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DO ELECTROMAGNETIC FIELDS ENHANCE THE EFFECTS OF ENVIRONMENTAL CARCINOGENS?

Jukka Juutilainen*
Department of Environmental Science, University of Kuopio, PO Box 1627, 70211 Kuopio, Finland

Epidemiological studies have reported an increased risk of leukaemia in children who are exposed to extremely low-frequency (ELF) magnetic fields (MF), suggesting that ELF MFs may be carcinogenic to humans. No carcinogenic effects have been found in animal studies that have tested ELF MFs alone. Similarly, genotoxicity studies have generally not shown effects from MFs alone. However, ELF MFs have been reported to enhance the effects of known carcinogenic or mutagenic agents in a few animal studies and in several *in vitro* studies. This paper discusses the findings of studies on such combined effects. The majority of *in vitro* studies have reported positive findings, which supports the conclusion that MFs of 100 μT or higher interact with other chemical and physical agents. Further studies should address biophysical mechanisms and dose–response relationship below 100 μT. Animal studies designed according to the classical initiation–promotion concept may not be sufficient for studying the cocarcinogenic effects of MFs, and further studies using novel study designs would be useful. Epidemiological data on the interaction between MFs and other environmental agents are scant and inconclusive, and any further studies may be difficult because of the scarcity of subjects with suitable combined exposures.

INTRODUCTION

Extremely low-frequency (ELF) magnetic fields (MFs) were classified as 'possibly carcinogenic to humans' by the International Agency for Research on Cancer[1]. This classification was mainly based on limited epidemiological evidence for an association between residential ELF MF exposure and childhood leukaemia. No carcinogenic effects have been found in animal studies that have tested ELF MFs alone. Similarly, genotoxicity studies have generally not shown effects from MFs alone, except for extremely strong ($\geq$50 mT) fields. However, ELF MFs have been reported to enhance the effects of known carcinogenic or mutagenic chemical or physical agents in a few animal studies and in several *in vitro* studies[1,2]. Previously two review articles[3,4] have been published, which attempted to analyse studies that have combined ELF MFs with other physical or chemical agents. In both reviews, the approaches were systematic comparisons of 'positive' and 'negative' studies. Rather than attempting to draw final conclusions about the existence or lack of effects (on a weight-of-evidence basis), it was considered that it is more fruitful to try to identify such differences in study characteristics that could explain differences in results and that would help to generate hypotheses for further studies. This paper further discusses the findings of the two reviews and other relevant data.

ANIMAL CARCINOGENICITY STUDIES

Animal studies that have combined MFs with known carcinogenic agents have produced equivocal results. Most of them have found no evidence of enhancement of carcinogenesis in MF-exposed animals, but a few positive findings have been reported. Among the positive findings are enhanced development of UV-induced skin tumours[5] and 7,12-dimethyl-benz[a]anthracene (DMBA)-induced mammary tumours[6–8] in animals exposed to ELF MFs. The mammary tumour findings were not substantiated in independent replication studies[9,10].

A total of 17 studies were reviewed on cocarcinogenic effects of 50–60 Hz MFs to identify possible common characteristics in the positive studies or any systematic differences between the negative and positive studies[3]. Examination of the negative studies revealed that most of them had used a single dose or a short-term exposure to an 'initiating' agent, followed by a chronic exposure to MF (considered a possible tumour 'promoter'). A typical example of this type of studies is a mouse study that provided no evidence for promotion of cancer initiated by ionizing radiation[11]. All positive studies, in contrast, had combined chronic MF exposure with other long-term exposure, i.e. the animals had been exposed to both MFs and a known carcinogen during an extended period of tumour development. In a positive skin tumour study, UV treatment was given during the whole experiment[5]. The duration of DMBA treatment was only 4 weeks in the mammary tumour studies[6,7,12], which is nevertheless a significant portion of the total study duration of 13 weeks.

Based on the findings of the review, it was hypothesised that experiments designed according to the classical two-step initiation–promotion concept may not be sufficient for revealing the possible

*Corresponding author: jukka.juutilainen@uku.fi

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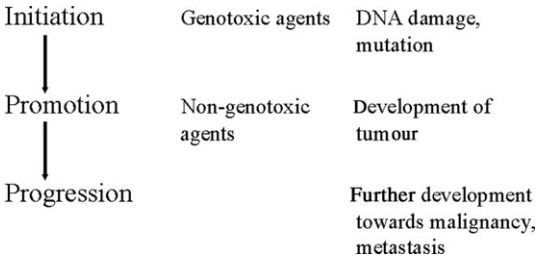

Figure 1. The three-step model of carcinogenesis.

carcinogenic effects of ELF MFs. The three broadly defined classic events in tumour development are initiation, promotion and progression (Figure 1). Of these events, initiation is usually considered to represent DNA damage leading to a mutation, and promotion can be caused by non-genotoxic agents. There is increasing evidence that the initiation–promotion–progression model is not adequate for describing the complex interaction of genotoxic and non-genotoxic carcinogens, and that 'initiation' (genotoxic exposure) does not necessarily precede 'promotion' (non-genotoxic carcinogens)[13]. It is also relevant to note in this context that human exposure is not adequately simulated by the classical experimental design of a short-term initiation followed by a repeated promoter treatment. Humans are exposed to a complex mixture of several different carcinogens at varying levels, and the exposures are typically long-term. Therefore, animal studies using the classical two-step initiator–promoter design may not be adequate for addressing all aspects of the possible carcinogenic effects of MFs.

