rat | Increased release |
| Tripp et al 2003<sup>90</sup> | 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<sup>91</sup> | 60 Hz - 1.2 µT for 7 days | Mel inhibition of MCF-7 cell growth | Decrease in growth inhibition |
| Harland and Liburdy, 1997<sup>92</sup> | 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<sup>93</sup> | 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<sup>94</sup> | 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<sup>95</sup> | 2 Hz - 0.3 mT, 1h/day for 3 days | Mel inhibition of breast cancer cells | No effect |
| Girgert et al 2010<sup>96</sup> | 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
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 | 108 M NG 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 | 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 | 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 | 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 | 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 | M NG | 60 Hz-occupational exposure | 3 consecutive days monitored | Urinary aMT6s | Overnight aMT6s | Decrease in aMT6s excretion in workers exposed for >2 h |
| Juutilainen et al, 2000 | 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 | 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 | 226 M electric utility workers | 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 | 115 M | Mean age = 44 | 60 Hz- 5 to 10 mG | At night for 5 consecutive nights | Urinary aMT6s | Overnight samples | Decrease |
| Burch et al, 2008 | 153 M | 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.
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 |
|----------------------------------------|--------------|-----|-------------|----------------------------------------------------------------|-------------------|------------------|------------------------|-------------------------------------|
| Wilson et al, 1990\(^{10}\)           | 42           | F, M| NG          | CPW electric blanket. 0.2-0.6 µT                                | 8 weeks           | Urinary aMT6s     | Urine voidings         | No effect                           |
| Schiffman et al, 1994\(^{11}\)        | 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\(^{12}\)         | 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\(^{13}\)           | 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\(^{14}\)           | 40           | M   | 18-35       | 60 Hz- 20 µT, continuous                                       | 23 h-07 h         | Pl Mel           | Hourly at night        | No effect                           |
| Åkerstedt et al, 1999\(^{15}\)        | 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\(^{16}\)           | 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\(^{17}\)          | 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\(^{18}\)           | 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\(^{19}\)           | 46           | F, M| 40-60       | 60 Hz-28.3 µT                                                  | 23 h – 07h        | Urinary aMT6s     | Morning urine samples  | No effect                           |
| Griefahn et al, 2001\(^{20}\)         | 7            | M   | 16-22       | 16.7 Hz- 200 µT                                               | 18h – 02 h        | Sal Mel          | Hourly for 24 h        | No effect                           |
| Haugsdal et al. 2001\(^{21}\)        | 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\(^{22}\)             | 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\(^{23}\)        | 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\(^{24}\)         | 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\(^{25}\)       | 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\(^{26}\)         | 10           | M   | 20-37       | 50 Hz- 20 µT                                                  | 20 h-08 h         | Ser Mel          | Hourly from 20 h to 08 h | No effect                           |
While the majority of papers failed to find any effect, others have reported either an increase in the hormonal concentrations or a decreased concentration. 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). 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 | 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 | 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 | 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 | 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 | 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 | 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 | 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 | 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 Wegorzynowicz, 1991 | Rats | 1 and 10 mT | 1 h daily for 10 days | Ser cortisol | Nighttime | Increase |
| | de Bruyn and de Jager, 1994 | 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 | 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 | 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 | Mice | 60 Hz- 500 µT | for 1–175 days | Ser corticosterone | Nighttime | Changes in Ser corticosterone |
| | Mostafa et al, 2002 | 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
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.\(^{151}\)

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.

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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
REFERENCES

1. Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. Am J Epidemiol. 1979;109:273–284.

2. Wertheimer N, Leeper E. Adult cancer related to electrical wires near the home. Int J Epidemiol. 1982;11:345–355.

3. Savitz DA, Wachtel H, Barnes FA, John EM, Tusvik JG. Case control study of childhood cancer and exposure to 60-Hz magnetic fields. Am J Epidemiol. 1988;128:21–38.

4. Aihlom A, Day N, Fyechting M, et al. A pooled analysis of magnetic fields and childhood leukemia. Br J Cancer. 2000;83:692–698.

5. Linet MS, Hatch EE, Kleinerman RA, et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. N Engl J Med. 1997;337:1–7.

6. McBride ML, Gallagher RP, Theriault G, et al. Power- frequency electric and magnetic fields and risk of childhood leukemia in Canada. Am J Epidemiol. 1999;149:831–842.

