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# PINEAL MELATONIN LEVEL DISRUPTION IN HUMANS DUE TO ELECTROMAGNETIC FIELDS AND ICNIRP LIMITS

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**The International Agency for Research on Cancer (IARC) classifies electromagnetic fields (EMFs) as 'possibly carcinogenic' to humans that might transform normal cells into cancer cells. Owing to high utilisation of electricity in day-to-day life, exposure to power-frequency (50 or 60 Hz) EMFs is unavoidable. Melatonin is a natural hormone produced by pineal gland activity in the brain that regulates the body's sleep–wake cycle. How man-made EMFs may influence the pineal gland is still unsolved. The pineal gland is likely to sense EMFs as light but, as a consequence, may decrease the melatonin production. In this study, more than one hundred experimental data of human and animal studies of changes in melatonin levels due to power-frequency electric and magnetic fields exposure were analysed. Then, the results of this study were compared with the International Committee of Non-Ionizing Radiation Protection (ICNIRP) limit and also with the existing experimental results in the literature for the biological effect of magnetic fields, in order to quantify the effects. The results show that this comparison does not seem to be consistent despite the fact that it offers an advantage of drawing attention to the importance of the exposure limits to weak EMFs. In addition to those inconsistent results, the following were also observedfrom this work: (i) the ICNIRP recommendations are meant for the well-known acute effects, because effects of the exposure duration cannot be considered and (ii) the significance of not replicating the existing experimental studies is another limitation in the power-frequency EMFs. Regardless of these issues, the above observation agrees with our earlier study in which it was confirmed that it is not a reliable method to characterise biological effects by observing only the ratio of AC magnetic field strength to frequency. This is because exposure duration does not include the ICNIRP limit. Furthermore, the results show the significance of disruption of melatonin due to exposure to weak EMFs, which may possibly lead to long-term health effects in humans.**

## INTRODUCTION

Melatonin is a natural hormone (also known as 5-methoxy-*N*-acetyltryptamine) produced by the body (pineal gland) and is regulated by the suprachiasmatic nucleus[1]. It controls the body's sleep/wake cycle or the circadian rhythms and is activated by darkness and depressed by light[2]. Plasma melatonin levels are high at night and almost undetectable during the day, and therefore, they serve as an effective indicator of the biological clock or the circadian rhythm[3]. Various factors are involved in this, including one's natural melatonin levels and the length of exposure. The necessary illuminance fluctuates from species to species. In addition to the intensity of light, wavelength of light is a vital factor determining the degree to which the clock is reset[4]. Melatonin is well excited by the blue light (420–440 nm)[4]. Within the last decade, thousands of well-documented publications have reported melatonin as a naturally occurring free-radical scavenger and as an inducer of antioxidant enzymes[5]. Melatonin promptly crosses the blood–brain barrier because of its permeability into the brain[6]; thus, it is accumulated in the central nervous system at significantly higher levels than exists in the blood[5]. Furthermore, it attenuates seizures and hence used in the effective treatment of juvenile intractable epilepsy[7]. Melatonin also interacts with the immune system[7, 8], which regulates the pineal gland functions of activated immune cells[9]. It was hypothesised that the reduction of melatonin levels with age aids the aging process[10].

In addition, melatonin has also been identified as an effective agent that avoids both the initiation and promotion of cancer[11]. Some evidence suggests that melatonin acts a free-radical scavenger and therefore reduced night time levels lead to cancer and other serious illnesses. A higher cancer incidence has been reported in people living and working in places exposed to higher-than-normal artificial magnetic fields associated with a reduction in nocturnal melatonin levels[11]. A considerable incidence of cancer due to the reduction of melatonin production as a result of jet lag or night shift work has been detected[12]. For example, the Danish government paid compensation to women who have developed breast cancer after long periods of working at night[13]. In recent decades, melatonin hypothesis has been argued in relation to the substantial increase in the incidence of breast cancer in

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industrialised countries[14–16]. The supposed risk is caused from reduced production of night-time melatonin due to exposure to light-at-night from household and street lighting and magnetic fields associated with the electricity supply. It has been proved by animal experiments (rats) that exposure to constant light leads to quick development of mammary gland tumours. In a study in human beings, the reduced hormone-related cancer rates were observed in the blind and the partly sighted and increased breast cancer rates in nightshift workers[17–21]. In contrast to these studies, Davis *et al.*[22] showed that exposure to residential magnetic fields is not associated with increased risk of developing breast cancer. In addition to these, recent studies (2012) showed influences of (i) magnetic fields produced by incubators on the production of melatonin in newborns[23]; (ii) electromagnetic field (EMF) exposures in the aetiology of male infertility[24] and 2.45-GHz wireless media on melatonin modulation in rats[25].

In early studies night-time melatonin output was found to be unchanged by mobile phone handset emissions, but there could be an effect on melatonin onset time[26]. The time of administration and dose of melatonin effect in both humans and animals were investigated in Golombek *et al.*[27]. and Papp *et al.*[28].The biological clock controls the development of the sleep–wake rhythm in infants,which is also as the regulation of other biological rhythms, including heart rate, body temperature, blood pressure and melatonin discharge[29, 30]. Hence, melatonin level is associated with the development of the biological clock in infants and would be a useful indicator of the sleep–wake rhythm development[31]. Blood samples (serum melatonin)[32], saliva[31] and the melatonin metabolite 9-hydroxymelatonin sulphate (6-OHMS) in urine[33] can be used to assess melatonin levels in the body. A study by Shinohara and Kodama[31] shows that salivary melatonin concentrations in infants between 06:00 and 22:00 decrease by age, and increase in morning values may possibly indicate an immature sleep–wake rhythm[31]. Plasma melatonin levels in adults start to decrease after 6.00 because of exposure to morning light and reach their lowest at 10.00 continuing the same level up until 21.00 and peak at night between 2.00 and 6.00[34]. In order to develop chronic diseases such as rheumatism, asthma, arrhythmia and leukemia, it takes 5–7 y of radiation exposure, which is considered dangerous[35].

Besides this, the World Health Organization has confirmed that prolonged alterations in sleep patterns suppress the body's ability to make melatonin[36]. In experiments in cells, tissues, organs and whole animals[33], melatonin has been revealed to protect against harm from known carcinogens, including ionising radiation. EMFs are characterised by many variables, such as the orientation of the magnetic field and its polarity. A study suggests that there may be a 'cumulative effect of magnetic field exposure on the stability of individual melatonin measurements over time'[37]. The hypothesis of melatonin disruption in those studies of human populations could be possibly due to factors other than field intensity level, such as transients or switching, or due to the field type (electric rather than magnetic field)[33]. Henshaw and Reiter[33], in reviewing the literature, found support for the hypothesis of melatonin disruption in those studies of human populations chronically exposed to both electric and magnetic fields. According to the Burch *et al.*[38] study of electric utility workers, certain EMF environments have a greater effect on melatonin levels and it was confirmed in a series of animal studies conducted by Kato *et al.*[39]. The effects of magnetic fields on pineal melatonin production have been studied in a number of studies[33] in volunteers exposed for relatively short periods. Carefully designed experimental studies of pineal melatonin disruption in human populations that are chronically exposed to extremely weak low-frequency (ELF) and radio-frequency magnetic fields[33] is critically important: (1) polarised fields; (2) protectiveness of melatonin in the presence of ELF magnetic fields—the experiments of Ishido *et al.* (2001) and (3) the effects of melatonin disruption on the risk of miscarriage and the effect for human foetal development. Exposure to electric and magnetic fields because of transportation[40], production and distribution of electricity (50 Hz in Australia and Europe and 60 Hz in North America) occurs everywhere, especially in industrialised countries. Many epidemiological studies of residential and occupational exposure to ELF (<300 Hz) magnetic fields have shown varying results, but in general, positive associations with different cancer forms such as Leukemia[41–44], brain tumours and breast cancer[12, 36]. In spite of this, a large proportion of the world's population is exposed to electricity in everyday activities (lighting, house electrical wiring, etc.); hence, the biological effects of EMFs and their possible consequences to humans attract more scientific interes[45].and is a subject of debate.

