

## 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 observed from 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<sup>(1)</sup>. It controls the body’s sleep/wake cycle or the circadian rhythms and is activated by darkness and depressed by light<sup>(2)</sup>. 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<sup>(3)</sup>. 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<sup>(4)</sup>. Melatonin is well excited by the blue light (420–440 nm)<sup>(4)</sup>. 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<sup>(5)</sup>. Melatonin promptly crosses the blood–brain barrier because of its permeability into the brain<sup>(6)</sup>; thus, it is accumulated in the central nervous system at significantly higher levels than exists in the blood<sup>(5)</sup>. Furthermore,

it attenuates seizures and hence used in the effective treatment of juvenile intractable epilepsy<sup>(7)</sup>. Melatonin also interacts with the immune system<sup>(7, 8)</sup>, which regulates the pineal gland functions of activated immune cells<sup>(9)</sup>. It was hypothesised that the reduction of melatonin levels with age aids the aging process<sup>(10)</sup>.

In addition, melatonin has also been identified as an effective agent that avoids both the initiation and promotion of cancer<sup>(11)</sup>. 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<sup>(11)</sup>. 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<sup>(12)</sup>. For example, the Danish government paid compensation to women who have developed breast cancer after long periods of working at night<sup>(13)</sup>. In recent decades, melatonin hypothesis has been argued in relation to the substantial increase in the incidence of breast cancer in

industrialised countries<sup>(14–16)</sup>. 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<sup>(17–21)</sup>. In contrast to these studies, Davis *et al.*<sup>(22)</sup> 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<sup>(23)</sup>; (ii) electromagnetic field (EMF) exposures in the aetiology of male infertility<sup>(24)</sup> and 2.45-GHz wireless media on melatonin modulation in rats<sup>(25)</sup>.

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<sup>(26)</sup>. The time of administration and dose of melatonin effect in both humans and animals were investigated in Golombek *et al.*<sup>(27)</sup> and Papp *et al.*<sup>(28)</sup>. 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<sup>(29, 30)</sup>. 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<sup>(31)</sup>. Blood samples (serum melatonin)<sup>(32)</sup>, saliva<sup>(31)</sup> and the melatonin metabolite 9-hydroxymelatonin sulphate (6-OHMS) in urine<sup>(33)</sup> can be used to assess melatonin levels in the body. A study by Shinohara and Kodama<sup>(31)</sup> 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<sup>(31)</sup>. 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<sup>(34)</sup>. 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<sup>(35)</sup>.

Besides this, the World Health Organization has confirmed that prolonged alterations in sleep patterns suppress the body's ability to make melatonin<sup>(36)</sup>. In experiments in cells, tissues, organs and whole animals<sup>(33)</sup>, 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'<sup>(37)</sup>. 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)<sup>(33)</sup>. Henshaw and Reiter<sup>(33)</sup>, 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.*<sup>(38)</sup> 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.*<sup>(39)</sup>. The effects of magnetic fields on pineal melatonin production have been studied in a number of studies<sup>(33)</sup> 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<sup>(33)</sup> 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<sup>(40)</sup>, 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<sup>(41–44)</sup>, brain tumours and breast cancer<sup>(12, 36)</sup>. 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 interest<sup>(45)</sup>, 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<sup>(46)</sup>. 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

melatonin levels due to power-frequency electric and magnetic fields exposure are analysed. Then, the results of this study are compared 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<sup>(47)</sup>. The study by Nordenson *et al.*<sup>(48)</sup> 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<sup>(48)</sup> 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<sup>(49)</sup> 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<sup>(49)</sup> that the gravitropic bending of flax seedling deviated anomalously from the expected values at very low amplitudes  $0.075 < A_{AC} < 5 \mu T$  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.

The ICNIRP guidelines protects the public and workers from adverse health effects caused by exposure to non-ionising radiation<sup>(50)</sup>. The ICNIRP limits are designed as guidelines to protect from low-frequency EMFs against nerve stimulation and from microwaves against body heating<sup>(51)</sup>. 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<sup>(52)</sup>. 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.*<sup>(53)</sup> 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 1. Studies relevant to biological effects from weak extremely low-frequency magnetic fields.**