7. Reichmanis M, Perry FS, Marino AA, Becker RO. Relation between suicide and the electromagnetic field of overhead power lines. Physiol Chem Phys. 1979;11:395–403.

8. Sobel E, Dunn M, Davaipour Z, Qian Z, Chui H. Elevated risk of Alzheimer's disease among workers with likely electromagnetic exposure. Neurology. 1996;47:1477–1481.

9. Davaipour Z, Sobel E. Long-term exposure to magnetic fields and the risks of Alzheimer's disease and breast cancer: further biological research. Pathophysiology. 2005;16:149–156.

10. Kheifets L, Goodwin FK. Melatonin inhibition and pinealectomy enhance development of 7, 12-dimethylbenz(a)anthracene-induced mammary tumors in the rat. Cancer Res. 1981;41:4432–4436.

11. Reinhberg AE, Touitou Y. Synchronisation and desynchronisation of the rhythms of circadian humans. Pathol Biol. 1989;37:487–495.

12. Touitou Y, Sulon J, Borjad A, et al. Adrenal circadian system in young and elderly human subjects: a comparative study. J Endocrinol. 1982;93:201–210.

13. Touitou Y, Sulon J, Borjad A, Sodoyez JC, Demey-Ponsart E. Melatonin inhibition and pinealectomy enhance development of 7, 12-dimethylbenz(a)anthracene-induced mammary tumors in the rat. Cancer Res. 1983;43:53–64.

14. 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.

15. Mailloux A, Benstaali C, Borjad A, Auzeby A, Touitou Y. Body temperature and locomotor activity as marker rhythms of aging of the circadian system in rodents. Exp Gerontol. 1993;28:733–740.

16. Touitou Y. Pinea and hypothalamic-pituitary-adrenal axis in search for interaction. In: Reiter RJ, Pang SF, eds. Advances in Pineal Research. Vol 3. London, UK: John Libbey; 1989:241–246.

17. Wilson BW, Anderson LE, Hilten DJ, Phillips RD. Chronic exposure to 60-Hz electric fields: effects on pineal function in the rat. Bioelectromagnetics. 1981;2:371–380.

18. Wilson BW, Chess EK, Anderson LE. 60-Hz electric field effects on pineal melatonin rhythms: time course for onset and recovery. Bioelectromagnetics. 1986;7:239–242.

19. Reiter RJ, Anderson LE, Buschbom RL, Wilson BW. Reduction of the nocturnal rise in pineal melatonin levels in rats exposed to 60-Hz electric fields in utero and for 23 days after birth. Life Sci. 1988;42:2203–2206.

20. Grotta LJ, Reiter RJ, Keng P, Michaelson S. Electric field exposure alters serum melatonin but not pineal melatonin synthesis in male rats. Bioelectromagnetics. 1994;15:427–437.

21. Touitou Y, Borjad A, Lambroz J, Selmaoui B. Is melatonin the hormonal missing link between magnetic field effects and human diseases. Cancer Causes Control. 2006;17:547–552.

22. Wilson BW, Chess EK, Dab W. Exploring the EMF-melatonin connection: a review of the possible effects of 50/60-Hz Electric and magnetic fields on melatonin secretion. Int J Occup Environ Health. 1996;2:37–47.

23. Yellon SM. Automatic 60-Hz magnetic field exposure effects on the melatonin rhythm in the pineal gland and circulation of the adult Djungarian hamster. J Pineal Res. 1994;16:136–144.

24. Wilson BW, Smith ME, Sasser LB, et al. Changes in the hypothalamus and pineal gland on Djungarian hamsters from short-term exposure to 60 Hz magnetic field. Annual Review of Research on Biological Effects of Electric and Magnetic Fields from the Generation, Delivery and Use of Electricity. US Department of Energy: A-30. Savannah, Georgia: 1993; October 31–November 4.
Los efectos de los campos magnéticos de frecuencias extremadamente bajas en la melatonia 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 melatonia, neurohormona secretada por la glándula pineal, posee propiedades oncásticas, ha surgido la “hipótesis melatoninérgica”, la cual plantea que la exposición a EMF podría disminuir la producción de melatonia 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 melatonia 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 “posiblement carcinogènes pour l’homme”. Comme la mélatonine, une neurohormone sécrétée par la glande pinéale, possède des propriétés oncاستiques, “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 électromagnétiques. 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.
58. Yellon SM. 60-Hz magnetic field exposure effects on the melatonin rhythm and photoperiodic control of reproduction. Am J Physiol. 1996;270:E186-E21.