Skin depth is insignificant at higher frequencies; hence, the most of the energy from the fields is absorbed near the skin surface. For example, at a 2450-MHz frequency, the skin depth is ~2 cm and at 10 GHz, it is ~0.4 cm[46]. In the light of this fact, in this work, the effects of low-frequency magnetic fields were investigated.

The remainder of this paper is organised as follows. More than one hundred experimental data of human and animal studies of changes in



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melatonin levels due to power-frequency electric and magnetic fields exposure are analysed. Then, the results of this study are comapred with the International Committee of Non-Ionizing Radiation Protection (ICNIRP) limit and also with the existing experimental results found in the literature for the biological effect of magnetic fields, in order to quantify the effects, and then the article is concluded.

## BIOLOGICAL EFFECTS AND ICNIRP LIMITS

The biological effects of EMFs are a research area that has generated controversial results regarding possible adverse health effects. The recommendation of the ICNIRP guidelines for exposure limit value for low-frequency EMF and microwaves aim to protect against nerve stimulation and body heating, respectively. The laboratory experiments of biological effects are obtained using biological effect = (experimental data−control data)/control data. Different biological effects can be compared by using this formula since units are dimensionless[47]. The study by Nordenson *et al.*[48] with a report of more references shows an increase in chromosomal aberrations in peripheral lymphocytes of train engine drivers exposed to 16 2/3 Hz magnetic fields from a few to over 100 μT. This study[48] supports the hypothesis that 'exposure to magnetic fields at mean intensities of 2–15 μT can induce chromosomal damage'. Apart from that, the hydrogen nuclear polarisation model[49] predicts a biological response for oscillating magnetic field strengths above 0.1 μT. The presence of a static magnetic field is required and biological effects can be expected for all frequencies below a few hundred hertz. Belova and Lednev found in 2001[49] that the gravitropic bending of flax seedling deviated anomalously from the expected values at very low amplitudes $0.075 <_{AC}< 5\ \mu T$ of the time-varying magnetic field. Since, no resonance frequencies occur in this model, in principle, all frequencies that occur in the environment up to several hundred hertz can give rise to biological effects. Regardless of that, the presence of the earth's magnetic field in parallel to the time-varying magnetic field is still required to be included. Besides this, the strength of this static magnetic field is not critical for the predicted biological effect. Some laboratory experimental evidences that are established in the literature for biological effects around these fields are indicated in Table 1.

**Table 1. Studies relevant to biological effects from weak extremely low-frequency magnetic fields.**

| No | Exposure value | Authors |
|---|---|---|
| 1 | 60 Hz, 1.2 μT | Blackman *et al.*[63] |
| 2 | 60 Hz, 4 μT | Farrell *et al.*[64] |
| 3 | 17 Hz, 0.2μ T | Novikov *et al.*[56] |
| 4 | 17 Hz, 1.25 μT | Novikov *et al.*[56] |
| 5 | 17 Hz, 0.3 μT | Novikov *et al.*[56] |
| 6 | 7 Hz, 0.05 μT | Persinger[65] |
| 7 | 7 Hz, 0.5 μT | Persinger[65] |
| 8 | 40 Hz, 0.005 μT | Persinger [65] |
| 9 | 40 Hz, 0.5 μT | Persinger[65] |
| 10 | 60 Hz, 0.001 μT | Prato *et al.* [66] |
| 11 | 10 Hz, 28.9 μT | Trebbi *et al.* [67] |

The ICNIRP guidelines protects the public and workers from adverse health effects caused by exposure to non-ionising radiation[50]. The ICNIRP limits are designed as guidelines to protect from low-frequency EMFs against nerve stimulation and from microwaves against body heating[51]. Apart from this, there are other international standards introduced on the basis of power density and electric field induced in the tissues, such as Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) limits[52]. The effects of electric fields on pineal melatonin production in rats are given in Table 2.

The effects of magnetic fields on pineal melatonin production are given in Table 3 (rats), as in Jahandideh *et al.*[53] and in Table 4 (human). In contrary to negative effects, some studies suggest positive effects of administrating melatonin for different health conditions, as indicated in Table 5.

## RESULTS AND DISCUSSION

In this section, results are obtained by analysing current experimental data of human and animal

**Table 2. Effects of electric fields on pineal melatonin production—RAT.**

| No | Exposure value | Exposure duration | Melatonin level | Authors |
|---|---|---|---|---|
| 1 | 60 Hz, 1.7–1.9 kV $m^{-1}$ | 20 h $d^{-1}$ × 30 d | Changed | Wilson *et al.*[68, 69] |
| 2 | 60 Hz, 3–30 kV $m^{-1}$ | 3 times/d × 21 d | Not changed | Wolpaw *et al.*[70] |
| 3 | 60 Hz, 39 kV $m^{-1}$ | <3 d | Not changed | Wilson *et al.*[68] |
| 4 | 60 Hz, 10, 65, 130 kV $m^{-1}$ | 19 h $d^{-1}$ × 23 d | Changed | Reiter *et al.*[71] |
| 5 | 60 Hz, 65 kV $m^{-1}$ | 20 h $d^{-1}$ × 21 d | Changed | Wilson *et al.*[72] |
| 6 | 60 Hz, 65 kV $m^{-1}$ | 20 h $d^{-1}$ × 30 days | Changed | Grota *et al.*[73] |
| 7 | 60 Hz, 65 kV $m^{-1}$ | 20 h $d^{-1}$ × 30 days | Changed | Sasser *et al.*[74] |



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**Table 3. Effects of magnetic fields on pineal melatonin production as in ref.[53]—RAT.**

| No | Exposure value | Polarisation | Exposure duration | Melatonin level | Authors |
|---|---|---|---|---|---|
| 1 | 50 Hz, 1 μT | Vertical | 24 h | Not changed | Bakos *et al.*[75] |
| 2 | 50 Hz, 1 μT | Horizontal | 24 h | Not changed | Bakos *et al.*[76] |
| 3 | 50 Hz, 1 μT | Horizontal | 720 h | Not changed | Selmaoui and Touitou[77] |
| 4 | 50 Hz, 1 μT | Vertical | 1008 h | Not changed | Kato *et al.*[78] |
| 5 | 50 Hz, 1 μT | Horizontal | 1008 h | Not changed | Kato *et al.*[78] |
| 6 | 50 Hz, 1.4 μT | Circular | 1008 h | Changed | Kato *et al.*[79] |
| 7 | 50 Hz, 1.4 μT | Circular | 1008 h | Changed | Kato *et al.*[39] |
| 8 | 50 Hz, 1.4 μT | Circular | 1008 h | Changed | Kato *et al.*[80] |
| 9 | 50 Hz, 5 μT | Horizontal | 12 h | Not changed | Selmaoui and Touitou[77] |
| 10 | 50 Hz, 5 μT | Vertical | 24 h | Not changed | Bakos *et al.*[81] |
| 11 | 60 Hz, 5 μT | Horizontal | 24 h | Not changed | John *et al.*[82] |
| 12 | 50 Hz, 10 μT | Vertical | 1 h | Not changed | Chacon[83] |
| 13 | 50 Hz, 10 μT | Horizontal | 12 h | Not changed | Selmaoui and Touitou[77] |
| 14 | 50 Hz, 10 μT | Horizontal | 720 h | Changed | Selmaoui and Touitou[77] |
| 15 | 50 Hz, 10 μT | Horizontal | 2184 h | Changed | Mevissen *et al.*[84] |
| 16 | 60 Hz, 50 μT | Vertical | 12 h | Changed | Rosen *et al.*[85] |
| 17 | 50 Hz, 50 μT | Vertical | 168 h | Not changed | Bakos *et al.*[86] |
| 18 | 50 Hz, 50 μT | Horizontal | 2184 h | Changed | Mevissen *et al.*[87] |
| 19 | 50 Hz, 100 μT | Vertical | 1 h | Not changed | Chacon[83] |
| 20 | 50 Hz, 100 μT | Horizontal | 12 h | Changed | Selmaoui and Touitou[77] |
| 21 | 50 Hz, 100 μT | Vertical | 24 h | Changed | Bakos *et al.*[75] |
| 22 | 50 Hz, 100 μT | Horizontal | 24 h | Not changed | Bakos *et al.*[76] |
| 23 | 60 Hz, 100 μT | Horizontal | 24 h | Not changed | John *et al.*[82] |
| 24 | 50 Hz, 100 μT | Vertical | 168 h | Not changed | Bakos *et al.*[86] |
| 25 | 50 Hz, 100 μT | Horizontal | 168 h | Changed | Selmaoui and Touitou[88] |
| 26 | 50 Hz, 100 μT | Horizontal | 336 h | Not changed | Fedrowitz *et al.*[89] |
| 27 | 50 Hz, 100 μT | Horizontal | 720 h | Changed | Selmaoui and Touitou[77] |
| 28 | 50 Hz, 500 μT | Circular | 4 h | Not changed | Tripp *et al.*[90] |
| 29 | 60 Hz, 500 μT | Horizontal | 24 h | Not changed | John *et al.*[82] |
| 30 | 50 Hz, 500 μT | Vertical | 24 h | Not changed | Bakos *et al.*[81] |
| 31 | 60 Hz, 1000 μT | Horizontal | 240 h | Not changed | John *et al.*[82] |
| 32 | 60 Hz, 1000 μT | Horizontal | 1008 h | Not changed | John *et al.*[82] |
| 33 | 50 Hz, 1000 μT | Vertical | 1 h | Changed | Chacon[83] |

