

Inhaled metal oxide nanoparticles' retention in the pulmonary tissue can be hindered by their relatively high solubilization counterbalancing their unfavorable action on the free pulmonary cells response

We hypothesized that pulmonary clearance vs. retention of metal oxide nanoparticles (NPs) is controlled not only by activity of phagocytes and other physiological mechanisms but also by the NP solubilization which, in some cases, may even prevail thus making the impact of these NPs on lungs quite feeble. To test this hypothesis, airborne Fe_2O_3 NPs with the mean diameter of $14 \pm 4 \text{ nm}$ produced by sparking from 99.99% pure iron rods were fed into a nose-only exposure device. Rats were inhaling these NPs for 4 h a day, 5 days a week during 3, 6 or 10 months at the mean concentration of $1.14 \pm 0.01 \text{ mg/m}^3$.

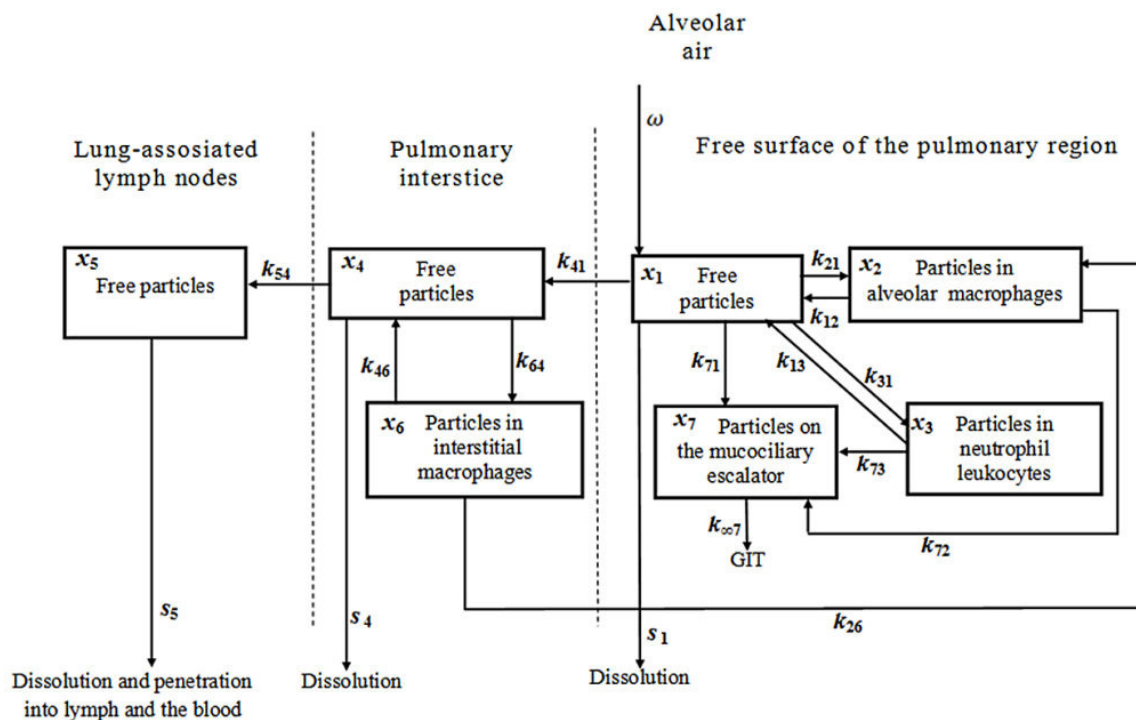


Fig. 1. Structure of the multi-compartmental model for the kinetics of retention and elimination of the Fe_2O_3 -NPs deposited in the pulmonary region of the lung. Here: ω is a function of particle deposition in the pulmonary region, and k_{ji} is a rate constant of particle translocation from compartment X_i into compartment X_j . Dotted lines are conventional boundaries between anatomical regions.

We obtained transmission electron microscopy images of NPs within alveolocytes. Besides, the Fe_2O_3 content of the lungs and lung-associated lymph nodes measured by the Electron Paramagnetic Resonance (EPR) spectroscopy was gradually increasing with time. However, it proved much lower as compared with

respective values known for the micrometric standard quartz dust DQ12 (having particle sizes of less than 5 μm) at similar exposure conditions.

We demonstrated that free pulmonary cell responses to both particulates were virtually the same, but Fe_2O_3 NPs collected from the inhaled air, even though insoluble in water, dissolved markedly in the cell free broncho-alveolar lavage fluid supernatant and in the sterile bovine blood serum. This may be considered an *in vitro* model of their *in vivo* solubilization.

We have identified parameters of the multicompartamental system model describing the toxicokinetics of inhaled nanoparticles after their deposition in the lower airways as a process controlled by their (a) high ability to penetrate through the alveolar membrane; (b) active endocytosis; (c) *in vivo* dissolution. This model satisfactorily imitated experimental Fe_2O_3 and thus corroborated our initial hypothesis demonstrating that, as concerns iron oxide NPs of the dimensions used, the dissolution-depending mechanisms proved to be dominant.

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