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Internalization, toxicity, and genotoxicity of ultra-small non-magnetic iron oxide (III) nanoparticles in cultured cell lines and Drosophila larvae in vivo

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Iron oxide nanoparticles have been used in the last years as therapeutic agents in biomedicine. Among the wide variety of these particles, the ultra-small (< 10 nm), non-magnetic ones, composed by a ferrihydrite core covered with tartaric and adipic acids (FeAT-NPs) are showing promising properties. In published data, these nanoparticles have shown an efficient absorption rate by the enterocytes, conserving their nanoparticulated form, and a good solubilization into free iron inside the cells but not in the intestinal lumen. All these characteristics allow FeAT-NPs to be considered as a potential anemia treatment. However, the solubilization of these nanoparticles inside the cytosol might produce reactive oxygen species (ROS) that could trigger protein, lipid, and DNA oxidative damage. Thus, a systematic investigation of their activity, including biological effects and chemical behavior, should be performed.

In this work, we evaluated FeAT-NPs uptake, as well as their solubilization within the cell cytosol of different human cell lines, using inductively coupled plasma mass spectrometry (ICP-MS), alone or in combination with high performance liquid chromatography (HPLC). Cell viability, cell proliferation and ROS induction were analyzed in these cell lines after exposure with different FeAT-NPs concentrations, and the possible induced genotoxicity was evaluated with the alkaline Comet and the micronucleus (MN) assays. In addition, in vivo toxicity and genotoxicity of these nanoparticles were evaluated using Drosophila melanogaster as the model organism, with the eye SMART assay that detects somatic mutation and mitotic recombination.

Results revealed that FeAT-NPs are taken up efficiently, in a cell type-dependent manner, with a minimum dissolution. These results correlated with no effects on cell proliferation and minor effects on cell viability and ROS induction for all the studied cell lines. With respect to genotoxicity, comet assay results revealed significant induced DNA damage only in nucleotide excision repair deficient GM04312 cells, whereas MN data show no clastogenic activity in Hep-G2 cells.

Additionally, the Drosophila results showed that FeAT-NPs were genotoxic in vivo only with the two highest tested concentrations (2 and 5 mmol·L-1 of Fe) in surface treatments. These data altogether seem to show that FeAT-NPs represent a safe alternative for anemia treatment, with high uptake level and controlled iron release.

Keywords:
Iron oxide nanoparticles; uptake and solubilization; cytotoxicity; genotoxicity: SMART, comet and micronucleus assays.