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# Effects of low frequency electromagnetic fields on expression of lymphocyte subsets and production of cytokines of men and women employed in a museum

Paolo Boscolo[a,*], Antonio Bergamaschi[c], Maria Bernadette Di Sciascio[a], Franco Benvenuti[d], Marcella Reale[b], Fabio Di Stefano[a], Pio Conti[b], Mario Di Gioacchino[a]

[a] *Department of Medicine and Sciences of Ageing (Unit of Clinical Allergology, Immunopathology and Occupational Medicine), University 'G. D'Annunzio', Via dei Vestini, 66100 Chieti, Italy*
[b] *Department of Oncology and Neurosciences, University 'G. D'Annunzio', Via dei Vestini, 66100 Chieti, Italy*
[c] *Occupational Medicine, University 'Tor Vergata', Roma, Italy*
[d] *I.S.P.E.S.L., Department of Industrial Hygiene, Monteporzio Catone, Roma, Italy*

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**Abstract**

The objective of this study was to analyse the immune response to electromagnetic fields (ELMFs) in seven men and eight women employed in a museum. The workers were exposed in a room to an ELMFs (range 0.2–3.6 μT and 40–120 V/m) induced by 50 Hz electricity for 20 h a week. Control groups consisted of 47 women and 39 men with a similar percentage of atopic subjects, age (range 30–51 years) and smoking habits of the workers included in the study. Levels of blood lead (Pb) and urinary *trans–trans* muconic acid, a metabolite of benzene (markers of exposure to traffic and smoking) of the control and exposed groups were similar. Lymphocyte subsets were determined in men and women using conjugated antibodies. Serum interleukin (IL) 4 and interferon γ and their 'in vitro' production by peripheral mononuclear blood cells (PMBCs) stimulated by phytohemoglutinin (PHA), as well as blastogenesis of PMBCs induced by PHA, were determined in women only. ELMF-exposed women showed a significant reduction in the percentage of B and NK $CD3^-$–$CD25^+$ lymphocytes and a slight reduction of $CD16^+$–$56^+$ NK lymphocytes. They also showed significantly lower levels of interferon γ in serum, or produced in the supernatants by PMBCs both spontaneously and stimulated by PHA, while they did not show significant changes in serum and 'in vitro' produced IL-4, or in blastogenesis of PMBCs. Men working in the museum showed, in relation to the controls, a statistically significant reduction in both number and percentage of $CD16^+$– $CD56^+$ and $CD3^-$–$CD25^+$ lymphocyte subsets. On the whole, this investigation demonstrates a reduction of blood NK lymphocytes and of the production of interferon

* Corresponding author. Tel.: +39-0871-3556704; fax: +39-0871-3556704.
*E-mail address:* boscolo@unich.it (P. Boscolo).


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γ in workers exposed to low frequency ELMFs. Recent studies have shown that stress and poor lifestyle induce the reduction of blood cytotoxic activities possibly acting on nervous functions. This may suggest that ELMFs reduces blood NK lymphocytes by combined effects on the immune and nervous systems. 

*Keywords:* Immune system; Lymphocyte subpopulations; Cytokines; Electromagnetic fields

## 1. Introduction

Several studies have reported that electromagnetic fields (ELMFs) may modify the human genome and induce malignancies. An increase in chromosomal aberrations has been found either among power linesmen with prolonged working activity (Valjius et al., 1993) or among laboratory employees exposed to high voltage (Skyberg et al., 1993). An increased risk of tumours, particularly brain cancer (Ryan et al., 1992) and leukaemia (Miller et al., 1996), has been found in subjects exposed to 50–60 Hz ELMFs. Increased mortality from malignant neoplasms, mainly from leukaemia, has been found among plastic ware workers exposed to radio-frequency ELMFs (Rossi et al., 1997). Increased incidence of cancer has been found in the area surrounding a radio and television transmitter in Great Britain (Dolk et al., 1997a). On the other hand, these results have not been confirmed by investigations performed on populations resident near other power transmitters in the same country (Dolk et al., 1997b). Although there is concern for the risk of cancer, until now, a clear relation between ELMFs exposure and the incidence of neoplasms has not been demonstrated, as the studies showed either contradictory results or the presence of confounding factors (Theriault, 1996).