No	Exposure value	Authors
1	60 Hz, 1.2 μT	Blackman <i>et al.</i> <sup>(63)</sup>
2	60 Hz, 4 μT	Farrell <i>et al.</i> <sup>(64)</sup>
3	17 Hz, 0.2 μT	Novikov <i>et al.</i> <sup>(56)</sup>
4	17 Hz, 1.25 μT	Novikov <i>et al.</i> <sup>(56)</sup>
5	17 Hz, 0.3 μT	Novikov <i>et al.</i> <sup>(56)</sup>
6	7 Hz, 0.05 μT	Persinger <sup>(65)</sup>
7	7 Hz, 0.5 μT	Persinger <sup>(65)</sup>
8	40 Hz, 0.005 μT	Persinger <sup>(65)</sup>
9	40 Hz, 0.5 μT	Persinger <sup>(65)</sup>
10	60 Hz, 0.001 μT	Prato <i>et al.</i> <sup>(66)</sup>
11	10 Hz, 28.9 μT	Trebbi <i>et al.</i> <sup>(67)</sup>

**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 <sup>-1</sup>	20 h d <sup>-1</sup> × 30 d	Changed	Wilson <i>et al.</i> <sup>(68, 69)</sup>
2	60 Hz, 3–30 kV m <sup>-1</sup>	3 times/d × 21 d	Not changed	Wolpaw <i>et al.</i> <sup>(70)</sup>
3	60 Hz, 39 kV m <sup>-1</sup>	< 3 d	Not changed	Wilson <i>et al.</i> <sup>(68)</sup>
4	60 Hz, 10, 65, 130 kV m <sup>-1</sup>	19 h d <sup>-1</sup> × 23 d	Changed	Reiter <i>et al.</i> <sup>(71)</sup>
5	60 Hz, 65 kV m <sup>-1</sup>	20 h d <sup>-1</sup> × 21 d	Changed	Wilson <i>et al.</i> <sup>(72)</sup>
6	60 Hz, 65 kV m <sup>-1</sup>	20 h d <sup>-1</sup> × 30 days	Changed	Grota <i>et al.</i> <sup>(73)</sup>
7	60 Hz, 65 kV m <sup>-1</sup>	20 h d <sup>-1</sup> × 30 days	Changed	Sasser <i>et al.</i> <sup>(74)</sup>

Table 3. Effects of magnetic fields on pineal melatonin production as in ref.<sup>(53)</sup>—RAT.

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

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)<sup>(54)</sup>. 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<sup>(55, 56)</sup>. In contrast to this, Blackman *et al.*<sup>(57)</sup> 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<sup>(58)</sup>, in addition to background EMFs and environmental conditions (temperature, light and humidity) that might influence these measurements<sup>(47)</sup>. Another reason for varying results of plasma melatonin level can be the dissimilar sensitivity to magnetic fields among species<sup>(59)</sup>.

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

Regardless of these facts, biological studies were not intended to clarify how weak fields can interact with biological molecules; rather, environmental frequencies and unrealistically 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<sup>(49, 51, 60, 61)</sup>.

Biological or health effects depend on frequency, the strength of EMFs, exposure duration, polarisation and biological system (animals, plants and chemicals)<sup>(47)</sup>. 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<sup>(47)</sup>.

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

Table 5. Melatonin administration.

