## A biophysical framework to analyze (pre-)clinical data on non-thermal effects

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## Abstract

**Introduction**: The existence of non-thermal effects of electromagnetic fields (EMF) is controversially discussed since decades. Earlier investigations did not identify evidences of for any risks of radiofrequency (RF) EMF at safety levels and denied the existence of non-thermal effects.

**Objectives**: Careful review of available preclinical and clinical data upon non-thermal effects, which are classified and analyzed by a novel membrane model

**Material and Methods**: Recently, preclinical studies ascertained additional cytotoxic effects, if RFhyperthermia (HT) is applied at 13.56 or 27 MHz in comparison to water bath (WB)-HT at the same temperature. These effects can be further enhanced by amplitude modulation (AM) in the Hz to kHz-range. Preclinical data are confirmed by clinical studies and observations, in particular if EMF applications with AM are considered.

**Results**: A subtle analysis of preclinical and clinical data of WB-HT and conventional HT reveals numerous hints that non-thermal effects exist. A critical evaluation of all available empirical data provides sufficient evidence for non-thermal effects EMF, which have the potential to improve oncologic treatments.

In the next step, plausible biophysical and electrophysiological models are evaluated to decipher these nonthermal effects. Nanoheating of protein clusters in lipid rafts has been postulated but needs excessive levels of local power not consistent with physical assessments. Basis for novel theories are models of ion channels, which function like rectifiers and low pass filter. It can be deduced that AM-RF induces ion fluxes and membrane vibrations at specific resonance frequencies. This model can explain non-thermal cytotoxic effects via ion disequilibrium (especially regarding Ca2+) and/or resonances with hole formation in the membrane, if AM-RF radiates for some time perpendicular to the membrane comprising a given density of ion channels.

**Conclusions**: Non-thermal effects induced by AM-RF are very probable. We recommend further evaluations. Higher effectiveness of AM-RF in tumors can occur because of their specific tumor environment, cancerspecific ion channels (channelomes) and membrane elasticities differing from normal tissues with increasing malignancy. Suitable oncological applications can lead to significant improvements.

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