studies of change in melatonin levels due to power-frequency (50 or 60 Hz) EMFs exposure and by comparing them with the international limit (ICNIRP) and with the evidence from laboratory studies, in order to quantify the biological effects. The results seem to be compatible with the ICNIRP limit and the evidence from laboratory studies of health effects that is found in the literature. Despite the inconsistent results of previous studies of melatonin disruption , there is a benefit of drawing attention to the impact of the exposure limits to weak EMFs.

Figures 1 and 2 compare magnetic and electric field strengths with the ICNIRP limit and some laboratory experimental evidence for biological effects around these fields. In the authors' evaluation, more than one hundred scientific articles were considered. These results seem to be compatible with the evidence from laboratory studies of the biological effects that is found in the majority of literature and the ICNIRP limit. The results of the authors' study show a considerable melatonin-level disruption due to exposure to weak EMFs, which would possibly lead to health effects in humans. Therefore, additional research is needed to understand how EMFs affect the long-term health in humans via melatonin disruption.

The reaction of the biological systems varies because of the direction of the generated magnetic field to the biological system (e.g.: parallel, perpendicular or at an angle)[54]. In addition to that, in some experiments, control system has been exposed to the earth's magnetic field or to a DC magnetic field that is equivalent to the DC field of the test system[55, 56]. In contrast to this, Blackman *et al.*[57] have carried out some experiments with shielding magnetic fields of the control system. The electric and magnetic field strengths are generally measured using field meters and suitable electric or magnetic field sensors. Each measurement instrument has measurement limitations and uncertainties[58], in addition to background EMFs and environmental conditions (temperature, light and humidity) that might influence these measurements[47]. Another reason for varying results of plasma melatonin level can be the dissimilar sensitivity to magnetic fields among species[59].



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**Table 4. The effects of magnetic fields on pineal melatonin production—HUMAN.**

| No | Exposure value | Exposure duration | Melatonin level | Authors |
|---|---|---|---|---|
| 1 | 50 Hz, 1 d in front of video display unit | 1 d | Changed (some) | Arnetz and Berg[91] |
| 2 | 50 Hz, 1 μT, continuous linear | 23 h | Not changed | Akerstedt *et al.* [92] |
| 3 | 60 Hz, 1.2 μT, human breast cancer cell *in vitro* | 7 d | Changed | Blackman *et al.* [63] |
| 4 | 60 Hz, utility workers, circular | 72 h | Not changed | Burch *et al.*[93] |
| 5 | 60 Hz, electric utility workers | 1 y | Changed (some) | Burch *et al.*[93] |
| 6 | 60 Hz, electric utility workers | 1 y | Changed | Burch *et al.*[94] |
| 7 | 60 Hz, electric utility workers | 1 y | Changed | Burch *et al.*[95] |
| 8 | 60 Hz, substations—3 phase, circular | 2 h | Changed (no effect due to 1—phase exposure) | Burch *et al.*[38] |
| 9 | 60 Hz, cell telephone use in electric utility workers | 25 min | Pattern | Burch *et al.*[96] |
| 10 | 50 Hz, 100 μT | 30 min | Not changed | Crasson *et al.*[97] |
| 11 | 60 Hz, night time bed room magnetic fields | 1171 nights | Changed | Davis *et al.*[98] |
| 12 | 60 Hz, 24 h personal magnetic field | 1888 d | Changed | Davis *et al.* [98] |
| 13 | 60 Hz, residential exposure, 0.039 μT | 72 h | Changed (some) | Davis *et al.* [98] |
| 14 | 60 Hz, 1 and 20 μT | 23 h | Not changed | Graham *et al.* [99] |
| 15 | 60 Hz, continuous circular sinusoidal | 23 h | Not changed | Graham *et al.* [100] |
| 16 | 60 Hz, laboratory generated, circular | 14 month | Changed (some) | Graham *et al.* [37] |
| 17 | 60 Hz, 28.3 μT | 8 h $d^{-1}$ | Not changed | Graham *et al.* [101] |
| 18 | 60 Hz, 28.3 μT, circular | 23 h | Not changed | Graham *et al.* [102] |
| 19 | 60 Hz, 28.3 μT, circular sinusoidal | 23 h | Not changed | Graham *et al.* [102] |
| 20 | 60 Hz, 127.3 μT, circular polarised | 23 h | Not changed | Graham *et al.* [102] |
| 21 | Direct current, 2-7 μT, static exposure | 22 h | Not changed | Haugsdal *et al.* [103] |
| 22 | 50 Hz, 0.7 μT (head), 3.5 μT (feet) | 11 weeks | Not changed | Hong *et al.* [104] |
| 23 | 60 Hz, sewing machine workers | 3 weeks | Changed (some) | Juutilainen *et al.* [105] |
| 24 | 60 Hz, 1 μT, continuous circular | 23 h | Not changed | Kaune *et al.*[106] |
| 25 | 60 Hz, sewing machine workers, >1 μT | 3 weeks | Changed (some) | Kumlin *et al.*[107] |
| 26 | 60 Hz, 735 kV power lines | 2 d | Changed | Levallois *et al.* [108] |
| 27 | 16.7 Hz, locomotive engineers, 1 and 20 μT | 30 min–4 h | Not changed | Pfluger and Minder[109] |
| 28 | 50 Hz, continuous and intermittent, linear and circular | 23 h | Not changed | Selmaoui *et al.*[110] |
| 29 | 50 Hz, 0.1–2.6 μT, substations | 9 h | Not changed | Touitou *et al.*[111] |
| 30 | 50 Hz, professional and residential exposure | 1–20 y | Not changed | Touitou *et al.*[111] |
| 31 | 60 Hz, electric blankets | 8 weeks | Changed | Wilson *et al.*[112] |
| 32 | 60 Hz, electric blanket, 0.2–0.6 μT | 8 weeks | Not changed | Wilson *et al.*[112] |
| 33 | 50 Hz, laboratory generated, circular | 2 y | Changed (some) | Wood *et al.*[113] |

Regardless of these facts, biological studies were not intended to clarify how weak fields can interact with biological molecules; rather, environmental frequencies and unrealiztically high amplitudes were used for exposure. A crucial problem that any interaction model must deal with is how a large enough signal-to-noise ratio can be obtained to enable the living cell to detect the signal. In addition to this, for strong signals, how the biological effects are obtained is well understood. For example, strong microwave radiation will heat body tissue, mainly by setting water dipoles into rotation, and strong low-frequency electric or magnetic fields will induce electric currents in the body, which lead to nerve excitation. On the other hand, for extremely weak electromagnetic signals, there is no generally accepted theory that can explain all the biological effects reported in the literature[49, 51, 60, 61].

Biological or health effects depend on frequency, the strength of EMFs, exposure duration, polarisation and biological system (animals, plants and chemicals)[47]. A considerable variation in the response of melatonin levels in biological systems was observed for the same frequency although with different EMF strength and the exposure duration. Our results confirmed that it is not a reliable method to characterise biological effects by observing only the ratio of AC magnetic field strength to frequency because exposure duration is not included in this limit, as indicated in our previous study[47].