No	Problem	Administered melatonin amount	Remarks	Authors
1	Cervical spinal cord damage—rats	30 mg kg <sup>-1</sup>	Melatonin may be useful in preventing the spinal cord against radiation toxicity	Aghazadeh <i>et al.</i> <sup>(114)</sup>
2	AD patients with rapid eye movement (REM) sleep behaviour disorder	5–10 mg d <sup>-1</sup> for 20 months	Melatonin was effective in suppressing REM sleep behaviour disorder	Anderson <i>et al.</i> <sup>(115)</sup>
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 <i>et al.</i> <sup>(116)</sup>
4	Convulsive seizures	50 mg d <sup>-1</sup> for a year	Seizures were under control	Carballo <i>et al.</i> <sup>(117)</sup>
5	Blood pressure patient	5 or 10 mg	Increased drop of blood pressure in type I diabetes	Cavallo <i>et al.</i> <sup>(118)</sup>
6	Eight patients with delayed sleep-phase syndrome	5 mg d <sup>-1</sup> for 4 weeks	Earlier onset of sleep and wake-up time	Dahlitz <i>et al.</i> <sup>(119)</sup>
7	Insomnia patients	0.1 mg or 0.3 mg	Increased duration of sleep and decreased sleep-onset latency	Dollins <i>et al.</i> <sup>(120)</sup>
8	Insomnia patients	3 mg d <sup>-1</sup> × 21 d	Improve the sleep	Fainstein <i>et al.</i> <sup>(121)</sup>
9	Patients with mild cognitive impairment (MCI)	3–9 mg d <sup>-1</sup> for 9–18 months	Proved significantly improved performance in neuropsychological assessment	Furio <i>et al.</i> <sup>(122)</sup>
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 <i>et al.</i> <sup>(123)</sup>
11	Insomnia patients	2 mg d <sup>-1</sup> for 1 week	Increased efficient and duration of sleep	Haimov <i>et al.</i> <sup>(124)</sup>
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 <i>et al.</i> <sup>(125)</sup>
13	Prophylaxis of cluster headache	10 mg d <sup>-1</sup>	Reduce cluster headache	Leone <i>et al.</i> <sup>(126)</sup> and Peres <i>et al.</i> <sup>(127)</sup>
14	Lung cancer patients	20 mg d <sup>-1</sup>	The efficacy of chemotherapy may be enhanced by the pineal hormone	Messina <i>et al.</i> <sup>(128)</sup>
15	Cardiac patient	2 mg	Increased cardiac vagal tone	Nishiyama <i>et al.</i> <sup>(129)</sup>
16	Maternal–foetal transfer of melatonin in pregnant women	3 mg	Fast and simply melatonin is transferred to the foetus in women	Okatani <i>et al.</i> <sup>(130)</sup>
17	Cirrhosis patients	—	Melatonin abnormalities in cirrhosis patients are related to liver insufficiency difficulty	Velissaris <i>et al.</i> <sup>(36)</sup>
18	DNA damage	300 mg	A significant decrease (50–70 %) in DNA damage	Vijayalaxmi <i>et al.</i> <sup>(131)</sup>
19	Survival rate—rats	125 and 250 mg	45 % survival without melatonin; 85 % survival with 250 mg melatonin	Vijayalaxmi <i>et al.</i> <sup>(132)</sup>
20	Tumour patients	14–18 mg d <sup>-1</sup>	Stimulated tumour growth in long photoperiods	Vijayalaxmi <i>et al.</i> <sup>(133)</sup>
21	Insomnia patients	0.3 mg	Increased efficiency of sleep and decreased sleep-onset latency	Wurtman and Zhdanova <sup>(134)</sup>

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<sup>(47)</sup>. Despite this, it is quite possible that

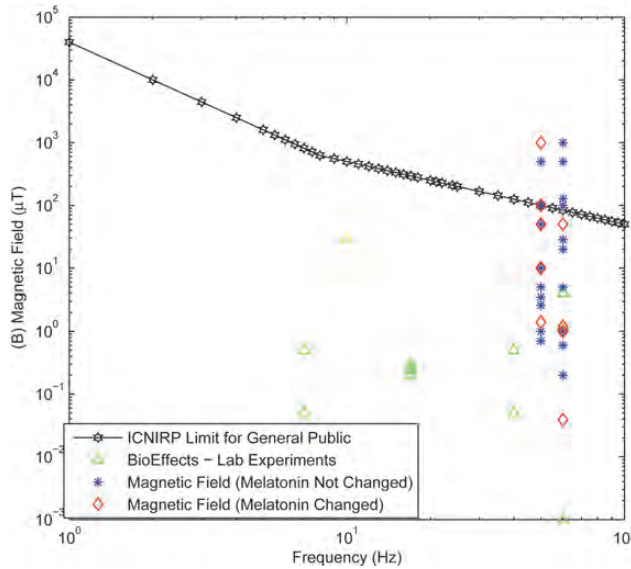


Figure 1. Plasma melatonin analysis—comparison of the magnetic field strength for different frequencies with the ICNIRP limit and experimental evidence for biological effects.

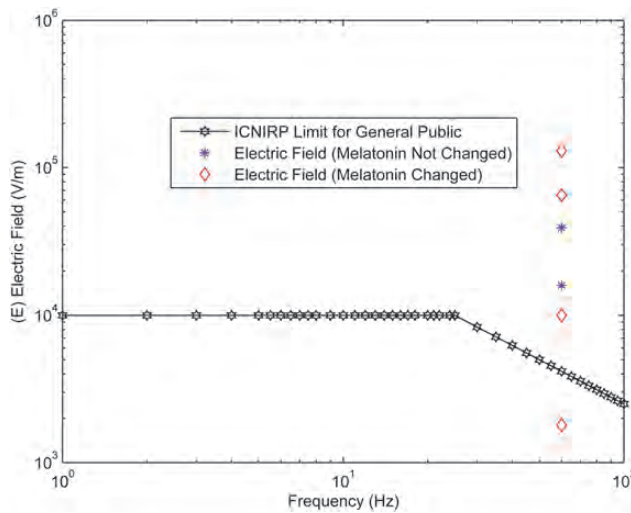


Figure 2. Plasma melatonin analysis—comparison of the electric field strength for different frequencies with the ICNIRP limit and experimental evidence for biological effects.

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<sup>(62)</sup>.

### 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

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.

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