

Titanium dioxide: Human health tier II assessment



01 July 2016

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Anatase (TiO ₂)	1317-70-0
Rutile (TiO ₂)	1317-80-2
Titanium oxide (TiO ₂)	13463-67-7

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit: www.nicnas.gov.au

Disclaimer

NICNAS has made every effort to assure the quality of information available in this report. However, before relying on it for a specific purpose, users should obtain advice relevant to their particular circumstances. This report has been prepared by NICNAS using a range of sources, including information from databases

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ACRONYMS & ABBREVIATIONS

Grouping Rationale

These chemicals are polymorphs (forms with different crystalline structures) of titanium dioxide. The most commonly occurring polymorph is rutile (CAS No. 1317-80-2), followed by anatase (CAS No. 1317-70-0), with brookite (no CAS No. and is not specifically listed on AICS) being less common. Unspecified titanium dioxide is assumed to be in the form of rutile, anatase or mixed forms.

The polymorphs of titanium dioxide can contain various primary particle sizes, including primary particles ≤ 100 nm, mostly present as agglomerates or aggregates. This assessment does not specifically address any health hazards anticipated from the nanomaterials (with particle sizes ≤ 100 nm and intentionally produced) of titanium dioxide, which are captured under the NICNAS working definition for industrial nanomaterials (<http://www.nicnas.gov.au/communications/issues/nanomaterials-nanotechnology/nicnas-working-definition-for-industrial-nanomaterial>), as risk assessment of nanomaterials is out of scope for applying the IMAP Framework. However, pigment-grade titanium dioxide is expected to have a fraction of primary particles ≤ 100 nm, which are not intentionally produced (Warheit, 2013).

When the polymorphic form of the chemical is not specifically stated, the chemical name 'titanium dioxide' may represent all three chemicals in this report.

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported for titanium dioxide and rutile under previous mandatory and/or voluntary calls for information. No specific information was reported for anatase.

Titanium dioxide has reported cosmetic use.

Titanium dioxide and rutile have one or more of the following reported domestic uses including in:

- colouring agents;
- paints (white pigment and opacifying agent);
- fillers; and
- adhesives (binding agents).

Titanium dioxide and rutile have reported commercial uses, including as additives in construction materials.

Titanium dioxide has reported site-limited use as stabilisers.

Titanium dioxide and rutile are listed on the 2006 High Volume Industrial Chemicals List (HVICL) with total reported volumes up to 1,000,000 tonnes for titanium dioxide and <1,000 tonnes for rutile.

Titanium dioxide has reported non-industrial use in sunscreens (Therapeutic Goods Administration—TGA).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation and Authorization and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset Initial Assessment Profile (SIAP); the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US Department of Health and Human Services, Household Products Database and various international assessments (KEMI, 2010).

Titanium dioxide (CAS No. 13463-67-7) has reported cosmetic uses:

- as a colourant (in cosmetics, toothpaste, sunscreen);
- as a light stabiliser;
- as an opacifying agent;
- in sunscreens;
- in personal care products (up to 30 % concentration); and
- as a carrier for dyes used in tattoo inks.

Titanium dioxide, anatase and rutile have one or more of the following reported domestic uses, including:

- in adhesives (binding agents);
- in surface treatments (0.1–15 % concentration in aerosol products);
- in cleaning/washing agents;
- as insulating materials;
- in odour agents;
- in paints, lacquers and varnishes and as colouring agents (e.g. rutile (high opacity pigments) and titanium dioxide are used as white pigments in white and pale coloured plastics, inks, ceramics, porcelain, vitreous enamels, paints, enamels, lacquers, paper, fibres and fabrics);
- in corrosion inhibitors; and
- in fillers.

Titanium dioxide, anatase and rutile have one or more of the following reported commercial uses, including in:

- construction materials;
- cutting fluids;
- photo chemicals and as reprographic agents;
- flame retardants and as extinguishing agents;
- grinding materials;
- impregnation materials;
- anti-set-off and anti-adhesive agents;
- welding and soldering agents (e.g. rutile sand is used for welding-rod-coating materials);
- pH-regulation agents;
- process regulators;
- absorbents and adsorbents;
- solvents;
- lubricants and additives.

Titanium dioxide, anatase and rutile have one or more of the following reported site-limited uses, including:

- as stabilisers;
- as intermediates in manufacturing acid resistant vitreous enamels, in specification paints, exterior paints and in acetate rayon;
- in electroplating agents;
- in complexing and flocculating agents; and
- as a source for titanium metal.

Titanium dioxide, anatase and rutile have one or more of the following non-industrial uses, including in:

- food/feedstuff flavourings and nutrients;
- agricultural and non-agricultural pesticides;
- preservatives; and
- pharmaceuticals.

Restrictions

Australian

No known restrictions have been identified for the chemicals.

