INVESTIGATION OF THE *IN VIVO* GENOTOXIC EFFECTS OF A TITANIUM DIOXIDE NANOMATERIAL IN *LACZ* PLASMID-BASED TRANSGENIC MICE

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Background

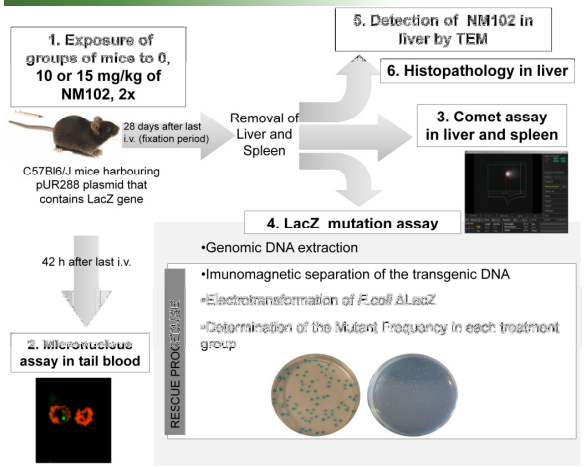
In a recent work, we showed that some rutile forms of titanium dioxide nanomaterials (TiO_2) were able to induce a significant increase in the frequency of micronucleated human lymphocytes (Tavares et al., Toxicol in vitro, 2014)

For an anatase form of TiO_2 (NM-102, JRC repository), a significant genotoxic effect was observed for a single concentration, and the result of genotoxicity assessment was considered equivocal, thereby requiring further investigation.

Objectives

To investigate the genotoxic potential of NM-102 *in vivo*, using an integrated analysis of multiple genotoxicity endpoints in the LacZ plasmid-based transgenic mouse model.

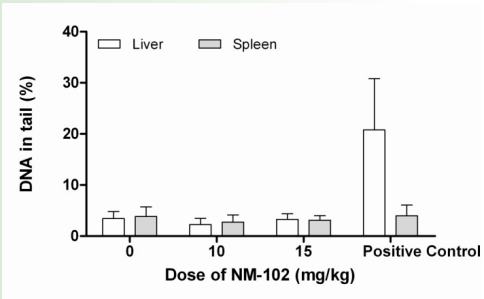
Methods



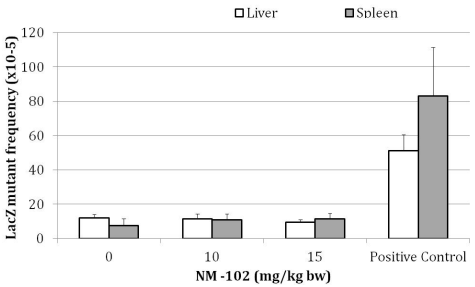
Nanomaterial	Phase	Impurities/ coating	Specific surface area (m^2/g)	Feret Min ± SD	Feret Max ± SD	Aspect ratio ± SD
TiO2, NM-102	Anatase	--	90	20.87 ± 1.6	33.0 ± 1.5	1.5 ± 1.3

Results

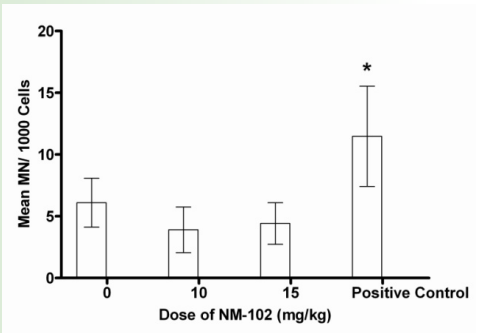
THE COMET ASSAY WITH LIVER AND SPLEEN CELLS YIELDED NEGATIVE RESULTS



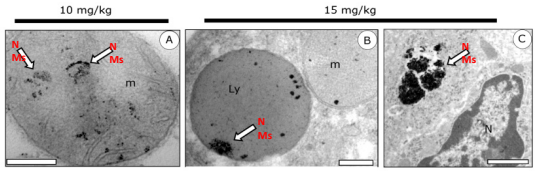
NONE OF THE DOSES INDUCED MUTATIONS IN THE *LACZ* GENE RECOVERED FROM LIVER AND SPLEEN, 28 DAYS AFTER EXPOSURE



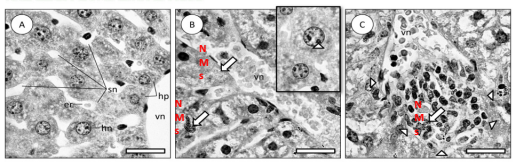
NO INDUCTION OF MICRONUCLEI IN BLOOD RETICULOCYTES, 42H AFTER IV ADMINISTRATION OF TiO_2 NM



HISTOLOGICAL ANALYSIS OF MOUSE LIVER



TEM ANALYSIS OF MOUSE LIVER



Conclusions

•No mutagenic effects could be disclosed for NM-102 in the liver or spleen of l*acZ* transgenic mice, in the tested conditions.

• Histological and TEM analyses confirmed the accumulation of NM-102 in mouse liver and a moderate inflammatory effect in this organ.

•The overall integration of the data strengthens the weight of evidence of an absence of TiO_2 genotoxicity *in vivo*, although the possibility of a secondary genotoxic effect driven by an inflammatory response within a longer time window or at higher doses cannot be excluded and should be further investigated.

No genotoxic effects of NM-102 *in vivo,* under the tested conditions

Bioaccumulation of TiO_2 NM in mouse liver, probably associated with the mild inflammatory effects observed

Louro et al., Environ Mol Mutagen. 2014 Mar 4.

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NANOGENOTOX

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