Although the genotoxic effects of ELMFs are not clearly demonstrated, it was shown that ELMFs modifies calcium fluxes in the membranes of immune cells of humans with effects on the release of tromboxane $B_2$ and interleukin 1 (Conti et al., 1985). Moreover, peripheral mononuclear blood cells (PMBCs) of humans exposed 'in vitro' to low frequency ELMFs showed changes in [$^3$H]thymidine incorporation following 'in vitro' stimulation by mitogens (Conti et al., 1983, 1986).

Giuliani et al. (1996) investigated 40 people exposed to amplitude modulated ELMFs produced by the radiofrequency emission of a TV broadcasting station. 'In vitro' cell proliferation tests performed with PMBCs of the exposed subjects were modified compared to those of a control group. Cyto-toxicity tests showed a significant reduction in NK activity when the PBMCs were re-irradiated 'in vitro' by radiofrequencies (639.25 MHz; 12 V/M average; 50 Hz amplitude modulated or by an ELMFs of 50 Hz; 0.67 mT).

Other investigations have shown that exposure to low frequency pulsed ELMFs increases interleukin (IL) 1 and IL-6 production by human PBMCs, either spontaneously or following stimulation with mitogens (Cossarizza et al., 1993).

Following exposure to magnetic resonance imaging of the brain of volunteers, the blood levels of both total and cytotoxic lymphocytes decreased, suggesting that the nervous system may regulate the trafficking of lymphocytes in peripheral blood, possibly acting on adhesion molecules (Reichard et al., 1996). It was also shown that the circadian biorhythm modifies, not only the release and production of neurohormones, but also blood levels of lymphocyte subsets (Boscolo et al., 1999a). Recent studies also reported that poor lifestyle or occupational stress may reduce the cytotoxic activity of peripheral blood lymphocytes, possibly acting on neuroendocrine functions (Kawakami et al., 1997; Morimoto et al., 1999; Morimoto et al., in press). With regard to this, it was demonstrated that neuroendocrine and immune systems are linked by several relationships, suggesting that they constitute a single network (Jankovic, 1992; Male et al., 1996).

This study had the purpose of both demonstrating the effects of low frequency ELMFs on the immune system of subjects exposed to ELMFs, and finding immune parameters which could be used as markers of exposure to ELMFs.

## 2. Subjects and methods

The exposed subjects were employees of a museum in a town in Central Italy. Their task, for approximately 20 h a week, was the surveillance of the premises through monitors in a room (surface approx. 200 $m^2$). An electric cable (360 V and 50 Hz) for the distribution of the electricity in the building was located approximately 2 m on the rear of the working places. The levels of ELMFs (50 Hz) in the room were measured by an EFA-3 EMR instrument (Wandel Golterman). Values (V/m and μT) were obtained from at least nine determinations (lasting 60 s), either in presence of electricity and with all monitors working, or in absence of electricity with staff performing the analysis at a distance of at least 10 m.

Eight women (mean age and range: 35 and 31–42 years, respectively) and seven men (mean age and range: 38 and 30–51 years, respectively) had been working for at least 2 years in the monitoring room of the museum. Three men and three women were atopic with a history of slight respiratory and/or cutaneous allergic symptoms. Two women and three men were smokers (less than 10 cigarettes a day). The control groups consisted of 47 women and 39 men resident in the same area of the workers in the museum, with similar ages and smoking habits. The frequency of atopy was also similar. Clinical assessment included a physical examination and standard routine blood and urine analysis (Sabbioni et al., 1992). Subjects taking drugs or who had recently suffered from diseases (including allergic symptoms) were excluded from the study.

Blood and urine samples of the examined subjects were collected in plastic cryovials (Nalgene, International PBI, Milano, Italy) at 08.00 h, using a standard procedure for avoiding contamination (Sabbioni et al., 1992). Blood lead (Pb) was determined by the atomic absorption spectrophotometers Perkin-Elmer 4100 ZL and Varian 300Z in three different laboratories. Urinary Trans–Trans-muconic acid, a metabolite of benzene, was analysed by HPLC (Imbriani et al., 1995).

