# Comparison of two $TiO_2$ nanoparticles toxicity on lung, blood and liver cells after repeated respiratory exposure in rats

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Titanium dioxide ($TiO_2$) nanoparticles (NPs) can cause negative health effects such as respiratory tract cancer in rats. However, mechanisms involved in $TiO_2$ NP-induced carcinogenicity have not been clearly defined and are yet poorly studied *in vivo*. The present study compared genotoxicity (DNA lesions with the comet assay and chromosomal damages with the micronucleus assay), oxidative stress (glutathione content) and inflammation (LBA numeration and cytokines) in rats exposed to 2 $TiO_2$ NPs (NM105: P25, 23 nm, 85% anatase / 15% rutile, 46 $m^2/g$; and NM101: Hombikat UV100, 7 nm, anatase, 300 $m^2/g$) in 3 instillations at a 4-days interval accounting for total final doses of 0.5, 2.5 and 10 mg/kg spread over 12 days. Endpoints were assessed at two time points, 2 hours and 35 days after the last instillation. This study confirmed two lung overload thresholds, previously described. The first one at 4.2µL/kg, above which lung inflammation and altered lung clearance were observed, and another at 10 µL/lung above which persistent lung inflammation was observed. Inflammation was also noticed in blood for NM101 at all doses after 2h and only at the two highest doses after 35 days, on the contrary to NM105 where blood inflammation was only observed after 2h at the highest dose. This inflammatory response was not associated with glutathione content modification for both NPs in lungs or in blood. In lungs, only NM105 induced genotoxicity in a delay manner at the two highest doses. In liver, MN101 did not cause any DNA damages on the contrary to MN105 which induced DNA lesions at the two highest high doses, but in a time independent manner. In the case of NM101, a temporary hepatic oxidative stress was observed at the two highest doses. Overall, $TiO_2$ NPs chosen here demonstrated much different toxicity profiles. NM105 seem genotoxic on lungs and liver, and NM101 seem more inflammatory. Thus nano-genotoxicity and oxidative stress could be influenced by surface reactivity as a consequence of coating or different crystalline forms. The rutile form could be more genotoxic, or at least in a mixture with anatase. Lung inflammation and clearance could be driven by a smaller size or higher surface area thus associated with lung burden.