In ionising radiation, dose is defined as the product of dose rate and time, and is expressed in J/kg. For ionising radiation, the risk of cancer is supposed to be dependent on the total accumulated dose. For acute effects, like cell death, it is known that there are dose-rate effects. Thus, it is important



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**Table 5. Melatonin administration.**

| No | Problem | Administrated melatonin amount | Remarks | Authors |
|---|---|---|---|---|
| 1 | Cervical spinal cord damage—rats | 30 mg $kg^{-1}$ | Melatonin may be useful in preventing the spinal cord against radiation toxicity | Aghazadeh *et al.*[114] |
| 2 | AD patients with rapid eye movement (REM) sleep behaviour disorder | 5–10 mg $d^{-1}$ for 20 months | Melatonin was effective in suppressing REM sleep behaviour disorder | Anderson *et al.* [115] |
| 3 | Melatonin and viral infections—rats | 250, 500 and 1000 μg melatonin per kg | Melatonin is an additional therapeutic alternative to fight viral diseases | Bonilla *et al.*[116] |
| 4 | Convulsive seizures | 50 mg $d^{-1}$ for a year | Seizures were under control | Carballo *et al.*[117] |
| 5 | Blood pressure patient | 5 or 10 mg | Increased drop of blood pressure in type I diabates | Cavallo *et al.*[118] |
| 6 | Eight patients with delayed sleep-phase syndrome | 5 mg $d^{-1}$ for 4 weeks | Earlier onset of sleep and wake-up time | Dahlitz *et al.*[119] |
| 7 | Insomnia patients | 0.1 mg or 0.3 mg | Increased duration of sleep and decreased sleep-onset latency | Dollins *et al.*[120] |
| 8 | Insomnia patients | 3 mg $d^{-1} \times 21$ d | Improve the sleep | Fainstein *et al.*[121] |
| 9 | Patients with mild cognitive impairment (MCI) | 3–9 mg $d^{-1}$ for 9–18 months | Proved significantly improved performance in neuropsychological assessment | Furio *et al.* [122] |
| 10 | Non-alcoholic fatty liver disease (NAFLD) progresses into non-alcoholic steatohepatitis (NASH) | 2×5 mg/daily for 12 weeks | Significantly improves plasma liver enzymes in NASH patients | Gonciarz *et al.*[123] |
| 11 | Insomnia patients | 2 mg $d^{-1}$ for 1 week | Increased efficient and duration of sleep | Haimov *et al.* [124] |
| 12 | Amyotrophic lateral sclerosis (ALS) patients | 30–60 mg | Melatonin crosses the blood–brain barrier. Melatonin is considered a composite for neuroprotection in ALS | Jacob *et al.*[125] |
| 13 | Prophylaxis of cluster headache | 10 mg $d^{-1}$ | Reduce cluster headache | Leone *et al.* [126] and Peres *et al.*[127] |
| 14 | Lung cancer patients | 20 mg $d^{-1}$ | The efficacy of chemotherapy may be enhanced by the pineal hormone | Messina *et al.*[128] |
| 15 | Cardiac patient | 2 mg | Increased cardiac vagal tone | Nishiyama *et al.*[129] |
| 16 | Maternal–foetal transfer of melatonin in pregnant women | 3 mg | Fast and simply melatonin is transferred to the foetus in women | Okatani *et al.*[130] |
| 17 | Cirrhosis patients | — | Melatonin abnormalities in cirrhosis patients are related to liver insufficiency difficulty | Velissaris *et al.*[36] |
| 18 | DNA damage | 300 mg | A significant decrease (50–70 %) in DNA damage | Vijayalaxmi *et al.*[131] |
| 19 | Survival rate—rats | 125 and 250 mg | 45 % survival without melatonin; 85 % survival with 250 mg melatonin | Vijayalaxmi *et al.*[132] |
| 20 | Tumour patients | 14–18 mg $d^{-1}$ | Stimulated tumour growth in long photoperiods | Vijayalaxmi *et al.*[133] |
| 21 | Insomnia patients | 0.3 mg | Increased efficiency of sleep and decreased sleep-onset latency | Wurtman and Zhdanova[134] |

whether the total dose is given in small fractions of very fast, highly intense radiation. In contrast to that, in non-ionising radiation, the acute effects are determined by the intensity of the radiation or fields, and in most cases, cumulative effects are not assumed to occur. The safety limits from ICNIRP aim to protect people against acute effects (nerve stimulation and body heating) and do not consider the long-term effects like cancer risk that are uncertain to be taken into the account. Considering this, the evidence of biological effects should be acceptable since the exposure limits can be firmly introduced only on the basis of established experimental results[47]. Despite this, it is quite possible that



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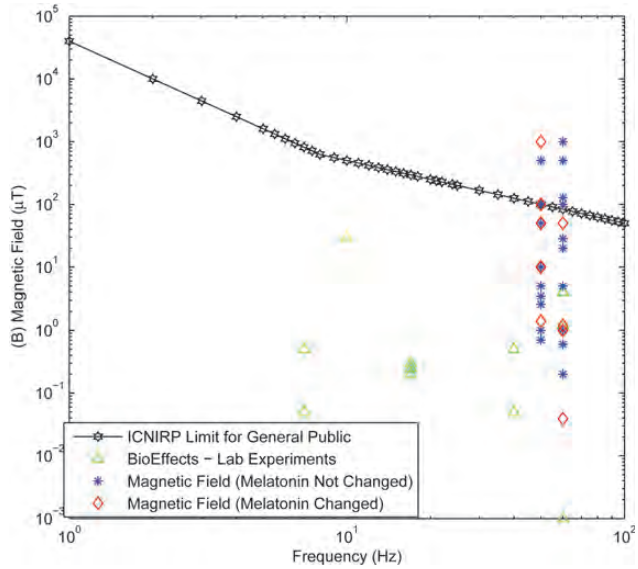


Figure 1. Plasma melatonin analysis—comparison of the magnetic field strength for different frequencies with the ICNIRP limit and experimental evidence for biological effects.

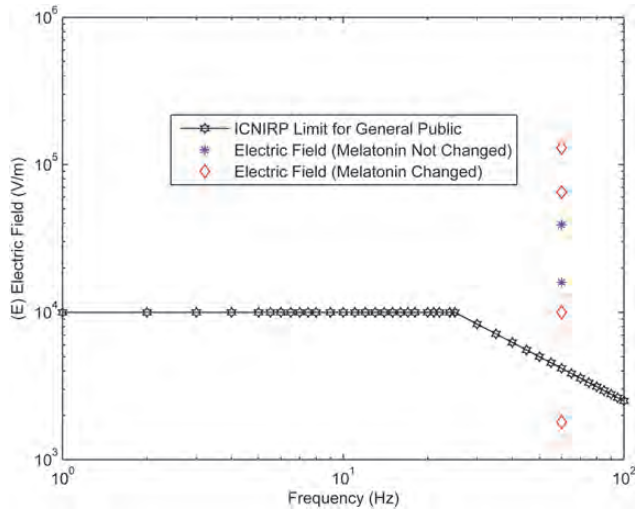


Figure 2. Plasma melatonin analysis—comparison of the electric field strength for different frequencies with the ICNIRP limit and experimental evidence for biological effects.

some experimental results go unpublished, because they do not reveal any effect of weak fields or they do not reproduce the previous results. This confirmation bias affects the outcome of the influence of magnetic fields on biological systems. The materials and methods of published data should be sufficient to analyse the experiments. Mechanistic laboratory studies are needed, both to strengthen the findings of an epidemiological study and to give suggestions on what exposure parameters should be included in the epidemiological studies. Irrespective of these, the results should be quantifiable and confirmed by independent studies[62].

