

Supplementary figures

Oral toxicological study of titanium dioxide nanoparticles with a crystallite diameter of 6 nm in rats

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Table S1. Titanium content in the liver, kidneys, and spleen of F344/DuCrIj rats treated with titanium dioxide nanoparticles for 28 days.

Sex	Organ	Dose (mg/kg bw/day)	Ti concentration (µg/g)	Organ weight (g)	Total Ti (µg)	Difference from control group (µg)	Daily Ti intakes in the last week (mg) ^a
Male	Liver	0	0.013 ± 0.003	6.007 ± 1.100	0.076 ± 0.011	-	-
		10	0.013 ± 0.002	5.573 ± 0.301	0.073 ± 0.015	< 0	1.25
		100	0.017 ± 0.004	5.500 ± 0.576	0.091 ± 0.025	0.015	12.44
		1,000	0.017 ± 0.008	5.518 ± 0.487	0.094 ± 0.042	0.018	124.80
	Kidneys	0	0.023 ± 0.006	1.417 ± 0.110	0.032 ± 0.007	-	-
		10	0.027 ± 0.015	1.439 ± 0.096	0.039 ± 0.023	0.007	1.25
		100	0.022 ± 0.002	1.377 ± 0.099	0.031 ± 0.004	< 0	12.44
		1,000	0.020 ± 0.004	1.369 ± 0.101	0.028 ± 0.004	< 0	124.80
	Spleen	0	0.029 ± 0.012	0.480 ± 0.027	0.014 ± 0.006	-	-
		10	0.025 ± 0.004	0.498 ± 0.020	0.013 ± 0.002	< 0	1.25
		100	0.025 ± 0.008	0.476 ± 0.037	0.012 ± 0.003	< 0	12.44
		1,000	0.031 ± 0.002	0.481 ± 0.029	0.015 ± 0.001	0.001	124.80
Female	Liver	0	0.015 ± 0.004	3.421 ± 0.105	0.051 ± 0.016	-	-
		10	0.013 ± 0.003	3.446 ± 0.124	0.045 ± 0.008	< 0	0.82
		100	0.015 ± 0.004	3.326 ± 0.150	0.050 ± 0.014	< 0	8.19
		1,000	0.026 ± 0.008 *	3.267 ± 0.168	0.084 ± 0.028 *	0.033	80.07
	Kidneys	0	0.025 ± 0.003	0.928 ± 0.075	0.024 ± 0.004	-	-
		10	0.024 ± 0.003	0.929 ± 0.051	0.023 ± 0.002	< 0	0.82
		100	0.032 ± 0.002	0.949 ± 0.033	0.030 ± 0.003	0.007	8.19
		1,000	0.034 ± 0.014	0.956 ± 0.037	0.032 ± 0.012	0.008	80.07
	Spleen	0	0.031 ± 0.002	0.347 ± 0.017	0.011 ± 0.000	-	-
		10	0.039 ± 0.008	0.342 ± 0.009	0.013 ± 0.003	0.003	0.82
		100	0.050 ± 0.026	0.356 ± 0.019	0.018 ± 0.010	0.007	8.19
		1,000	0.044 ± 0.005	0.344 ± 0.023	0.015 ± 0.002	0.004	80.07

Values are mean ± S.D. * $P < 0.05$, compared with the 0 mg/kg bw/day group. ^a Daily titanium intake was calculated by multiplying the daily TiO₂ doses by the atomic mass of Ti (47.867) divided by the molar mass of TiO₂ (79.866).

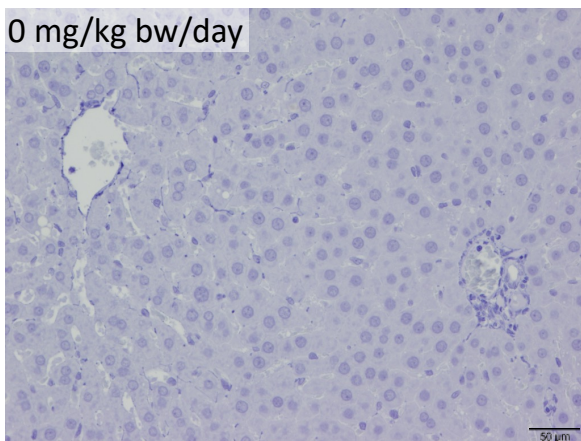
Table S2. Titanium content in the liver, kidneys, and spleen of F344/DuCrIj rats treated with titanium dioxide nanoparticles for 90 days.

