NANOSIZED TITANIUM DIOXIDE PARTICLES: EVALUATION OF GENOTOXIC EFFECTS IN HUMAN LYMPHOCYTES

Nanosized titanium dioxide particles: evaluation of genotoxic effects in human lymphocytes

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The number of consumer products containing nanomaterials (NM) in the European market showed a 6-fold increase in 2010 (RIVM report, 2010), reflecting the growing relevance of nanotechnology and the broad field of applications of NM across consumer, medical and industrial products. Although the use of NM may offer enormous benefits, it may also pose risks to human health, especially to workers who may face higher exposure, and to environment. Several studies have reported that the greater surface area per mass renders NM more reactive than larger-sized particles of similar chemistry. Size, surface properties, agglomeration state, biopersistence and dose are also likely to modify cell responses to NM, presenting a challenge to the assessment of their potential hazards to human health. Titanium dioxide (TiO2) and zinc oxide (ZnO) nanoparticles (NP) are frequently used in sunscreens and cosmetics. Although cytotoxic and genotoxic properties of TiO2-NP and ZnO-NP have been investigated, conflicting results have been reported. Differences inherent to cell lines, NPs characterization, dispersion protocols, exposure times and assays, together with the lack of positive NM controls have lead to difficulties in the toxicity assessment of those NM. As a part of a larger project (www.nanogenotox.eu), aimed at establishing a robust methodology to evaluate the potential genotoxicity of manufactured NM, the objective of the present work was to characterize the potential genotoxic effects of TiO2-NP (anatase, hydrophilic rutile, hydrophobic rutile and rutile/anatase) in primary cultures of human lymphocytes.

The cytokinesis-block micronucleus (CBMN) assay was carried out according to OECD guidelines. Dispersions of each NP were freshly prepared and cultures were exposed to NP concentrations (5-250 μg/mL), during 30h. Concurrent control cultures were processed: vehicle control, positive control (mytomicin C, MMC) and a reference NP (ZnO-NP).

The results show that none of the four TiO2-NP tested induced a dose-related increase in MN frequency in lymphocytes. Likewise, the cytokinesis-block proliferation index (CBPI) was not significantly affected by TiO2-NP treatments, indicating no influence on cell cycle progression. As to the positive control, MMC induced a significant increase in the frequency of MN and a concomitant decrease in the CBPI, whereas ZnO-NP caused a decrease in the CBPI without affecting the frequency of MN.

In conclusion, the results suggest that the tested TiO2-NP are not clastogenic or aneugenic in human lymphocytes, under the selected test conditions. Further data using different cell types and other endpoints, together with the study of *in vivo* genotoxic and

toxicokinetics parameters, are expected to clarify if these TiO2-NP can be considered as non-genotoxic to humans.

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