## CONCLUSION

Changes in human and animal melatonin levels due to power-frequency (50 or 60 Hz) electric and magnetic fields exposure were compared with the ICNIRP limits and with the evidence of the



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laboratory studies of the biological effects that are found in the literature, in order to quantify the biological effects. The results seem to be compatible with the international limit (ICNIRP) and the evidence from laboratory studies of health effects that are found in the literature. Although studies of melatonin disruption showed inconsistent results from different laboratories, there is a benefit of drawing attention to the significance of the exposure limits to weak EMFs. In the ICNIRP limit, the acute effects are determined by the intensity of the radiation and cumulative effects are not assumed to occur. Beside this, the above observation agrees with our earlier study in which it was confirmed that it is not a reliable method to characterise biological effects by observing only the ratio of AC magnetic field strength to frequency as the exposure duration is not included in this limit. In addition, the results also emphasise consideration of the importance of the exposure limits due to weak EMFs. Another limitation in the field of extremely low-frequency EMFs is the challenge of replicating existing experimental results. Even though the evidence obtained in the laboratory studies has been produced by independent research groups, these experiments have not been repeated, independently. Consequently, additional research is needed to further explore the controversy of the long-term effects of EMFs that could change human melatonin levels.

## REFERENCES


1. Zee, P. C. and Goldstein, C. A. *Treatment of shift work disorder and jet lag*. Curr. Treat. Options Neurol. **12**, 396–411 (2010).
2. Trinder, J., Armstrong, S., Obrien, C., Luke, D. and Martin, M. *Inhibition of melatonin secretion onset by low levels of illumination*. J. Sleep Res. **5**, 77–82 (1996).
3. Armstrong, S. *Melatonin and circadian control in mammals*. Cell. Mol. Life Sci. **45**(10), 932–938 (1989).
4. 'Biological clock—circadian rhythm'. http://www.crystalinks.com/biologicalclock.html.
5. Tan, D. X. *Melatonin and brain*. Curr. Neuropharmacol. **8**(3), 161 (2010).
6. Reiter, R. J., Manchester, L. C. and Tan, D. X. *Neurotoxins: Free radical mechanisms and melatonin protection*. Curr. Neuropharmacol. **8**, 194–210 (2010).
7. Banach, M., Gurdziel, E., Jedrych, M. and Borowicz, K. K. *Melatonin in experimental seizures and epilepsy*. Pharmacol Rep. **63**(1), 1–11 (2011).
8. Carrillo-Vico, A., Guerrero, J., Lardone, P. and Reiter, R. *A review of the multiple actions of melatonin on the immune system*. Endocrine **27**(2), 189–200 (2005).
9. Skwaro-Sonta, K., Majewski, P., Markowska, M., Obap, R. and Olsznska, B. *Bidirectional communication between the pineal gland and the immune system*. Can. J. Physol. Pharmacol. **81**, 342–349 (2003).
10. Bubenik, G. A. and Konturek, S. J. *Melatonin and aging: prospects for human treatment*. J. Physiol. Pharmacol. **62**(1), 13–19 (2011).
11. Reiter, R. J. *Melatonin suppression by static and extremely low frequency electromagnetics fields: relationship to the reported increased incidence of cancer*. Rev. Environ. Health **10**, 171–186 (1994).
12. Schernhammer, E., Rosner, B., Willett, W., Laden, F., Colditz, G. and Hankinson, S. *Epidemiology of urinary melatonin in women and its relation to other hormones and night work*. Cancer Epidemiol. Biomarkers Prev. **13**(62), 936–943 (2004).
13. Chustecka, Z. *Denmark pays compensation for breast cancer after night-shift work*. Medscape Med. News (2009).
14. Stevens, R. G. *Electric power use and breast cancer: a hypothesis*. Am. J. Epidemiol. **125**, 556–561 (1987).
15. Sanchez-Barcelo, E. J., Cos, S. and Mediavilla, M.D. *Influence of pineal gland function on the initiation and growth of hormone-dependent breast tumours. Possible mechanisms*. In: Gupta, D., Attanasio, A. and Reiter, R. J., Eds. Brain Research Promotion. pp. 221–232 (1988).
16. Brainard, G. C., Kavet, R. and Kheifets, L. I. *The relationship between electromagnetic field and light exposures to melatonin and breast cancer risk: a review of the relevant literature*. J. Pineal Res. **26**, 65–100 (1999).
17. Hahn, R. A. *Profound bilateral blindness and the incidence of breast cancer*. Epidemiology **2**, 208–210 (1991).
18. Feychting, M., Österlund, B. and Ahlbom, A. *Reduced cancer incidence among the blind*. Epidemiology **9**, 490–494 (1998).
19. Hansen, J. *Light at night, shiftwork, and breast cancer risk*. J. Natl. Cancer Inst. **93**(20), 1513–1515 (2001).
20. Swerdlow, A. *Shift work and breast cancer: a critical review of the epidemiological evidence*. Res. Rep. **132** (2003).
21. Verkasalo, P. K., Pukkala, E., Stevens, R. G., Ojamo, M. and Rudanko, S. L. *Inverse association between breast cancer incidence and degree of visual impairment in finland*. Br. J. Cancer **80**(9), 1459–1460 (1999).
22. Davis, S., Mirick, D. K. and Stevens, R. G. *Residential magnetic fields and the risk of breast cancer*. Am. J. Epidemiol. **155**(5), 446–454 (2002).
23. Bellienia, C. V., Teia, M., Iacoponib, F., Tatarannoa, M. L., Negroa, S., Proiettia, F., Longinia, M., Perronea, S. and Buonocorea, G. *Is newborn melatonin production influenced by magnetic fields produced by incubators?* Early Hum. Dev. **88**(8), 707–710 (2012).
24. Kumar, S., Behari, J. and Sisodi, R. *Impact of electromagnetic field exposures in the aetiology of male infertility*. Endocr. Abs. **28**, P287 (2012).
25. Naziroglu, M., Celik, O., Ozgul, C., Cig, B., Dogan, S., Bal, R., Gumral, N., Rodriguez, A. B. and Pariente, J. A. *Melatonin modulates wireless (2.45 GHz)-induced oxidative injury through TRPM2 and voltage gated* $Ca^{2+}$ *channels in brain and dorsal root ganglion in rat*. Physiol. Behav. **105**(3), 683–692 (2012).
26. Wood, A. W., Loughran, S. P. and Stough, C. *Does evening exposure to mobile phone radiation affect*