Sex	Organ	Dose (mg/kg bw/day)	Ti concentration (µg/g)	Organ weight (g)	Total Ti (µg)	Difference from control group (µg)	Daily Ti intakes in the last week (mg) ^a
Male	Liver	0	0.014 ± 0.002	6.553 ± 0.644	0.090 ± 0.013	-	-
		100	0.019 ± 0.005	6.400 ± 0.468	0.121 ± 0.026	0.031	17.83
		300	0.022 ± 0.020	6.649 ± 0.399	0.144 ± 0.125	0.055	56.13
		1,000	0.017 ± 0.006	6.183 ± 0.501	0.106 ± 0.028	0.016	179.02
	Kidneys	0	0.046 ± 0.024	1.578 ± 0.076	0.073 ± 0.039	-	-
		100	0.034 ± 0.008	1.622 ± 0.104	0.055 ± 0.014	< 0	17.83
		300	0.036 ± 0.015	1.613 ± 0.086	0.058 ± 0.025	< 0	56.13
		1,000	0.031 ± 0.004	1.586 ± 0.098	0.048 ± 0.005	< 0	179.02
	Spleen	0	0.023 ± 0.008	0.570 ± 0.043	0.013 ± 0.004	-	-
		100	0.037 ± 0.014	0.569 ± 0.049	0.021 ± 0.009	0.008	17.83
		300	0.046 ± 0.040	0.583 ± 0.035	0.027 ± 0.023	0.014	56.13
		1,000	0.045 ± 0.020	0.553 ± 0.035	0.025 ± 0.012	0.012	179.02
Female	Liver	0	0.018 ± 0.004	3.751 ± 0.122	0.066 ± 0.016	-	-
		100	0.015 ± 0.002	3.693 ± 0.149	0.055 ± 0.006	< 0	10.78
		300	0.020 ± 0.017	3.640 ± 0.182	0.073 ± 0.067	0.007	32.14
		1,000	0.061 ± 0.098	3.624 ± 0.176	0.219 ± 0.359	0.153	106.93
	Kidneys	0	0.040 ± 0.007	1.021 ± 0.057	0.040 ± 0.006	-	-
		100	0.034 ± 0.010	1.027 ± 0.032	0.035 ± 0.010	< 0	10.78
		300	0.047 ± 0.031	1.000 ± 0.051	0.047 ± 0.033	0.007	32.14
		1,000	0.043 ± 0.013	1.001 ± 0.041	0.043 ± 0.012	0.002	106.93
	Spleen	0	0.036 ± 0.010	0.386 ± 0.019	0.014 ± 0.004	-	-
		100	0.034 ± 0.007	0.385 ± 0.013	0.013 ± 0.002	< 0	10.78
		300	0.049 ± 0.030	0.372 ± 0.023	0.018 ± 0.011	0.004	32.14
		1,000	0.111 ± 0.176	0.374 ± 0.027	0.042 ± 0.068	0.028	106.93

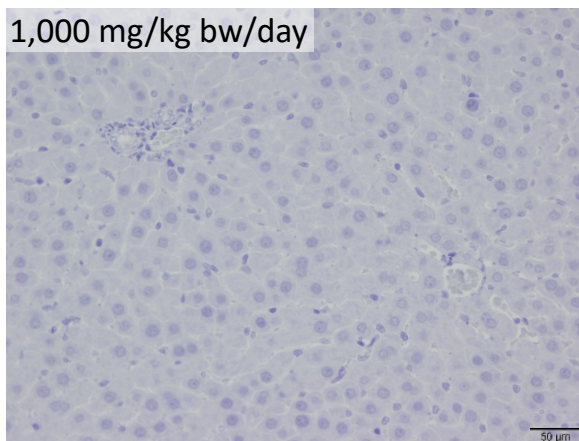
^a Daily titanium intake was calculated by multiplying the daily TiO₂ doses by the atomic mass of Ti (47.867) divided by the molar mass of TiO₂ (79.866).

A. Liver

0 mg/kg bw/day

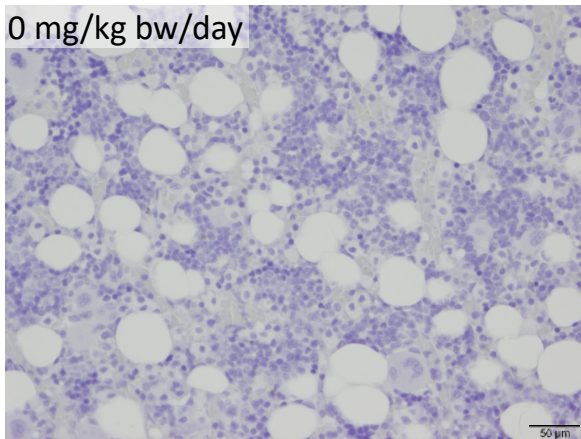


1,000 mg/kg bw/day



B. Bone marrow

0 mg/kg bw/day



1,000 mg/kg bw/day

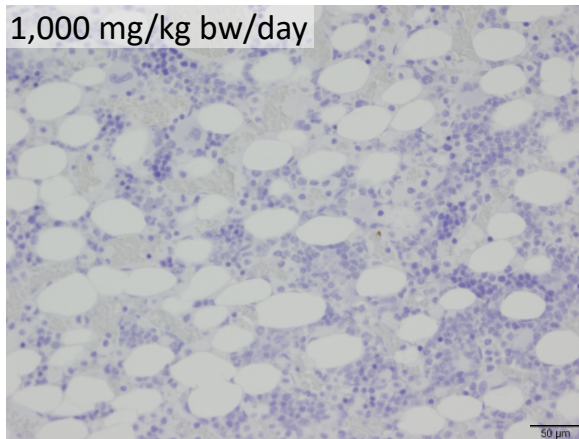


Figure S1. Representative images of immunohistochemical detection of γ -H2AX in the liver (A) and bone marrow (B). No increase in γ -H2AX positive cells was noticed in either organ. Scale bars are 50 μ m.