Fluorescein isothiocyanate (FITC) and phycoerythrin (PE)-conjugated antibodies (Becton–Dickinson, San Jose, CA, USA) were used to determine lymphocyte subsets. The antibodies were CD4–CD45RO [to evaluate $CD4^+$–$45RO^+$ 'memory' and $CD4^+$–CD45RO- 'naive or virgin' helper lymphocytes (Male et al., 1996)], $CD3^-$–CD8, CD16–56 (NK cells), CD19 (B lymphocytes), CD3-HLA-DR (activated T, B and NK lymphocytes) and CD3–CD25 (T and B lymphocytes activated by IL-2). Two-colour flow-cytometry analysis was performed by FACscan (Becton–Dickinson, San Jose, CA, USA) (Fleiscer et al., 1988).

Serum IgE as well as serum interleukin (IL) 4, and interferon γ of the women were determined by ELISA (ELISA, R&D Systems, Minneapolis, MN, USA) (Fridas et al., 1996).

'In vitro' production of IL-4 and interferon γ was determined in the PBMCs of the women exposed to ELMFs and of 17 control women (resident in the same area and with similar age, smoking habit and percentage of atopy of the exposed subjects). PBMCs were incubated for 24 h at 37°C in a 0.5% $CO_2$-humidified atmosphere in polypropylene tubes (Falcon, Italy) with or without phytohemoglutinin (PHA) 20 μg/ml (Defco). At the end of the incubation period, cell-free supernatants were harvested and stored at −20°C until the assay of IL-4 and interferon γ (ELISA, R&D Systems, Minneapolis, MN, USA) (Fridas et al., 1996).

In the ELMF-exposed women and in the above reported 17 controls, the blastogenesis of PBMCs was also determined 'in vitro' according to Boyum (1968) and Conti et al. (1983, 1986). Blastogenesis was determined as stimulation index (S.I.), which is the rate between [$^3$H]thymidine incorporation by PBMCs in the presence of PHA and without PHA in the incubation liquid.

The results were analysed using the SYSTAT software.

## 3. Results

The levels of exposure to ELMFs in the rooms are reported in Table 1. Values determined in presence of electricity and with the monitors working were not uniform, but differed at short distance. However, they were greatly higher than those determined in absence of electricity (0.005–0.007 μT and 0.2–1.2 V/m).

Blood Pb and urinary Trans–Trans-muconic acid of both female and male workers exposed to ELMFs in the museum did not show statistically significant differences in relation to those of control subjects. (Table 2). The blood Pb of males was much higher than that of females, while urinary Trans–Trans-muconic acid levels did not show any difference.

Table 1
Levels of exposure to electromagnetic fields of 50 Hz in a museum

| | Mean | Range |
|---|---|---|
| *Working places* | | |
| μT | 1.6 | 0.2–3.6 |
| V/m | 90 | 24–120 |
| *Nearby rooms* | | |
| μT | 3 .6 | 0.3–7.2 |
| V/m | 37 | 14–53 |

Lymphocyte subsets may be expressed as the number of cells/volume of blood or as percentage of the total number of lymphocytes. In this study, the differences in the values of lymphocyte subpopulations between the group of workers ex-

Table 2
Blood metals and urine *trans–trans* muconic acid of women and men exposed to electromagnetic fields in a museum

| (μg/l) | Control | | | Exposed | | |
|---|---|---|---|---|---|---|
| | No. | Median | 25th–75th percentiles | No. | Median | 25th–75th Percentiles |
| Women | | | | | | |
| Blood lead | 47 | 5.9 | 4.9–7.0 | 8 | 6.1 | 4.6–6.9 |
| Urine *trans–trans* muconic acid | 18 | 42.0 | 19.1–107.5 | 8 | 44.1 | 22.6–92.0 |
| Urine *trans–trans* muconic acid (μg/g creatinine) | 18 | 33.5 | 13.2–92.5 | 8 | 30.2 | 14.5–76.5 |
| Men | | | | | | |
| Blood lead | 39 | 10.1 | 6.7–11.9 | 7 | 10.1 | 8.3–12.4 |
| Urine *trans–trans* muconic acid | 12 | 35.2 | 18.1–78.8 | 7 | 29.4 | 25.9–60.9 |
| Urine *trans–trans* muconic acid (μg/g creatinine) | 12 | 26.7 | 12.1–54.0 | 7 | 21.0 | 13.5–46.5 |