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*subsequent melatonin production?* Int. J. Radiat. Biol. **82**(2), 69–76 (2006).
27. Golombek, D. A., Escolar, E., Burin, L. J., Sanchez, M. G. and Cardinali, D. P. *Time-dependent melatonin analgesia in mice: inhibition by opiate or benzodiazepine antagonism*. Eur. J. Pharmacol. **194**, 25–30 (1991).
28. Papp, M., Litwa, E., Lason-Tyburkiewicz, M. and Gruca, P. *Effects of melatonin in a place preference conditioning depend on the time of administration*. Pharmacol. Rep. **62**, 1023–1029 (2010).
29. Mirmiran, M., Maas, Y. G. and Ariagno, R. L. *Development of fetal and neonatal sleep and circadian rhythms*. Sleep Med. Rev. **7**, 321–334 (2003).
30. McGraw, K., Hoffmann, R., Harker, C. and Herman, J. H. *The development of circadian rhythms in a human infant*. Sleep **22**, 303–310 (1999).
31. Shinohara, H. and Kodama, H. *Relationship between circadian salivary melatonin levels and sleep–wake behavior in infants*. Pediatr. Int. **53**, 29–35 (2011).
32. Semm, P. *Pineal function in mammals and birds is altered by earth-strength magnetic fields*. In: Moore-Ede, M. C., Campbell, S. S. and Reiter, R. J., Eds. Electromagnetic fields and circadian rhythmicity, Birkhauser (1992).
33. Henshaw, D. and Reiter, R. *Do magnetic fields cause increased risk of childhood leukaemia via melatonin disruption?* Bioelectromagnetics Suppl. **7**, S86–S97 (2005).
34. Benloucif, S., Burgess, H. J. and Klerman, E. B. *Measuring melatonin in humans*. J. Clin. Sleep Med. **4**, 66–69 (2008).
35. Bueno, M. *The Great Book of the Healthy House*. In: Editor, R, Ed. 50–106 (1992).
36. Velissaris, D., Karamouzos, V., Polychronopoulos, P. and Karanikolas, M. *Chronotypology and melatonin alterations in minimal hepatic encephalopathy*. J. Circadian Rhythms **7**, 1–6 (2009).
37. Graham, C., Cook, M., Sastre, D. R. A. and Gerkovich, M. *Multi-night exposure to 60 Hz magnetic fields: effects on melatonin and its enzymatic metabolite*. J. Pineal Res. **28**(1), 1–8 (2000).
38. Burch, J., Reif, J., Noonan, C. and Yost, M. *Melatonin metabolite levels in workers exposed to 60-Hz magnetic fields: work in substations and with 3-phase conductors*. J. Occup. **42**(2), 136–142 (2000).
39. Kato, M., Honma, K., Shigemitsu, T. and Shiga, Y. *Circularly polarized 50-Hz magnetic field exposure reduces pineal gland and blood melatonin concentrations of long-evans rats*. Neurosci. Lett. **166**(1), 59–62 (1994).
40. Halgamuge, M. N., Abeyratne, C. D. and Mendis, P. *Measurement and analysis of electromagnetic fields from trams, trains and hybrid cars*. Radiat. Prot. Dosim. **141**(3), 255–268 (2010).
41. Ahlbom, A., Day, N. and Feychting, M. *A pooled analysis of magnetic fields and childhood leukemia*. Br. J. Cancer **83**, 692–698 (2000).
42. Savitz, D. A., Wachtel, H., Barnes, F. A., John, E. M. and Tvrdik, J. G. *Case-control study of childhood cancer and exposure to 60-Hz magnetic fields*. Am. J. Epidemiol. **128**(1), 21–38 (1988).
43. Wertheimer, N. and Leeper, E. *Adult cancer related to electrical wires near the home*. Int. J. Epidemiol. **11**(4), 345–355 (1982).
44. Wertheimer, N. and Leeper, E. *Electrical wiring configurations and childhood cancer*. Am. J. Epidemiol. **109**(3), 273–284 (1979).
45. Eberhardt, J. L. and Halgamuge, M. N. *Reply to comment on 'Study of charged particle's behavior in a biological cell exposed to AC-DC electromagnetic fields' and on 'Comparison between two models of interaction between electric and magnetic fields and proteins in cell membranes'*. Environ. Eng. Sci. **28**(10), 753–754 (2011).
46. Durney, C. H. *Radiofrequency radiation dosimetry handbook*. Technical Report. Brooks Air Force Base (1986).
47. Abeyrathne, C. D., Farrell, P. M. and Halgamuge, M. N. *Analysis of biological effects and limits of exposure to weak magnetic fields*. In: Proceedings of the 5th International Conference on Information and Automation for Sustainability. Colombo, Srilanka, pp. 415–420 (2010).
48. Nordenson, I., Hansson-Mild, K., Jarventaus, H., Hirvonen, A., Sandstrom, M., Wilen, J., Blix, N. and Norppa, H. *Chromosomal aberrations in peripheral lymphocytes of train engine drivers*. Bioelectromagnetics **21**, 1–10 (2001).
49. Belova, N. A. and Lednev, V. V. *Extremely weak alternating magnetic fields affect the gravitropic response in plants*. Biophysics **46**(1), 121–124 (2001).
50. ICNIRP. *Guidelines for limiting exposure to time-varying electric and magnetic fields (1 Hz to 100 kHz)*. Health Phys. **99**, 818–836 (2010).
51. Halgamuge, M. N., Persson, B. R. R., Salford, L. G., Mendis, P. and Eberhardt, J. L. *Comparison between two models for interactions between electric and magnetic fields and proteins in cell membranes*. Environ. Eng. Sci. **26**(10), 1473–1480 (2009).
52. ARPANSA. *Measurements of residential power frequency magnetic fields*. Australian Radiation Protection and Nuclear Safety Agency, Technical Report (2002) ISSN 0157-1400.
53. Jahandideh, S., Abdolmaleki, P. and Movahedi, M. M. *Comparing performances of logistic regression and neural networks for predicting melatonin excretion patterns in the rat exposed to ELF magnetic fields*. Bioelectromagnetics **31**, 164–171 (2010).
54. Blackman, C. F., Blanchard, J. P., Benane, S. G. and House, D. E. *Effect of ac and DC magnetic field orientation on nerve cells*. Biochem. Biophys. Res. Commun. **220**, 807–811 (1996).
55. Lednev, V. V. *Bioeffects of weak combined constant and variable magnetic fields*. Biophysics **41**(1), 241–252 (1996).
56. Novikov, V. V., Novikov, G. V. and Fesenko, E. E. *Effect of weak combined static and extremely low-frequency alternating magnetic fields on tumor growth in mice inoculated with the Ehrlich ascites carcinoma*. Bioelectromagnetics **30**(5), 343–351 (2009).
57. Blackman, C. F., Benane, S. G. and House, D. E. *Frequency dependent interference by magnetic fields of nerve growth factor induced neurite outgrowth in pc-12 cells*. Bioelectromagnetics **16**, 387–395 (1995).
58. Stratakis, D., Miaoudakis, A., Katsidis, C., Zacharopoulos, V. and Xenos, T. *On the uncertainty estimation of electromagnetic field measurements using*