59. Niehaus M, Brüggemeyer H, Behre HM, Lerchl A. Growth retardation, testicular stimulation, and increased melatonin synthesis by weak magnetic fields (50 Hz) in Djungarian hamsters. Phodopus sungorus. Biochem Biophys Res Commun. 1997;234:707-711.

60. Lerchl A, Zachmann A, Ali MA, Reiter RJ. The effects of pulsing magnetic fields on pineal melatonin synthesis in a teleost fish (brook trout, Salvelinus fontinalis). Neurosci Lett. 1998;256:171-173.

61. Dyche J, Anch AM, Fogler KA, Barnett DW, Thomas C. Effects of power frequency electromagnetic fields on melatonin and sleep in the rat. Emerg Health Threats J. Epub 2012 Apr 20.

62. Selmaoui B, Toulou 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.

63. Selmaoui B, Toulou Y. Age-related differences in serum melatonin and pineal NAT activity and in the response of rat pineal to a 50-Hz magnetic field. Life Sci. 1994;62:2291-2297.

64. Bakos J, Nagy N, Thöröczy G, Szabó LD. Sinusoidal 50 Hz, 500 microT magnetic field has no acute effect on urinary 6-sulphatoxymelatonin in Wistar rats. Bioelectromagnetics. 1995;16:377-380.

65. Bakos J, Nagy N, Thöröczy G, Szabó LD. Urinary 6-sulphatoxymelatonin excretion is increased in rats after 24 hours of exposure to vertical 50 Hz, 100 microT magnetic field. Bioelectromagnetics. 1997;18:190-202.

66. Bakos J, Nagy N, Thöröczy G, Szabó LD. One week of exposure to 50 Hz, vertical magnetic field does not reduce urinary 6-sulphatoxymelatonin excretion of male wistar rats. Bioelectromagnetics. 2002;23:245-248.

67. Fedrowitz M, Westermann J, Löschner W. Magnetic field exposure increases cell proliferation but does not affect melatonin levels in the mammary gland of female Sprague Dawley rats. Cancer Res. 2002;62:1356-1363.

68. Kroeker G, Parkinson D, Friend J, Peeling J. Neurochemical effects of static magnetic field exposure. Surg. Neurol. 1996;45:62-66.

69. Löschner W, Mevissen M, Lerchl A. Exposure of female rats to a 100-mG, 50 Hz magnetic field has no acute effect on pineal melatonin production in pinealocytes. Bioelectromagnetics. 1998;19:119-123.

70. Burchard JF, Nguyen DH, Monardes HG, Petitclerc D. Lack of effect of 10 kV/m 60 Hz electric field exposure on serum melatonin, and prolactin levels in rats exposed to pulsed DC magnetic fields. Bioelectromagnetics. 1998;19:318-329.

71. Lee JM Jr, Stormshak F, Thompson JM, Hinesen P, et al. Melatonin secretion and puberty in female lambs exposed to EMF: a replicate study. Bioelectromagnetics. 1996;11:169-173.

72. Rogers WR, Reiter RJ, Smith HD, Barlow-Walden L. Rapid-onset/offset, variably scheduled 60 Hz electric and magnetic field exposure reduces nocturnal serum melatonin concentration in nonhuman primates. Bioelectromagnetics. 1995;(Suppl 3):119-122.

73. Yellon SM, Truong HN. Melatonin rhythm onset in the adult Siberian hamster: influence of photoperiod but not 60-Hz magnetic field exposure on melatonin content in the pineal gland and in circulation. J Biol Rhythms. 1998;13:52-59.

74. Burchard JF, Nguyen DH, Block E. Effects of electric and magnetic fields on nocturnal melatonin concentrations in dairy cows. J Dairy Sci. 1998;81:722-727.

75. Burchard JF, Nguyen DH, Monardes HG. Exposure of pregnant dairy heifer to magnetic fields at 60 Hz and 30 microT. Bioelectromagnetics. 2007;28:471-476.

80. Rodriguez M, Petitclerc D, Burchard JF, Nguyen DH, Block E. Blood melatonin and prolactin concentrations in dairy cows exposed to 60 Hz electric and magnetic fields during 8 h photoperiods. Bioelectromagnetics. 2004;25:508-515.

81. Fernie KJ, Bird DM, Petiticler D. Effects of electromagnetic fields on photophaseic circulating melatonin levels in American kestrels. Environ Health Perspect. 1999;107:901-904.

