Bundesamt
für Strahlenschutz

**Spotlight on EMF Research**

# Spotlight on “Effect of 1800 MHz radiofrequency field exposure on cytokine and signal transduction protein expression in differentiated THP-1 cells” by Bellier et al. in International Journal of Radiation Biology (2024)

**Category [radiofrequency, in vitro study]**

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Competence Centre for Electromagnetic Fields (KEMF)

# 1 Putting the paper into context by the BfS

Immune cells need to communicate with each other and with other cells of the organism. For this intercellular communication, they secrete so-called cytokines, proteins that send specific messages which can promote or shut down inflammatory processes in other cells. To respond to such cues and change their behaviour appropriately, cells use an intracellular network of signalling proteins. These signal transduction proteins integrate incoming information and relay it to coordinate the cell's specific functions and genetic programme.

Whether, how and to what extent radiofrequency electromagnetic fields (RF-EMF) might affect immune cells or other immune system components under different circumstances has been the subject of a considerable number of animal and cell studies [2]. Overall, the results have been contradictory and inconsistent, possibly due to differences in methodology and study quality. Rigorous research is required to address these questions accurately.

# 2 Results and conclusions from the perspective of Bellier et al.

The present study by Bellier et al. [1] aimed to contribute to the body of evidence on possible effects of RF-EMF on the immune system. It focused on the innate branch of the immune system, the body's first line of defence, in particular on macrophages (a type of white blood cells). The THP 1 cell line, derived from a human patient with blood cancer, was used as a cellular model. THP-1 cells can be induced to become macrophage-like using the substance phorbol 12-myristate 13-acetate (PMA) and are considered a valid tool to study macrophage biology [3].

The PMA treated THP-1 cells were exposed to either continuous wave (CW) or to modulated RF-EMF with properties similar to those of global system for mobile communications (GSM), at a frequency of 1.8 GHz with a time- and spatial-average specific absorption rate (SAR) of 2.0 W/kg computationally evaluated at the position of the cell monolayer. The cell cultures were placed in two separate computer-controlled waveguide chambers designed for RF-EMF (2 W/kg) or sham (0 W/kg) exposures [4]. These chambers were then positioned within a single incubator system. By continuously monitoring the air temperature within the waveguides during exposure, the temperature difference between the sham and RF-EMF groups was maintained at less than 0.11 °C. Exposures lasted for 0.5, 4.0 or 24 hours and cells were processed for endpoint analysis immediately after exposure. Two separate positive and appropriate negative controls were included in parallel. Five independent experiments were performed.

Multiplex magnetic bead technology was used to quantitatively determine the levels of six cytokines in the THP-1 cell supernatant and the levels of nine different signal transduction proteins and their phosphorylated forms (indicating their activation state) in the THP-1 cell extracts. THP-1 cell samples were coded to ensure blinding of the investigators during endpoint analysis. The data were statistically evaluated using linear mixed-effects models with exposure (sham or RF-EMF) and exposure duration as fixed effects, and independent experiments as a random effect. A doubling or halving of individual protein levels in RF-EMF-exposed cultures compared to sham-exposed cultures was considered a biologically meaningful response.

Among the six cytokines, of which three passed the detection threshold, only IL-6 showed a statistically significant but less than twofold increase in the supernatants of THP-1 cells from the GSM-like modulated condition compared to sham-exposure. Among the nine signal transduction proteins, there was only a statistically significant interaction between GSM-like modulated exposure and exposure duration for the activation of NF-κB. I.e., only at the 4.0 hour time point, there was an almost twofold increase in activated NF-κB in RF-EMF- relative to sham-exposed THP-1 cells. None of these findings remained statistically significant after correction for multiple hypothesis testing.

The authors concluded that under the experimental conditions used, there was no evidence for effects of exposure to RF-EMF on several messenger components of the innate immune system. They recommend further studies using other relevant cell types and exposure settings.

# 3 Comments by the BfS

From the perspective of radiation protection, the present study addresses a relevant research question. Immune cells are highly dynamic due to the need to rapidly change their behaviour in response to appropriate signals from their environment. Unintentional interference with their function could lead to adverse health effects. Previous research has investigated whether exposures to RF-EMF at levels below the ICNIRP (International Commission on Non-Ionizing Radiation Protection) limit levels could affect various immune system components and immune cell functions. The evidence has been inconclusive [2].

The current study formulated a clear research question focusing on human macrophages, an innate immune cell type. RF-EMF exposures in continuous wave or GSM-like exposure mode were tested for up to one day. Given the acute responsiveness of the proteins studied [5, 6], the exposure period of up to one day is considered adequate. Positive controls provided target values for physiologically relevant responses. The study is notable for its transparency and the relatively high number of independent experiments (five). The data analysis can be reproduced using the publicly deposited source data and the explicitly formulated statistical model. The researchers found no evidence for effects on several important messenger proteins used for communication between immune cells. They also found no effects on signalling molecules inside the cells that process incoming information to best adapt the cell's behaviour to its changing environment.

Regarding the relevance of the results for radiation protection, it should be noted that the exposure level in this study was set according to the basic restriction value for the local SAR of the head and torso for the general public, as recommended by ICNIRP [7], which specifies that the SAR must be averaged over a volume of 10 g of tissue mass. The SAR averaging volume of the cell monolayer considered in this study has a significantly smaller mass than 10 g. Within a 10 g averaging volume, there could be regions with local SAR values significantly exceeding 2 W/kg, while the overall average still complies with the basic restriction. Consequently, a homogeneous exposure of the monolayer with a SAR of 2 W/kg does not represent a worst-case scenario, which in reality could lead to very localized exposures in the human body exceeding 20 W/kg [8]. However, for fat and muscle tissue below the upper layer of the skin, no SAR hot spots are expected [8]. Therefore, the studied exposure scenario would represent a worst-case scenario for fat and muscle tissue-resident macrophages.

Some signal transduction proteins like NF-κB or STAT5 were not activated by the positive control anisomycin. Lipopolysaccharide (LPS) is known to activate NF-κB [6], but it was only used as a positive control for the cytokine and not the signal transduction measurements. Consequently, it is unclear whether the activation of all signal transduction proteins could be reliably measured by the method applied. There are studies on cells related to macrophages suggesting that low or high RF-EMF exposure levels activate NF-κB, a key protein that regulates pro-inflammatory responses [9, 10]. Although the present study did not show an increase in inflammatory cytokines such as IL-1β, which would otherwise be expected if NF-κB were activated, it cannot fully dispute these previous findings regarding NF-κB for the reason given above.

Overall, the present study sets high analytical standards and could serve as a template for future in vitro investigations into biological effects of RF-EMF exposures. It is important to note that the macrophage-like cells investigated here were in their basal state, and their response to RF-EMF was compared to two potent activators of macrophages. Therefore, it can only be concluded that in this study, RF-EMF exposure was unable to activate macrophages from their resting state. Future research could investigate the effects of RF-EMF exposures on additional immune cells and during their response to stimulants such as LPS or other pathogen-associated molecular patterns and danger signals, as well as relevant cytokines.

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