Title *

Intrinsic and cell-based oxidative properties of nanomaterials and associated oxidative stress responses determined by multiple assays

Abstract *

The ability of nanomaterials (NMs) to generate oxidants/reactive oxygen species (ROS), often referred to as Oxidative Potential (OP), is a promising metric to predict the NM-toxic potency. The evaluation and testing of this hypothesis were a central aim of the nanOxiMet project. We investigated a panel of 16 NMs in different suspensions (water & cell media) regarding their OP by Electron Paramagnetic Resonance spectroscopy (EPR), dithiothreitol, 2',7'-Dichlorofluorescein-acetate (DCF-DA) and antioxidant depletion assay. Cell-based OP and oxidative stress was analysed using similar approaches, i.e. fluorescence spectroscopy, EPR and antioxidant depletion. Associated oxidative stress responses were addressed according to the 3-Tier approach in macrophage and epithelial cell lines by evaluation of mRNA expression of Nrf2-regulated genes, mRNA/protein expression of inflammatory genes and analysis of (oxidative) DNA damage, lipid peroxidation and protein oxidation. When comparing the intrinsic OP assays complementary results were found whereby two principle groups of ROS-detection approaches could be specified: (1) assays sensitive to (transition)metals (e.g. Cu, Ni) and (2) assays sensitive to materials triggering electron transfer (e.g. Ag, CB). The most suitable method to determine (intra)cellular ROS formation was the DCFH-DA assay. Among the oxidative stress responses HO-1, glutathione depletion, Fpg-comet and cell viability (WST) assay were identified as most suitable. Based on our findings several NMs caused marked oxidative stress responses while having low/negligible intrinsic OP, whereas other NMs with a marked OP only triggered minimal oxidative stress responses in cells. In conclusion intrinsic OP assays are useful tools to assess for the potential toxicity of NMs. However, cell-based OP/ROS analyses and oxidative stress responses should be included at least to minimal extent, to reduce misclassification.

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