82. Dell’Omo G, Costantini D, Lucini V, Antonucci G, Nonno R, Polichetti A. Magnetic fields produced by power lines do not affect growth, serum melatonin, leukocytes and fledging success in wild kestrels. Comp Biochem Physiol C. Toxicol Pharmacol. 2009;150:372-376.

83. Reiter RJ, Tan DX, Poeggeler B, Kavet R. Inconsistent suppression of nocturnal pineal melatonin synthesis and serum melatonin levels in rats exposed to pulsed DC magnetic fields. Bioelectromagnetics. 1998;19:318-329.

84. Burchard JF, Nguyen DH, Monardes HG, Petitclerc D. Lack of effect of 10 kV/m 60 Hz electric field exposure on pregnant dairy heifer hormones. Bioelectromagnetics. 2004;25:308-312.

85. Lerchl A, Nonaka KO, Reiter RJ. Pineal gland “magnetosensitivity” to static magnetic fields is a consequence of induced electric currents (eddy currents). J Pineal Res. 1991;10:109-116.

86. Richardson BA, Yaga K, Reiter RJ, Morton DJ. Pulsed static magnetic field effects on in-vitro pineal indoleamine metabolism. Biochim Biophys Acta. 1992;1137:59-64.

87. Rosen LA, Barber I, Lyle DB. A 0.5 G, 60 Hz magnetic field suppresses melatonin production in pinealocytes. Bioelectromagnetics. 1998;19:123-127.

88. Breidel H, Niehaus M, Lerchl A. Direct suppressive effects of weak magnetic fields (50 Hz and 16.2/3 Hz) on melatonin synthesis in the pineal gland of Djungarian hamsters (Phodopus sungorus). J Pineal Res. 2000;29:228-233.

89. Lewy H, Massot O, Toulou Y. Magnetic field (50 Hz) increases N-acetyltransferase, hydroxy-indole-O-methyltransferase activity and melatonin release through an indirect pathway. Int J Radiat Biol. 2003;79:431-435.

90. Tripp HM, Warman GR, Arendt J. Circularly polarised MF (500 microT 50 Hz) does not acutely suppress melatonin secretion from cultured Wistar rat pineal glands. Bioelectromagnetics. 2003;24:118-124.

91. Liburdy RP, Sloma TR, Sokolic R, Yaswen P. ELF magnetic fields, breast cancer, and melatonin: 60 Hz fields block melanin's oncostatic action on ER+ breast cancer cell proliferation. J Pineal Res. 1993;14:89-97.

92. Harland JD, Liburdy RP. Environmental magnetic fields inhibit the antiproliferative action of tamoxifen and melatonin in a human breast cancer cell line. Bioelectromagnetics. 1997;18:555-562.

93. Brockman CF, Benane SG, House DE. The influence of 1.2 microT, 60 Hz magnetic fields on melatonin- and tamoxifen-induced inhibition of MCF-7 cell growth. Bioelectromagnetics. 2001;22:122-128.

94. Ishido M, Nitta H, Kabuto M. Magnetic fields (MF) of 50 Hz at 1.2 microT as well as 100 microT cause uncoupling of inhibitory pathways of adenyl cyclase mediated by melanotin 1a receptor in MF-sensitive MCF-7 cells. Carcinogenesis. 2001;22:1043-1048.

95. Leman ES, Sisken BF, Zimmer S, Anderson KW. Studies of the interactions between melatonin and 2 Hz, 0.3 mT PEMF on the proliferation and invasion of human breast cancer cells. Bioelectromagnetics. 2001;22:178-84.

96. Girgert R, Hanf V, Emons G, Gründker C. Signal transduction of the melanotin receptor M1 is disrupted in breast cancer cells by electromagnetic fields. Bioelectromagnetics. 2010;31:237-245.

97. Pfluger DH, Minder CE. Effects of exposure to 16.7 Hz magnetic fields on urinary 6-hydroxymelatonin sulfate excretion of Swiss railway workers. J Pineal Res. 1996;21:91-100.

98. Arnetz BB, Berg M. Melatonin and adrenocorticotropic hormone levels in video display unit workers during work and leisure. J Occup Environ Med. 1996;38:1108-1110.

99. Wood AW, Armstrong SM, Sait ML, Devine L, Martin MJ. Changes in human plasma melatonin profiles in response to 50 Hz magnetic field exposure. J Pineal Res. 1998;25:116-127.