IN VITRO AND SHORT-TERM ANIMAL STUDIES

After the initial finding of MF-enhanced skin tumourigenesis in mice exposed to UV radiation[5], experiments were conducted to explain how MF exposure could modify the biological effects of UV radiation. The results indicate that MFs of the order of 100 μT enhance UV-induced effects on proliferation and cell cycle in yeast[14] and modify skin apoptotic response to UV[15]. Motivated by these findings and several other studies suggesting interaction of MFs with other environmental agents[1,2], a systematic review was conducted to analyse data from *in vitro* studies and short-term animal studies that have combined ELF MF exposure with other physical or chemical agents[4]. Rather than a classical qualitative review, the authors chose to use the results of original studies as data for a new summarising analysis ('meta-analysis'). The data were analysed by systematic comparison of study characteristics between positive and negative studies to identify possible consistent patterns that could serve as a basis for hypotheses and for planning new studies.

The majority of the 65 studies reviewed were positive, which supports the conclusion that MFs interact with other chemical and physical exposures. Publication bias is unlikely to explain the findings. Interactions were observed with ionizing radiation, UV radiation and several different chemical agents, and affected endpoints included many cancer-relevant endpoints such as genotoxicity, apoptosis, cytotoxicity, differentiation, intercellular communication, oxidative stress and cell proliferation.

Interestingly, a non-linear 'dose–response relationship' was found, showing a minimum percentage of positive studies at flux densities between 1 and 3 mT. Another interesting pattern was that the percentage of positive studies was highest if MF exposure preceded the other exposure, whereas a lower percentage of positive findings was reported in studies that used simultaneous exposures or MF exposure after the other exposure. This pattern was consistently seen for fields below 1 mT, for those above 3 mT, for studies on genotoxic endpoints and for those on non-genotoxic endpoints.

EPIDEMIOLOGICAL STUDIES

Very little epidemiological data are available on possible combined effects of ELF MFs with other environmental agents. Navas-Acien *et al.*[16] investigated brain tumour risk in a cohort of male Swedish workers and addressed possible interaction between occupational exposure to ELF MF and chemical substances with known or suspected carcinogenic effects. Exposure to MFs and nine chemicals were assessed using job-exposure matrices based on occupational codes. Among subjects not exposed to chemicals, no evidence was seen for increased risks associated with MF exposure. The risk of glioma was increased among workers exposed to petroleum products independent of the level of MF exposure. However, lead, pesticides/herbicides and solvents were associated with increased glioma risk only in subjects who were also exposed to high or moderate levels of MFs. Hakansson *et al.*[17] conducted a case–control study of endocrine glands (adrenal gland, thyroid gland and parathyroid gland) tumours, and reported increased risks associated with welding, which was interpreted as a possible association with exposure to ELF MFs. Risk of adrenal gland tumours was also associated with exposure to solvents, but analysis of interaction did not show any evidence of synergistic effects.

DISCUSSION AND CONCLUSIONS

It is of interest that, in the *in vitro* and short-term animal studies reviewed[4], combined effects were

particularly often reported if MF exposure preceded other exposures. This observation suggests that MF exposure alters biological responses to subsequent exposure to other physical and chemical agents, and gives further support to the conclusion[3] that animal studies based on the classical initiation–promotion approach (initiator first followed by promoter) may not be sufficient to reveal possible cocarcinogenic effects of MFs. Confirmation of the positive findings[5] and additional animal studies using novel designs would therefore be useful.

Another interesting finding of the meta-analysis[4] was the apparent non-linear 'dose–response' with a minimum between 1 and 3 mT. This might give useful hints of the biophysical mechanism of the effects reported. The only known interaction mechanism showing a diphasic relationship with magnetic flux density is the 'radical pair mechanism'. MFs are known to affect the recombination probability of radical pairs and therefore influence the yield of free radicals[18]. The radical pair mechanism can be divided into a 'high field effect' (HFE) and a 'low field effect' (LFE), both of which are theoretically well understood[19–21], and have also been experimentally demonstrated in cell-free biochemical systems[22]. The MF effect on radical pairs should have a minimum or disappear at the limit between the LFE and HFE at around one to a few mT[22], depending on the nature of the radicals and the surrounding molecules.

The animal and *in vitro* studies reporting interactions between MFs and other agents have generally used MFs of 100 μT or higher. Therefore, the findings are not directly relevant for explaining epidemiological findings suggesting increased risk of childhood leukaemia at around 0.4 μT. However, the available data are not sufficient for assessing the exposure–response relationship at low fields and the possible existence of a threshold; fields below 1 μT were not even tested in any of the studies reviewed. Furthermore, confirmed adverse effects even at 100 μT would have important consequences for risk assessment and management, including the need to reconsider the exposure limits for MFs. Further studies should address the radical pair mechanism as a possible explanation for combined effects with MFs and explore the dose–response relationship below 100 μT.

Epidemiological studies would also be valuable, but it may be difficult to identify large enough populations exposed to both environmental carcinogens and high levels of ELF MFs.

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