# Toxic and Proarrhythmic Effects of Airborne Particulate Matter Exposure. In-vitro, In-vivo and In-silico Study

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Particulate matter (PM) is one of the most dangerous air pollutants for health. It is related to an increase in cardiovascular diseases and the appearance of arrhythmias. However, the pathophysiological mechanisms have not been well established. This study aims to evaluate the toxic and proarrhythmic effects of PM.

To evaluate the cytotoxic effect, 148 PM filters were collected from monitoring stations. The PM was extracted using Soxhlet systems and 15 dilutions were made in DMSO. The MTT assay was performed on the cultures to assess cell viability, which decreased as the PM concentration increased. A lethal dose 50 (LC50) of 1.44 mg/ml was obtained by regression analysis. This value was adopted as the $IC_{50}$ value for in silico studies. Subsequently, mathematical equations of the PM effect were incorporated into the atrial and ventricular myocyte models. Different PM concentrations (from 0 nM to 6 nM) were simulated and their effect on electrophysiological characteristics in the single-cell models and on the vulnerability to reentries in 2D models of ventricular and atrial tissue was evaluated. As the concentration of PM increased, a larger effect of blocking the calcium current was observed, generating reductions of the action potential duration of up to 53% and 42% at the highest PM concentration in atrial and ventricular cells, respectively. Flattening of the restitution curve and induction of arrhythmic episodes were also observed as the vulnerability of the tissues to reentries increased.

To verify the results, we used mice with inhalation exposure to vaporized aerosols, which generate high levels of PM. In-vivo programmed electrical stimulation in the exposed mice suggested a trend for a decreased ventricular effective refractory period as well as significantly increased inducible ventricular arrhythmogenesis compared to room air control animals.

The results suggest cytotoxic and proarrhythmic effects of PM in a concentration-dependent manner.