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*field sensors: a general approach*. Radiat. Prot. Dosim. **133**(4), 240–247 (2009).
59. Touitou, Y., Bogdan, A., Lambrozo, J. and Selmaoui, B. *Is melatonin the hormonal missing link between magnetic field effects and human diseases?* Cancer Causes Control **17**, 547–552 (2006).
60. Adair, R. *Constraints on biological effects of weak extremely low frequency electromagnetic fields.* Phys. Rev. A **43**(2), 1039–1048 (1991).
61. Halgamuge, M. N. and Abeyratne, C. D. *Behavior of charged particles in a biological cell exposed to AC-DC electromagnetic fields.* Environ. Eng. Sci. **28**(1), 1–10 (2011).
62. Repacholi, M. H. *Radiofrequency field exposure standards: current limits and relevant bioeffects data.* In: Gandhi, O. P., Ed., Biological Effects and Medical Applications of Electromagnetic Energy. Prentice Hall (1990).
63. Blackman, C. F., Benane, S. and House, D. E. *The influence of 1.2 muT,60 Hz magnetic fields on melatonin—and tamoxifen-induced inhibition of MCF-7 cell growth*. Bioelectromagnetics **22**, 122–128 (2001).
64. Farrell, J., Litovitz, T., Penafiel, M., Montrose, C., Doinov, P., Barber, M., Brown, K. and Litovitz, T. *The effect of pulsed and sinusoidal magnetic fields on the morphology of developing chick embryos.* Bioelectromagnetics **18**(6), 431–438 (1997).
65. Persinger, M. A. *Differential numbers of foci of lymphocytes within the brains of lewis rats exposed to weak complex nocturnal magnetic fields during development of experimental allergic encephalomyelitis.* Int. J. Neurosci. **119**, 166–184 (2009).
66. Prato, F. S., Desjardins-Holmes, D., Keenliside, L. D., McKay, J. C., Robertson, J. A. and Thomas, A. W. *Light alters nociceptive effects of magnetic field shielding in mice: intensity and wavelength considerations.* J. R. Soc. **6**, 17–28 (2009).
67. Trebbi, G., Borghini, F., Lazzarato, L., Torrigiani, P., Calzoni, G. L. and Betti, L. *Extremely low-frequency weak magnetic fields enhance resistance of NN tobacco plants to tobacco mosaic virus and elicit stress-related biochemical activities.* Bioelectromagnetics **28**(3), 214–223 (2007).
68. Wilson, B. W., Anderson, L. E. and Hilton, I. *Chronic exposure to 60-Hz electric fields: effects on pineal function in the rat*. Bioelectromagnetics **2**, 371–380 (1981).
69. Wilson, B. W., Anderson, L. E. and Hilton, I. *Erratum: chronic exposure to 60-Hz electric fields: effects on pineal function in the rat*. Bioelectromagnetics **4**, 293 (1983).
70. Wolpaw, J. R., Seegal, R. F. and Satya-Murti, S. *Chronic effects of 60-Hz electric and magnetic fields on primate central system function*. New York State Power Lines Project. Technical Report, Wadsworth Labs (1987).
71. Reiter, R. J., Anderson, L. E. and Buschbom, R. L. *Reduction in 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. **42**, 2203–2206 (1988).
72. Wilson, B. W., Chess, E. K. and Anderson, L. E. *60-Hz electric-field effects on pineal melatonin rhythms: time course for onset and recovery.* Bioelectromagnetics **7**(2), 239–242 (1986).
73. Grota, L. J., Reiter, R. J. and Keng, P. *Electric field exposure alters serum melatonin but not pineal melatonin synthesis in male rats.* Bioelectromagnetics **15**, 427–437 (1994).
74. Sasser, L. B., Morris, J. E. and Buschbom, R. L. *Effect of 60 Hz electric fields on pineal melatonin during various times of the dark period. Annual Review of Research on Biological Effects of 50 and 60 Hz Electric and Magnetic Fields.* Department of Energy (1991).
75. Bakos, J., Nagy, N., Thuroczy, G. and Szabo, L. D. *Urinary 6-sulphatoxymelatonin excretion is increased in rats after 24 hours of exposure to vertical 50 Hz, 100 microT magnetic field.* Bioelectromagnetics **18**(2), 190–192 (1997).
76. Bakos, J., Nagy, N., Thuroczy, G. and Szabo, L. D. *Urinary 6-sulphatoxymelatonin excretion of rats is not changed by 24 hours of exposure to a horizontal 50-Hz, 100-muT magnetic field*. Electrobiol. Magnetobiol. **18**(1), 23–31 (1999).
77. Selmaoui, B. and Touitou, Y. *Sinusoidal 50-Hz magnetic fields depress rat pineal NAT activity and serum melatonin. Role of duration and intensity of exposure.* Life Sci. **57**(14), 1351–1358 (1995).
78. Kato, M., Honma, K., Shigemitsu, T. and Shiga, Y. *Horizontal or vertical 50-Hz, 1-microT magnetic fields have no effect on pineal gland or plasma melatonin concentration of albino rats.* Neurosci. Lett. **168**(1–2), 205–208 (1994).
79. *Effects of exposure to a circularly polarized 50-Hz magnetic field on plasma and pineal melatonin levels in rats.* Bioelectromagnetics **14**(2), 97–106 (1993).
80. Kato, M., Honma, K., Shigemitsu, T. and Shiga, Y. *Recovery of nocturnal melatonin concentration takes place within one week following cessation of 50 Hz circularly polarized magnetic field exposure for six weeks.* Bioelectromagnetics **15**(5), 489–492 (1994).
81. Bakos, J., Nagy, N., Thuroczy, G. and Szabo, L. D. *Sinusoidal 50 Hz, 500 microT magnetic field has no acute effect on urinary 6-sulphatoxymelatonin in Wistar rats.* Bioelectromagnetics **16**(6), 377–380 (1995).
82. John, T. M., Liu, G. Y. and Brown, G. M. *60 Hz magnetic field exposure and urinary 6-sulphatoxymelatonin levels in the rat*. Bioelectromagnetics **19**(3), 172–180 (1998).
83. Chacon, L. *50-Hz sinusoidal magnetic field effect on in vitro pineal N-acetyltransferase activity*'. Electrobiol. Magnetobiol. **19**(3), 339–343 (2000).
84. Mevissen, M., Lerchl, A. and Loscher, W. *Study on pineal function and DMBA-induced breast cancer formation in rats during exposure to a 100-mG, 50 Hz magnetic field*. J. Toxicol. Environ. Health **48**(2), 169–185 (1996).
85. Rosen, L. A., Barber, I. and Lyle, D. B. *60 Hz magnetic field suppresses melatonin production in pinealocytes.* Bioelectromagnetics **19**(2), 123–127 (1998).
86. Bakos, J., Nagy, N., Thuroczy, G. and Szabo, L. D. *One week of exposure to 50 Hz, vertical magnetic field does not reduce urinary 6-sulphatoxymelatonin excretion of male Wistar rats.* Bioelectromagnetics **23**(3), 245–248 (2002).
87. Mevissen, M., Lerchl, A., Szamel, M. and Loscher, W. *Exposure of DMBA-treated female rats in a 50-Hz,*



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*50 microtesla magnetic field: effects on mammary tumor growth, melatonin levels, and T lymphocyte activation*. Carcinogenesis **17**(5), 903–910 (1996).
88. Selmaoui, B. and Touitou, 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. **64**(24), 2291–2297 (1999).
89. Fedrowitz, M., Westermann, J. and Loscher, W. *Magnetic field exposure increases cell proliferation but does not affect melatonin levels in the mammary gland of female sprague dawley rats.* Cancer Res. **62**(5), 1356–1363 (2002).
90. Tripp, H. M., Warman, G. R. and Arendt, J. *Circularly polarised MF (500 micro T 50 Hz) does not acutely suppress melatonin secretion from cultured Wistar rat pineal glands.* Bioelectromagnetics **24**(2), 118–124 (2003).
91. Arnetz, B. B. and Berg, M. *Melatonin and adrenocorticotropic hormone levels in video display unit workers during work and leisure*. J. Occup. Environ. Med. **38**, 1108–1110 (1996).
92. Akerstedt, T., Arnetz, B., Ficca, G. and Paulsson, L. E. *Low frequency electromagnetic fields suppress.* J. Sleep Res. **26**, 260 (1997).
93. Burch, J. B., Reif, J. S., Yost, M. G., Keefe, T. J. and Pitrat, C. A. *Nocturnal excretion of a urinary melatonin metabolite among electric utility workers.* Scand. J. Work Environ. Health **24**(3), 183–189 (1998).
94. Burch, J. B., Reif, J. S., Yost, M. G., Keefe, T. J. and Pitrat, C. A. *Reduced excretion of a melatonin metabolite in workers exposed to 60 Hz magnetic fields.* Am. J. Epidemiol. **150**, 27–36 (1999).
95. Burch, J. B., Reif, J. S. and Yost, M. G. *Geomagnetic disturbances are associated with reduced nocturnal excretion of a melatonin metabolite in humans.* Neurosci. Lett. **266**(3), 209–212 (1999).
96. Burch, J. B., Reif, J. S., Noonan, C. W., Ichinose, T., Bachand, A. M., Koleber, T. L. and Yost, M. G. *Melatonin metabolite excretion among cellular telephone users.* Int. J. Radiat. Biol. **78**, 1029–1036 (2002).
97. Crasson, M., Beckers, V., Pequeux, C. H., Claustrat, B. and Legros, J. J. *Daytime 50 Hz magnetic field exposure and plasma melatonin and urinary 6-sulfatoxymelatonin concentration profiles in humans.* J. Pineal Res. **31**, 234–241 (2001).
98. Davis, S., Kaune, W. T., Mirick, D. K., Chen, C. and Stevens, R. G. *Residential magnetic fields, light-at-night, and nocturnal urinary 6-sulfatoxymelatonin concentration in women*. Am. J. Epidemiol. **154**(7), 591–600 (2001).
99. Graham, C., Cook, M. R., Riffle, D. W., Gerkovich, M. M. and Cohen, H. D. *Nocturnal melatonin levels in human volunteers exposed to intermittent 60 Hz magnetic fields.* Bioelectromagnetics **18**, 166–171 (1996).
100. Graham, C., Cook, M. R., Riffle, D. W., Gerkovich, M. M. and Cohen, H. D. *Human melatonin during continuous magnetic field exposure.* Bioelectromagnetics **18**, 166–171 (1996).
101. Graham, C., Cook, M. R., Gerkovich, M. M. and Sastre, A. *Examination of the melatonin hypothesis in women exposed at night to EMF or bright light*. Environ. Health Perspect. **109**(5), 501–507 (2001).
102. Graham, C., Sastre, A., Cook, M. R. and Gerkovich, M. M. *All-night exposure to EMF does not alter urinary melatonin, 6-OHMS or immune measures in older men and women*. J. Pineal Res. **31**, 109–113 (2001).
103. Haugsdal, B., Tynes, T., Rotnes, J. S. and Griffiths, D. *A single nocturnal exposure to 27 millitesla static magnetic fields does not inhibit the excretion of 6-sulfatoxymelatonin in healthy young men*. Bioelectromagnetics **22**, 1–6 (2001).
104. Hong, H. C., Kurukowa, Y., Kabuto, M. and Ohtsuka, R. *Chronic exposure to ELF magnetic fields during night sleep with electric sheet: effects on diurnal melatonin rhythms in men*. Bioelectromagnetics **22**, 138–143 (2001).
105. Juutilainen, J., Stevens, R. G., Anderson, L. E., Hansen, N. H., Kilpeläinen, M., Kumlin, T., Laitinen, T., Sobel, E. and Wilson, B. W. *Nocturnal 6-hydroxymelatonin sulfateexcretion in female workers exposed to magnetic fields.* J. Pineal Res. **28**, 97–104 (2000).
106. Kaune, W., Davis, S. and Stevens, R. *Relation between residential magnetic fields, light-at-night, and nocturnal urine melatonin levels in women*. EPRI Report TR-1007242-VI. Fred Hutchinson Research Center (1997).
107. Kumlin, T., Hansen, N. H., Kilpelainen, M., Kukkonen, S., Laitinen, J., Stevens, R. W., Wilson, B. W. and Juutilainen, J. *Biological effects of LF EMF.* Norwegian Radiation Protection Authority. Technical Report (1997).
108. Levallois, P., Dumont, M., Touitou, Y., Gingras, S., Mâsse, B., Gauvin, D., Kröger, E., Bourdages, M. and Douville, P. *Effects of electric and magnetic fields from high-power lines on female urinary excretion of 6-sulfatoxymelatonin*. Am. J. Epidemiol. **154**(7), 601–609 (2001).
109. Pfluger, D. H. and Minder, C. E. *Effects of exposure to 16.7 Hz magnetic fields on urinary 6-hydroxymelatonin sulfateexcretion of Swiss railway workers.* J. Pineal Res. **21**, 91–100 (1996).
110. Selmaoui, B., Lambrozo, J. and Touitou, Y. *Magnetic fields and pineal function in humans: evaluation of nocturnal acute exposure to extremely low frequency magnetic fields on serum melatonin and urinary 6-sulfatoxy-melatonin circadian rhythm*. Life Sci. **58**, 1539–1549 (1996).
111. Touitou, Y., Lambrozo, J., Camus, F. and 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. **284**, R1529–R1535 (2003).
112. Wilson, B. W., Wright, C. W., Morris, J. E., Buschbom, R. L., Brown, D. P., Miller, D. L., Sommers-Flannigan, R. R. and Anderson, L. E. *Evidence for an effect of ELF electromagnetic fields on human pineal gland function*. J. Pineal Res. **9**, 259–269 (1990).
113. Wood, A., Sait, M., Armstrong, S. and Martin, M. *Effects of 50 Hz magnetic fields on human physiology: plasma melatonin levels.* In: Proceedings of the 2nd International Conference on Bioelectromagnetism, Melbourne, Australia, pp. 161–162 (1998).
114. Aghazadeh, S., Azarnia, M., Shirazi, A., Mahdavi, S. R. and Zangii, B. M. *Protective effect of melatonin*