Table 3
Lymphocyte subsets of women exposed to electromagnetic fields in a museum[a]

| No. lymphocytes ($10^3$/ml) and % of lymphocytes | Control ($n = 47$) | | Exposed ($n = 8$) | |
|---|---|---|---|---|
| | Median | 25th–75th percentiles | Median | 25th–75th percentiles |
| Lymphocytes | 1999 | 1780–2605 | 2128 | 2077–2362 |
| $CD3^+$ | 1421 | 1270–1811 | 1640 | 1544–1952 |
| $CD4^+$ | 884 | 711–1213 | 1139 | 943–1237 |
| $CD3^+$–$CD8^+$ | 520 | 442–726 | 621 | 511–743 |
| $CD16^+$–$CD56^+$ | 398 | 310–489 | 335 | 228–424 |
| $CD19^+$ | 210 | 138–291 | 190 | 156–264 |
| $CD3^-$–$HLA–DR^+$ | 330 | 263–431 | 293 | 223–323 |
| $CD3^+$–$HLA–DR^+$ | 124 | 92–176 | 124 | 74–159 |
| $CD3^-$–$CD25^+$ | 95 | 71–126 | 81 | 68–88* |
| $CD3^+$–$CD25^+$ | 246 | 187–351 | 283 | 186–320 |

[a] Mann–Whitney *U*-test. Statistical significant difference: $^*P < 0.01$.

posed to ELMFs and the controls were slightly statistically more significant when the lymphocyte subsets were expressed as percentage.

Women exposed to ELMFs, compared to control subjects, did not show significant differences in the blood values of the lymphocyte subpopulations $CD3^+$, $CD4^+$, $CD4^+$–$CD45RO$, $CD4^+$–$CD45RO^+$, $CD3^+$–$CD8^+$, $CD19^+$, $CD3^+$–$HLA\text{-}DR^+$, $CD25^+$ or $CD3^+$–$CD25^+$ (Table 3). On the other hand, ELMF-exposed women showed a significant reduction of the percentage of $CD3^-$–$CD25^+$ B and NK lymphocytes (Fig. 1) and a slight, but not significant, reduction of $CD16^+$–$CD56^+$ NK lymphocytes and $CD3$-$HLA\text{-}DR^+$ NK and B activated lymphocytes (Male et al., 1996).

The serum IgE of ELMF-exposed women was not significantly different in relation to that of the controls (Table 4). On the other hand, serum interferon γ (but not IL-4) of ELMF-exposed women was lower than that of control women (Table 4).

'In vitro' production of interferon γ (but not of IL-4) by PBMCs of ELMF-exposed female workers was lower than that of control subjects, either spontaneously or in the presence of PHA (Table 5).

Moreover, the spontaneous production of IL-4 by PBMCs did not show a significant reduction.

[$^3$H]Thymidine incorporation by PBMCs of ELMF-exposed females was not different from that of the control subjects, both in the presence and absence of PHA in the incubation liquid: the S.I. (median, and 25th and 75th percentiles) of control females was 54.5 and 37.6–71.4, and the S.I. of ELMF-exposed females was 66.1 and 62.1–70.1.

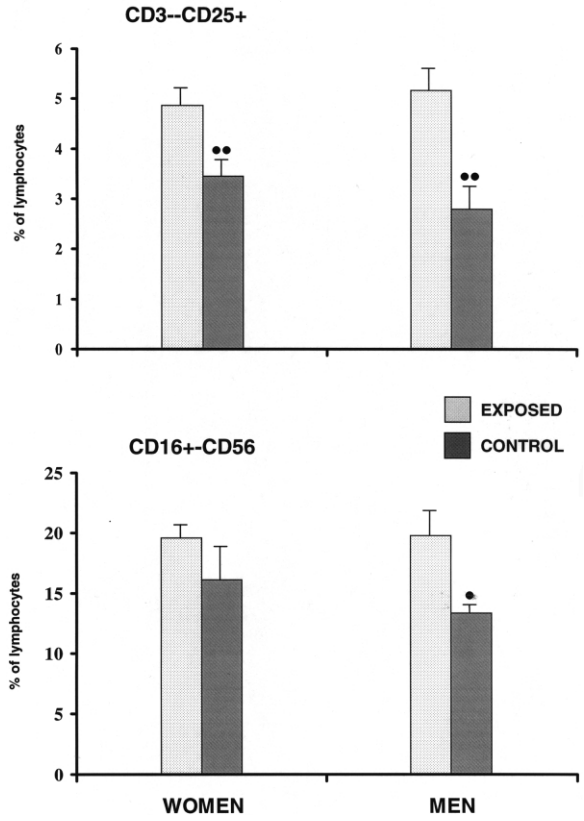


Fig. 1. Blood $CD16^+$–$56^+$ and $CD3^-$–$CD25^+$ lymphocyte subsets (expressed as a percentage of total lymphocytes) of women and men exposed to ELMFs in a museum. Values are expressed as mean ± E.S. Mann-Whitney U-test. (Control women: $n = 47$; control men: $n = 39$; ELMF exposed women: $n = 8$; ELMF exposed men: $n = 7$, Mann-Whitney U-test. Statistical significant difference: $^*P < 0.05$, $^{**}P < 0.01$.

