Titanium dioxide

Toxicological Data on the Unburnt Ingredient

[+ve, positive; -ve, negative; ?, equivocal; with, with metabolic activation; without, without metabolic activation]

In vivo

Species	Test conditions	Endpoint	Results	Reference
Mouse ($B6C3F_{1)}$, 4-5 males/group	Intraperitoneal (i.p.) injection of titanium dioxide (13463-67-7) 0, 0.25, 0.5 or 1 g/kg bw/day for 3 days. Peripheral blood lymphocytes were examined for micronucleated PCEs 48 hr after the last dose.	Chromosome damage	+ve (weak) [A high quality study.]	NTP, 1988
Mouse ($B6C3F_1$), 5 males/group (except trial 2 with 3 mice at the top dose)	Three trials, each involving daily i.p. injection for 3 days. Trial 1: 0, 0.25, 0.5 and 1 g/kg bw/day. Trial 2: 0, 1.5 and 2 g/kg bw/day (only one mouse at top dose – presumably the other two died). Trial 3: 0, 0.5, 1 and 1.5 g/kg bw/day. In each case bone marrow cells were	Chromosome damage	+ve (weak) Some evidence in all three trials. [A high quality study.]	NTP, 1988

	examined for micronucleated PCEs, 24 hr after the final dose.			
Mouse ($B6C3F_1$), 8 males/group	Titanium dioxide (13463-67-7) was given in two trials at 0, 0.625, 1.25 and 2.5 g/kg bw by single i.p. injection. Bone marrow cells were examined for chromosome aberrations 17 or 36 hr after dosing.	Chromosome damage	-ve [A high quality study.]	NTP, 1989
Mouse ($B6C3F_1$), 4 males/group	Titanium dioxide (13463-67-7) was given at 0, 0.625, 1.25 and 2.5 g/kg bw by single i.p. injection; bone marrow cells were scored for SCEs 23 hr after dosing.	Chromosome effects	-ve [A high quality study.]	NTP, 1989
Rat	A single oral dose of 1 g/kg bw was given in an assay for DNA damage. [No further details are given in the citation.]	DNA damage	-ve	Kitchin & Brown, 1989
Rat (Wistar), 30 females/group	A single intratracheal instillation of titanium	DNA damage	-ve	Rehn et al. 2003

	dioxide was given in saline (0.15, 0.3, 0.6 or 1.2 mg) - either P25 (untreated, hydrophilic surface; apparently 80:20 anatase:rutile) or T805 (dispersed, fumed TD, treated with octyl silane to produce a hydrophobic surface). Particle diameter was said to be about 20 nm in each case, though electron transmission microscopy suggested bigger particles, highly aggregated and agglomerated. Lung sections were taken at 90 days and 8-oxoguanidine (an oxidative DNA adduct) quantified by image analysis.			
Rat (Wistar), females	Exposure to titanium dioxide with examination for the formation of DNA adducts in lung tissue.	DNA damage	-ve	Gallagher et al. 1994

	[No further details are given in the citation.]			
Drosophila melanogaster (Canton-S), males	Adult fruit flies were fed a solution containing 0 or 1480 ppm titanium dioxide (13463-67-7) for 3 days, mated with Basc females to produce 3 broods and monitored for the induction of sex-linked recessive lethals.	Mutation	-ve [A high quality study.]	NTPa
Drosophila melanogaster (Canton-S), males	Adults were injected with 0 or 5680 ppm titanium dioxide (13463-67-7) suspension, mated with Basc females to produce 3 broods and monitored for the induction of sex-linked recessive lethals.	Mutation	-ve [A high quality study.]	NTPa
Drosophila melanogaster, males and females	Fruit flies were fed titanium dioxide (13463-67-7) for 2 days at 0, 100 or 300 mM (24 g/l) in the somatic mutation (wing	Mutation	-ve	Tripathy et al. 1990

	spot) assay. [No further details are given in the citations.]			

