

## ***In vitro* and *ex-vivo* assessment of toxicity of tattoo ink metal nanoparticles**

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Tattoo inks can contain different amounts of metal nanoparticles (MNPs < 100 nm) that, with their unique physicochemical properties, may result into novel mechanisms of biological uptake and cause additional skin or systemic toxicities. We investigated toxic effects of both reference standards of MNPs and real samples of tattoo inks by *in vitro* and *ex-vivo* skin models. *In vitro* toxicity was evaluated by MTS assays on human skin-derived cells (fibroblast and keratinocyte). No toxicity was observed for Al<sub>2</sub>O<sub>3</sub>, Cr<sub>2</sub>O<sub>3</sub> and TiO<sub>2</sub> MNPs on both cell lines, whereas CuO MNPs showed a dose-dependent toxicity. Furthermore, fibroblasts were also sensitive to high concentration of ZnO MNPs. Ink samples were then injected by tattoo needles into human skin explants *ex-vivo*. Histological analysis showed pigment distribution deep into the dermis and near dermal vessels, suggesting a possible systemic diffusion. Moreover, the presence of an inflammatory infiltrate was observed. Immunohistochemical analysis showed increased cell senescence and DNA damage in the tattooed areas. Altogether, our results indicate that tattoo technique can result into exposure to toxic MNPs and skin damage.