Table 4
Cytokines and serum IgE of women exposed to electromagnetic fields in a museum[a]

| Cytokines (pg/ml) | Control ($n = 47$) | | Exposed ($n = 8$) | |
|---|---|---|---|---|
| | Median | 25th–75th percentiles | Median | 25th–75th percentiles |
| IgE (IU/l) | 25 | 10–79 | 45 | 23–80 |
| Interleukin-4 | 4.74 | 4.32–5.44 | 3.55 | 2.49–4.65 |
| Interferon γ | 2.87 | 1.49–4.17 | 1.17 | 0.83–1.63* |

[a] Mann–Whitney *U*-test.
*Statistical significant difference: $P < 0.001$.

Table 5
'In vitro' production of cytokines by mononuclear blood cells incubated with or without phytohemoagglutinin (PHA) of women exposed to electromagnetic in a museum[a]

| Cytokines (pg/ml) | Control ($n = 17$) | | Exposed ($n = 8$) | |
|---|---|---|---|---|
| | Median | 25th–75th percentiles | Median | 25th–75th percentiles |
| Interleukin-4 without PHA | 1.70 | 1.29–3.01 | 0.90 | 0.80–1.38 |
| Interleukin-4 with PHA | 3.30 | 1.60–5.80 | 1.40 | 1.29–2.09 |
| Interferon γ without PHA | 0.81 | 0.49–1.10 | 0.25 | 0.22–0.30** |
| Interferon γ with PHA | 27.20 | 8.30–51.50 | 9.00 | 5.35–14.20* |

[a] Mann–Whitney *U*-test.
* Statistical significant difference: $P < 0.05$.
** Statistical significant difference: $P < 0.001$.

Urinary Trans–Trans-muconic acid levels determined in 26 women (eight exposed to ELMFs and 18 controls) were significantly correlated with NK $CD16^+$–$56^+$ cells both related to volume of urine ($r = 0.531$; $P < 0.01$) and to urinary creatinine ($r = 0.570$; $P < 0.01$) using Pearson's correlation coefficient.

Serum IgE of men exposed to ELMFs in the museum did not show significant differences in relation to the values of the control subjects (Table 6).

Men exposed to ELMFs did not present differences, compared to control men, in the blood levels of $CD3^+$, $CD4^+$, $CD4^+$–CD45RO, $CD4^+$–$CD45RO^+$, $CD3^+$–$CD8^+$, $CD19^+$, $CD3^+$–HLA-$DR^+$, $CD25^+$ and $CD3^+$–$CD25^+$ (Table 6). On the other hand, exposed males showed a statistically significant reduction in both the number and percentage of NK $CD16^+$–$56^+$ lymphocyte subsets and B and NK $CD3^-$–$CD25^+$ lymphocyte subsets (Table 6 and Fig. 1). Moreover, $CD3^-$–HLA-$DR^+$B and NK-activated lymphocyte subsets did not show a significant reduction.

Table 6
Serum IgE and lymphocyte subsets of men exposed to electromagnetic fields in a museum[a]

| No. lymphocytes ($10^3$/ml) and % of lymphocytes | Control ($n = 39$) | | Exposed ($n = 7$) | |
|---|---|---|---|---|
| | Median | 25th–75th percentiles | Median | 25th–75th percentiles |
| IgE (IU/ml) | 85 | 26–483 | 105 | 27–226 |
| Lymphocytes | 2505 | 2220–2685 | 2310 | 2038–2495 |
| $CD3^+$ | 1690 | 1500–1919 | 1650 | 1213–1790 |
| $CD4^+$ | 970 | 835–1080 | 780 | 742–1010 |
| $CD3^+$–$CD8^+$ | 595 | 520–850 | 564 | 488–827 |
| $CD16^+$–$56^+$ | 480 | 295–670 | 236 | 222–328* |
| $CD19^+$ | 290 | 233–355 | 235 | 175–289 |
| $CD3^-$–HLA–$DR^+$ | 418 | 345–517 | 264 | 249–313 |
| $CD3^+$–HLA–$DR^+$ | 129 | 87–196 | 169 | 135–333 |
| $CD3^-$–$CD25^+$ | 130 | 80–165 | 78 | 56–90** |
| $CD3^+$–$CD25^+$ | 300 | 227–366 | 270 | 245–320 |

[a] Mann–Whitney *U*-test.
* Statistical significant difference: $P < 0.05$.
** Statistical significant difference: $P < 0.01$.