100. Burch JB, Reif JS, Yost MG, Kefee TJ, Pitrat CA. Nocturnal excretion of a urinary melanotin metabolite among electric utility workers. Scand J Work Environ Health. 1998;24:183-189.

101. Burch JB, Reif JS, Yost MG, Kefee TJ, Pitrat CA. Reduced excretion of a melanotin metabolite in workers exposed to 60 Hz magnetic fields. Am J Epidemiol. 1999;150:27-36.
sulfatoxymelatonin with in-bed 60-Hz magnetic field exposure or illumination from high-power lines on female urinary excretion of 6-sulfatoxymelatonin rhythms in men.

G. Experiments on the effects of a continuous 16.7 Hz magnetic field on older men and women.

magnetic field exposure and plasma melatonin and urinary 6-sulfo-metabolite.

Bioelectromagnetics. 1996;58:1539-1549.

exposed to 60 Hz magnetic fields: effects on melatonin and its enzymatic function. J Pineal Res. 1983;5:381-389.

Portet R, Cabanes J. Development of young rats and rabbits exposed to a strong electric field. Bioelectromagnetics. 1988;9:95-104.

Thompson JM, Stormshak F, Lee JM Jr, Hess DL, Painter L. Cortisol secretion and growth in ewe lambs chronically exposed to electric and magnetic fields of a 60-Hertz 500-kilovolt AC transmission line. J Anim Sci. 1995;73:3274-3280.

Burchardt DF, Nguyen DH, Richard L, Block E. Biological effects of electric and magnetic fields on productivity of dairy cows. J Dairy Sci. 1996;79:1549-1554.

Szemerszky R, Zelena D, Barna I, Bárdos G. Stress-related endocrinological and psychopathological effects of short- and long-term 50Hz electromagnetic field exposure in rats. Brain Res Bull. 2010;81:92-99.

Martinez-Samano J, Torres-Durán PV, Juárez-Oropesa MA, Verduzco-Díaz L. Effect of acute extremely low frequency electromagnetic field exposure on the antioxidant status and lipid levels in rat brain. Arch Med Res. 2012. Epub ahead of print. 2012.04.003

Hackman RM, Graves HB. Corticosterone levels in mice exposed to high-intensity electric fields. Behav Neuro Endocrinol. 1981;32:201-213.

Gorzynska E, Wegrzynowicz R. Glucose homeostasis in rats exposed to magnetic fields. Invest Radiol. 1991;26:1095-1100.

Gorzynska E, Wegrzynowicz R. Structural and functional changes in organelles of liver cells in rats exposed to magnetic fields. Environ Res. 1991;55:188-198.

de Bruyn L, de Jager L. Electric field exposure and evidence of stress in mice. Environ Res. 1994;65:149-160.

Picazo ML, Miguel MP, Romo MA, Varela L, Franco P, Gianonatti C, Bardasano JL. Changes in mouse adrenal gland function under second-generation chronic exposure to ELF magnetic fields. I. males. Electro Magnetiobiol. 1996;15:85-88.

Marino AA, Wolcott RM, Chervenak R, et al. Coincident nonlinear changes in the endocrine and immune systems due to low-frequency magnetic field exposure. Environ Res. 2003;91:55-66.

Marriott AL, De Lucas MC, Brinkhous KM. The effects of ELF magnetic fields on human plasma melatonin secretion. J Pineal Res. 1981;2:105-121.

Cocchi M, Gobbo G, Bravo G, Scaringi M, Roccato L. No association between occupational exposure to ELF magnetic field and urinary 6-sulfo-melatonin in workers. Bioelectromagnetics. 2006;27:667-673.

Juutilainen J, Kumlin T. Occupational magnetic field exposure and melatonin interaction with light-at-night. Bioelectromagnetics. 2006;27:423-426.

Clark ML, Burch JB, Yost MG, et al. Biomonitoring of estrogen and melatonin metabolites among women residing near radio and television broadcasting transmitters. Occup Environ Med. 2007;64:1140-1156.

130. Free MJ, Kaune WT, Phillips RD, Cheng HC. Endocrinological effects of strong 60-Hz electric fields on rats. Bioelectromagnetics, 1981;2:105-121.

131. Quinlan WJ, Petronadas D, Lebda N, Pettit S, Michaelson SM. Neuroendocrine parameters in the rat exposed to 60 Hz electric fields. Bioelectromagnetics, 1985;6:381-389.

