Title *

Lowering aspect ratio to control the biological effects of TiO_2 nanofibres (NF)

Abstract *

TiO_2 NF are a novel fibrous nanomaterial with promising applications in many fields, but with poor toxicological characterization. In this study, we assessed toxicity endpoints of commercially available anatase TiO_2 NF before and after ball milling, which lowered their aspect ratio (AR) from 1:29 to 1:5.

In murine macrophages and human airway cell models treated with short and long TiO_2NF, we compared cell viability, oxidative stress, expression of inflammatory markers and trans-epithelial electric resistance (TEER); cell morphology and particle uptake were investigated by SEM and confocal microscopy, along with hemolytic activity of long and short NF. TiO_2 nanoparticles and crocidolite were used as non-fibrous and fibrous benchmark materials.

Long TiO_2 NF were more cytotoxic than shorter NF and particles, and exhibited a markedly higher hemolytic activity. Long TiO_2 NF decreased the TEER of airway cell monolayers. Aspect ratio reduction significantly mitigated these effects. Macrophages efficiently internalized short but not long NF, the latter causing severe cell stretching and deformation. Short NF increased the expression of pro-inflammatory markers in macrophages, an effect suppressed by the inhibition of phagocytosis. 14d after pharyngeal aspiration, long NF increased cytokines in BAL of animals.

Whereas long TiO_2 NF caused significant toxic effects *in vitro*, AR reduction markedly mitigated the effects on cell viability, hemolysis and epithelial barrier competence, though it enhanced macrophage activation. In contrast, AR reduction lowered *in vivo*inflammation. This discrepancy is consistent with an enhanced macrophage activation following phagocytosis, which may improve the clearance of shorter TiO_2 NF. On the other hand, frustrated phagocytosis and bio-persistency may underlie the *in vivo* toxicity of long TiO_2 NF. In conclusion, AR reduction represents an effective “safe by design” strategy for lowering NF toxicity.

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