In vitro

Test system	Test conditions	Endpoint	Activation status	Results	Reference
Mouse lymphoma cells (L5178Y)	Tested at up to 0.05 (with S9) and 0.1 mg/ml (without S9) in duplicate tests. No signs of toxicity.	Mutation	With and without S9	-ve [A high quality study.]	NTPb
Mouse lymphoma, cells (L5178Y)	Various other reports of mouse lymphoma mutation assays are likely to be for the same NTP study as described above.	Mutation	With and without S9	-ve [Probably reports of the same study as above]	Myhr & Caspary, 1991; Shelby & Stasiewicz, 1984; Tennant et al. 1987a,b
Mouse lymphoma cells (L5178Y)	Cells were exposed to titanium dioxide (1317-80-2 21 nm) at seven concentrations (0.25-2 mg/ml) for 1 hr and then exposed to UV/visible light for 50 minutes.	Mutation	Without	-ve	Nakagawa et al. 1997
Human bronchial cells (BEAS-2B)	Cells were exposed to anatase and rutile particles of different sizes at 10 μg/ml. In the Comet assay (evaluating DNA damage) rutile of 200 nm and anatase of 10, 20, 200 and >200 nm were used. The potential for induction of micronuclei	DNA damage Chromosome damage	Without	DNA damage: +ve [10 and 20 nm anatase, 200 nm rutile.] Chromosome damage: +ve [10 and 200 nm anatase.]	Gurr et al. 2005

	(chromosome damage) was examined by incubation with 200 nm rutile or 10, 200 or >200 nm anatase for 24 hr.				
Chinese hamster ovary cells	Titanium dioxide (13463-67-7) was tested at up to 25 µg/ml for 2 hr (with S9) or 8 hr (without S9). The cells were harvested at 10.5 hr (without S9) or 12.5 hr (with S9) and scored for chromosome aberrations.	Chromosome damage	With and without S9	-ve (Equivocal result in 1st trial with S9, repeat trial was clean.) [A high quality study.]	NTP, 1985
Chinese hamster ovary cells	In the same study titanium dioxide (13463-67-7) was tested at up to 25 µg/ml for 2-hr (with S9) or 26 hr (without S9) and the cells scored at 28 hr for sister chromatid exchanges (SCE).	Chromosome effects	With and without S9	-ve [A high quality study.]	NTP, 1985
Chinese hamster ovary cells	Various other reports on the ability of titanium dioxide to induce chromosome aberrations or sister chromatid exchanges (SCEs) are likely to be for the same NTP studies as described above.	Chromosome damage and effects	With and without S9	-ve [Probably the same studies as described above.]	Ivett et al. 1989; Shelby & Stasiewicz, 1984; Tennant et al. 1987a,b
Chinese hamster cells (CHL/IU)	Cells were exposed to titanium dioxide (1317-80-2 21 nm)	Chromosome damage	Without	-ve without irradiation	Nakagawa et al. 1997

	at six concentrations (25-800 μg/ml) for around 2 hr, with examination for chromosome aberrations after a further 20-hr incubation. [Parallel tests were also conducted (at 0.78-50 μg/ml) with exposure to UV/visible light for 50 minutes.]			+ve with irradiation	
Syrian hamster embryo fibroblast cells	In a study comparing effects of particle size, cells were incubated with up to 10 μg/ml fine (>200 nm) or ultrafine (<20 nm) particles for 12-72 hr, and examined for micronucleus induction.	Chromosome damage	Without	+ve for ultrafine particles -ve for fine particles	Rahman et al. 2002
Chinese hamster ovary cells (K1)	Incubation with 0, 1, 2 or 5 μM (≤0.4 mg/l) titanium dioxide (13463-67-7) for 24 hr, with examination for the induction of sister chromatid exchanges (SCEs). Incubation with 0-20 μM (≤1.6 mg/l) for 18 hr in the standard micronucleus assay or 24 hr in the cytokinesis-block micronucleus assay. In each case	Chromosome damage and effects	Without	+ve (Dose-dependant increase in SCE frequency. Slight (but statistically significant) increase in micronuclei in the standard assay. Greater increase in the cytokinesis-block micronucleus assay.)	Lu et at. 1998