132. González-Cruz E, Wegrzynowicz R. Glucose homeostasis in rats exposed to magnetic fields. Invest Radiol. 1991;26:1095-1100.

134. Marino AA, Wolcott RM, Chervenak R, et al. Coincident nonlinear changes in the endocrine and immune systems due to low-frequency magnetic field exposure. Environ Res. 2003;91:55-66.

135. Portet R, Cabanes J. Development of young rats and rabbits exposed to a strong electric field. Bioelectromagnetics. 1988;9:95-104.

136. Thompson JM, Stormshak F, Lee JM Jr, Hess DL, Painter L. Cortisol secretion and growth in ewe lambs chronically exposed to electric and magnetic fields of a 60-Hertz 500-kilovolt AC transmission line. J Anim Sci. 1995;73:3274-3280.

137. Martínez-Samano, J, Torres-Durán PV, Juárez-Oropesa MA, Verduzco-Díaz L. Effect of acute extremely low frequency electromagnetic field exposure on the antioxidant status and lipid levels in rat brain. Arch Med Res. 2012. Epub ahead of print. 2012.04.003

138. Hackman RM, Graves HB. Corticosterone levels in mice exposed to high-intensity electric fields. Behav Neuro Endocrinol. 1981;32:201-213.

139. Gómez-Cruz E, Wegrzynowicz R. Glucose homeostasis in rats exposed to magnetic fields. Invest Radiol. 1991;26:1095-1100.

140. Gómez-Cruz E, Wegrzynowicz R. Structural and functional changes in organelles of liver cells in rats exposed to magnetic fields. Environ Res. 1991;55:188-198.

141. de Bruyn L, de Jager L. Electric field exposure and evidence of stress in mice. Environ Res. 1994;65:149-160.

142. Picazo ML, Miguel MP, Romo MA, Varela L, Franco P, Gianonatti C, Bardasano JL. Changes in mouse adrenal gland function under second-generation chronic exposure to ELF magnetic fields. I. males. Electro Magnetiobiol. 1996;15:85-88.

143. Marino AA, Wolcott RM, Chervenak R, et al. Coincident nonlinear changes in the endocrine and immune systems due to low-frequency magnetic fields. Neuroimmunomodulation. 2001;9:65-77.

144. Mostafa RM, Mostafa YM, Ennaceur A. Effects of exposure to extremely low-frequency magnetic field of 2 G intensity on memory and corticosterone level in rats. Physiol Behav. 2002;76:589-595.

145. Bonhomme-Faireur L, Macé A, Bezire Y, et al. Alterations of biological parameters in mice chronically exposed to low-frequency (50 Hz) electromagnetic fields. Life Sci. 1998,62:1271-1280.

146. Maresh CM, Cook MR, Cohen HD, Graham C, Gunn WS. Exercise testing in the evaluation of human responses to powerline frequency fields. Aviat Space Environ Med. 1988;59:1139-1145.
147. Gamberale F, Olson BA, Eneroth P, Lindh T, Wennberg A. Acute effects of ELF electromagnetic fields: a field study of linesmen working with 400 kV power lines. *Br J Ind Med.* 1989;46:729-737.

148. Selmaoui B, Lamberoz J, Touitou Y. Endocrine functions in young men exposed for one night to a 50-Hz magnetic field. A circadian study of pituitary, thyroid and adrenocortical hormones. *Life Sci.* 1997;61:473-486.

149. Ghione S, Del Seppia C, Mezzasalma L, Emdin M, Luschi P. Human head exposure to a 37 Hz electromagnetic field: effects on blood pressure, somatosensory perception, and related parameters. *Bioelectromagnetics.* 2004;25:167-175.

150. Blankenburg M, Haberland L, Elvers HD, Tannert C, Jandrig B. High throughput omics technologies: potential tools for the investigation of influences of EMF on biological systems. *Curr Genomics.* 2009;10:86–92.

151. Girgert R, Grundker C, Emons G, VHant V. Electromagnetic fields alter the expression of estrogen receptor cofactors in breast cancer cells. *Bioelectromagnetics.* 2008;29:169–176.

152. Willon BW, Matt KS, Morris JE, Sasser LB, Miller DL, Anderson LE. Effects of 60 Hz magnetic field exposure on the pineal and hypothalamic-pituitary-gonadal axis in the Siberian hamster (Phodopus sungorus). *Bioelectromagnetics.* 1999;20:224-232.