## 4. Discussion

This study demonstrates a reduction of NK lymphocytes in the peripheral blood of men and women exposed to ELMFs induced by 50 Hz electricity. These results are in agreement with those of Giuliani et al., who found reduced cytotoxicity in people exposed to ELMFs produced by television transmitters when their blood cells were re-irradiated 'in vitro' with radiofrequencies or with an ELMFs of 50 Hz (Giuliani et al., 1996).

The women investigated in this study showed lower levels of blood Pb than men with similar exposure to an urban environment (Boscolo et al., 1999b). This may be in part explained by the higher number of blood erythrocytes (containing most of blood Pb) present in men than in women (Castellino et al., 1995). Moreover, it was shown that the hormonal status of fertile women enhances the storage of Pb in bones (Castellino et al., 1995).

The correlation of NK cells with urinary *trans–trans* muconic acid in women with low levels of environmental exposure suggests that low levels of exposure to benzene, produced by vehicular traffic or active or passive smoking, may stimulate NK activity. This datum needs to be confirmed in further studies.

A statistically significant reduction of serum interferon γ and a reduced 'in vitro' production of interferon γ by PMBCs, both spontaneously or following stimulation with PHA, has been found in women exposed to ELMFs in the museum. It may not be excluded that lower levels of NK and B $CD3^-–CD25^+$ lymphocytes and NK $CD16^+–CD56^+$ lymphocytes in peripheral blood of women and men exposed to ELMFs may depend on a reduced production of interferon γ by immune cells. With regard to this, it is known that interferon γ, which is produced by T and NK lymphocytes, may activate NK lymphocytes with an 'autocrine loop'.

It was recently demonstrated that lifestyle and/or occupational stress can reduce blood cytotoxic activity (Kawakami et al., 1997; Morimoto et al., 1999; Morimoto et al., in press). This was also found in subjects with a psychological behaviour characterised by difficulty in expressing feelings (Dewaraja et al., 1997). The effects of ELMFs exposure on the cytotoxic immune cells of the workers in the museum may thus increase those dependent on occupational stress. Therefore, we do not ignore that the effects of ELMFs may be, in part, mediated by those of nervous functions which are closely connected with immune ones (Jankovic, 1992; Male et al., 1996). The combined effects of exposure to ELMFs and occupational stress on neuroendocrine functions may also explain the reduced melatonin and adreno-corticotropic hormone levels in video display unit workers during their working activity (Arnetz and Berg, 1996).

Although lifestyle and stress may modify blood cytotoxic activity, the determination of blood NK $CD16^+–56^+$ and B and NK $CD3^-–CD25^+$ lymphocyte subsets, which were found to be reduced by ELMFs exposure in this study, may be considered a useful biomarker of exposure to ELMFs. However, immune parameters used as biomarkers of exposure to noxious agents may be influenced by several environmental and/or individual factors. For these reasons, they should be used only for homogenous groups of persons with an adequate control group as reference (Van Loweren, 1999).

In another study performed by our group (not yet completed), several NK lymphocyte subsets (including the $CD16^+–56^+$ and $CD3^-–CD25^+$) and 'in vitro' production of interferon γ were found to be significantly reduced in fertile women exposed to amplitude modulated radiofrequencies. These women (mean age 35 years) were mainly housewives not exposed to high levels of urban environmental compounds (Boscolo et al., 1999b) or performing stressful activities.

So far, the mechanisms by which ELMFs reduces blood cytotoxic activity have not been clearly elucidated, until now. For this reason, we are unable to establish for ELMF-exposed humans the normal range of blood values of NK lymphocytes. Moreover, we are unable to establish safe levels of exposure to ELMFs, since there are no studies on the dose–response effects of ELMFs in humans.

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