	titanium dioxide was added to the culture medium having been suspended in DMSO. No titanium dioxide precipitate was seen at up to 10 μM in culture, but no comment is made for any higher concentration.				
Chinese hamster ovary cells (K5)	Cells were exposed to titanium dioxide (13463-67-7) at 0.025-10 μg/ml (-S9) or 0.25-10 μg/ml (+S9) for 48 hr, with examination for the induction of micronuclei. The difficulty dissolving titanium dioxide was noted and precipitation was reported at ≥0.5 μg/ml (-S9) and ≥ 1 μg/ml (+S9).	Chromosome damage	With and without S9	-ve [Limited solubility would have reduced the concentration to which cells were exposed.]	Miller et al. 1995
Rat liver epithelial cells	Two ultrafine titanium dioxide preparations (1317-70-0, uncoated and 1317-80-2, coated with aluminium hydroxide and stearic acid; both 20 nm) and one pigment grade titanium dioxide (1317-70-0, 170 nm) were tested at 5, 10 and 20 μg/ml with and	Chromosome damage	Without	-ve (with and without irradiation)	Linnainmaa et al. 1997

	without UV irradiation. Cells were examined for the induction of micronuclei.				
Mouse lymphoma cells (L5178)	Cells were exposed to titanium dioxide (1317-80-2 particle size 21 and 255 nm, and 1317-70-0 particle size 255 and 420 nm) at four or five concentrations in the range 3-3200 μg/ml, for around 2 hr, in a single cell gel assay for DNA damage. [Parallel tests were also conducted with exposure to UV/visible light for 50 minutes.]	DNA damage	Without	+ve (1317-80-2, 255 nm caused a dose-dependant increase in mean tail length without irradiation. When irradiated, positive results were reported for all samples except 1317-70-0, 255 nm.)	Nakagawa et al. 1997
Rat liver cells	Hepatocytes were incubated with titanium dioxide (13463-67-7), and then examined for unscheduled DNA synthesis.	DNA damage (indicative test)	N/A	-ve	Tennant et al. 1987b
Hamster cells	A test for DNA damage. [No further details are given in the citations.]	DNA damage	Not stated in the citations	-ve	Poole et al. 1986
Human embryonic lung fibroblasts	Titanium dioxide was tested for the incorporation of tritiated thymidine in a test for DNA damage.	DNA damage (indicative test)	Without	-ve	Lemaire et al. 1982
Syrian hamster cells	Cell transformation assays were	Cell transformation	Not stated in	-ve	DiPaolo & Casto, 1979;

	conducted to determine whether cells exposed to titanium dioxide more closely resemble a cancerous state. [No further details are given in the citations.]		the citations		Mikalsen et al. 1988
Hamster cells (SA7/SHE)	Cell transformation, viral enhanced.	Cell transformation	Not stated in the citation	-ve	Heidelberger et al. 1983
Salmonella typhimurium strains TA97, TA98, TA100 and TA1535	Titanium dioxide (13463-67-7) was tested in an Ames test, including a preincubation step, at up to 10 mg/plate. Solubility was exceeded at 1 mg/plate.	Mutation	With and without S9 derived from rat and hamster liver	-ve [A high quality study.]	NTP, 1984; Zeiger et al. 1988
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA	Titanium dioxide was tested in an Ames test, including a preincubation step, at up to 5 mg/plate.	Mutation	With and without S9	-ve	JCIETIC
Salmonella typhimurium strains TA97 and TA102	Titanium dioxide was tested in an Ames test, including a preincubation step, at up to 1 mg/plate.	Mutation	With and without S9	-ve [Limited study; at least 4 strains are currently recommended.]	Fujita et al. 1994
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 TA1538 and	Titanium dioxide (13463-67-7) was tested in the Ames test in four laboratories at a dose range that did not exceed	Mutation	With and without S9 derived from rat, hamster	-ve	Dunkel et al 1985

Escherichia coli (WP2uvrA)	10 mg/plate [no further details are given].		and mouse liver		
Salmonella typhimurium 4-5 strains	Titanium dioxide (13463-67-7) was tested in the Ames test at up to 10 μg/plate.	Mutation	With and without S9	-ve [Probably the same as NTP, 1984]	Tennant et al. 1987a,b
Bacillus subtilis	Rec assay	DNA damage (indicative test)	No data given in the citations	-ve	Kada et al. 1980; Kanematsu et al. 1980
Salmonella typhimurium strains TA98, TA100 and TA102	Titanium dioxide (1317-80-2 21 nm) was tested at 5, 10, 20 and 40 mg/ml with or without exposure to UV/visible light for 10 or 50 minutes. Revertants were scored after incubation for 48 hr.	Mutation	Without	-ve (with and without irradiation)	Nakagawa et al. 1997

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