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*on spinal cord damage after gamma irradiation*. In: Proceedings of the 6th World Congress on Alternatives and Animal Use in the Life Sciences, Tokyo, Japan, pp. 535–538 (2008).
115. Anderson, K. N., Jamieson, S., Graham, A. J. and Shneerson, J. M. *Rem sleep behaviour disorder treated with melatonin in a patient with alzheimer's disease*. Clin. Neurol. Neurosurg. **110**, 492–495 (2008).
116. Bonilla, E., Valero, N., Chacn-Bonilla, L. and Medina-Leedertz, S. *Melatonin protects mice infected with venezuelan equine encephalomyelitis virus*. Cell. Mol. Life Sci. **53**, 430–434 (1997).
117. Molina-Carballo, A., Munoz-Hoyos, A., Reiter, R. J., Sanchez-Forte, M., Moreno-Madrid, F., Rufo-Campos, M., Molina-Font, J. A. and Acuña-Castroviejo, D. *Utility of high doses of melatonin as adjunctive anticonvulsant therapy in a child with severe myoclonic epilepsy: two years experience*. J. Pineal Res. **23**, 97–105 (1997).
118. Cavallo, A., Daniels, S. R., Dolan, L. M., Bean, J. A. and Khoury, J. C. *Blood pressure-lowering effect of melatonin in type 1 diabates*. J. Pineal Res. **36**, 262–266 (2004).
119. Dahlitz, M., Alvarez, B., Vibnau, J., English, J., Arendt, J. and parkes, J. D. *Delayed sleep phase syndrome response to melatonin*. Lancet **337**, 1121–1124 (1991).
120. Dollins, A. B., Zhdanova, I. V., Wurtman, R. J., Lynch, H. J. and Deng, M. H. *Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance*. Proc. Natl. Acad. Sci. (PNAS). **91**(5), 1824–1828 (1994).
121. Fainstein, I., Bonetto, A., Brusco, L. I. and Cardinali, D. P. *Effects of melatonin in elderly patients with sleep disturbance*. Curr. Ther. Res. **58**, 990–1000 (1997).
122. Furio, A. M., Brusco, L. I. and Cardinali, D. P. *Possible therapeutic value of melatonin in mild cognitive impairment: a retrospective study*. J. Pineal Res. **43**, 404–409 (2007).
123. Gonciarz, M., Gonciarz, Z., Bielanski, W., Mularczyk, A., Konturek, P. C., Brzozowski, T. and Konturek, S. J. *The pilot study of 3-month course of melatonin treatment of patients with nonalcoholic steatohepatitis: effect on plasma levels of liver enzymes, lipids and melatonin*. J. Physiol. Pharmacol. **61**(6), 705–710 (2010).
124. Haimov, I., Lavie, P., Laudon, M., Herer, P., Vigder, C. and Zisapel, N. *Melatonin replacement therapy of elderly insomniacs*. Sleep **18**(7), 598–603 (1995).
125. Jacob, S., Poeggeler, B., Weishaupt, J. H., Sirén, A. L., Hardeland, R., Bähr, M. and Ehrenreich, H. *Melatonin as a candidate compound for neuroprotection in amyotrophic lateral sclerosis (ALS): high tolerability of daily oral melatonin administration in ALS patients*. J. Pineal Res. **33**(3), 186–187 (2002).
126. Leone, M., D'Amico, D., Moschiano, F. and Bussone, F. F. G. *Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups*. Cephalagia **16**, 494–496 (1996).
127. Peres, M. F. and Rozen, T. D. *Melatonin in the preventive treatment of chronic cluster headache*. Cephalagaal **21**(1), 993–995 (2001).
128. Messina, G., Lissoni, P., Marchiori, P., Bartolacelli, E., Brivio, F. and Magotti, L. *Enhancement of the efficacy of cancer chemotherapy by the pineal hormone melatonin and its relation with the psychospiritual status of cancer patients*. J. Res. Med. Sci. **15**(4), 225–228 (2010).
129. Nishiyama, K., Yasue, H., Moriyama, Y., Tsunoda, R., Ogawa, H., Yoshimura, M. and Kugiyama, K. *Acute effects of melatonin administration on cardiovascular autonomic regulation in healthy men*. Am. Heart J. **141**, E9 (2001).
130. Okatani, Y., Okamoto, K., Hayashi, K., Wakatsuki, A., Tamura, S. and Sagara, Y. '*Maternal-fetal transfer of melatonin in pregnant women near term*'. J. Pineal Res. **25**(3), 129–134 (1998).
131. Vijayalaxmi, A., Reiter, R. J., Herman, T. S. and Meltz, M. L. *Melatonin and radioprotection from genetic damage: in vivo/in vitro studies with human volunteers*. Mut. Res. **371**, 221–228 (1996).
132. Vijayalaxmi, A., Meltz, M. L., Reiter, R. J., Herman, T. S. and Sree, K. K. *Melatonin and protection from whole-body irradiation: survival studies in mice*. Mut. Res. **425**, 21–27 (1999).
133. Vijayalaxmi, A., Thomas, C. R., Reiter, R. J. and Herman, T. S. *Melatonin: form basic research to cancer treatment clinics*. J. Clin. Oncol. **20**, 2575–2601 (2002).
134. Wurtman, R. J. and Zhdanova, I. *Improvement of sleep quality by melatonin*. Lancet **346**(8974), 541–544 (1995).

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