International

The chemicals are listed on the following (CosIng):

EU Cosmetics Regulation 1223/2009 Annex VI— List of UV filters allowed in cosmetic products— maximum concentration in ready for use preparation $\leq 25\%$ (w/w).

Titanium dioxide (CAS No. 1343-67-7) under the name white pigment CI 77891 is used as a cosmetic colourant and is specifically listed under Annex IV— List of colourants allowed in cosmetic products.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

Titanium dioxide has an exposure standard of 10 mg/m^3 time weighted average (TWA) (Safe Work Australia).

International

The following exposure standards are identified for titanium dioxide (Galleria Chemica):

Exposure limits of $3\text{--}6 \text{ mg/m}^3$ TWA in different countries such as Denmark, Estonia, Iceland, Norway, Sweden and Switzerland.

Exposure limits of 10 mg/m^3 TWA in different countries such as Canada, the United States of America (USA), the United Kingdom, France, Latvia, Spain and Poland.

Health Hazard Information

This report used toxicological data available for titanium dioxide (CAS number, polymorph composition or primary particle size not stated in most studies), which may contain a range of primary particle sizes. However, some studies conducted using the chemicals as primary particles $\leq 100 \text{ nm}$ have also been included where relevant (e.g. to further support a negative conclusion for particles $> 100 \text{ nm}$).

Toxicokinetics

Titanium dioxide has low water solubility and is insoluble in hydrochloric acid (OECD, 2013) and, therefore, is expected to have low bioavailability from all routes of exposure.

Groups of rats ($n = 3/\text{sex}/\text{dose}$) exposed for seven days to diets containing four forms of titanium dioxide (platelet forms of thick and thin rutile and amorphous forms of rutile and anatase) equivalent to 30 mg/kg bw showed similarly low absorption levels. The main route of excretion was through faeces for all forms (OECD, 2013).

An inhalation study in male rats exposed to aerosols of anatase ($16.5 \pm 1.7 \text{ mg/m}^3$, mass median aerodynamic diameter (MMAD) = $1 \mu\text{m}$) or rutile ($19.3 \pm 3.1 \text{ mg/m}^3$, MMAD = $0.83 \mu\text{m}$) for seven hours showed similar levels of the chemical retained in the lungs on days 1, 8, 27 and 132 post exposure (OECD, 2013).

Inhaled titanium dioxide was found to deposit in the lungs of rats, with a small fraction translocated to local lymph nodes and interstitial spaces. However, smaller particles tended to have a longer retention time in the lung and greater interstitial translocation compared with larger particles. Following particle inhalation, clearance from the lungs can be impaired under particle overload conditions (NICNAS, 2013).

Acute Toxicity

Oral

Titanium dioxide has low acute oral toxicity based on results from animal tests.

The median lethal dose (LD50) for titanium dioxide was reported to be $>5000 \text{ mg/kg}$ bw in Sprague Dawley (SD) rats and Charles River (CD-1) mice, in two studies conducted according to the OECD test guidelines (TG) 420 and 425, respectively. The studies reported neuron vacuoles in the hippocampus, hydropic degeneration and necrosis in mouse liver cells; and grey coloured faeces in rats (OECD, 2013; REACH).

Another study (OECD TG 401) reported an LD50 >2000 mg/kg in SD rats. No signs of toxicity were reported.

Dermal

No acute dermal toxicity data are available to derive an LD50 value for the chemicals. However, the chemicals are considered to have low acute dermal toxicity.

The insoluble chemical particles are not expected to sufficiently penetrate through the skin, to cause systemic toxicity effects.

To further support low acute dermal toxicity of titanium dioxide, dermal penetration studies on titanium dioxide nanoparticles indicated that they do not reach viable skin cells (NICNAS, 2012; SCCS, 2013; TGA, 2013).

Inhalation

Titanium dioxide has low acute inhalation toxicity based on results from animal tests.

The median lethal concentrations (LC50) were reported to be >3.43 mg/L (56 % particle size <3.5 µm, mass median aerodynamic (MMAD) diameter = 3.2 µm) and >5.09 mg/L (20 % particle size <3.5µm, MMAD = 7.0 µm) in male and female rats, respectively. No signs of toxicity were reported. However, gross pathology showed mottled and pale lungs in some test animals (OECD, 2013; REACH).

Corrosion / Irritation

Skin Irritation

The chemicals are not expected to be irritating to the skin.

Two skin irritation studies (OECD TG 404) conducted using titanium dioxide in New Zealand White rabbits indicated that the chemical was non-irritating (zero Draize scores for erythema and oedema) or slightly irritating (slight/mild erythema and no oedema) to the skin (OECD, 2013; REACH).

Titanium dioxide particles ~100 nm (consisting of 21 % anatase and 79 % rutile) were also reported as not irritating to the skin of rabbits (NICNAS, 2012; SCCS, 2013).

Eye Irritation

The chemicals are not expected to be irritating to the eyes.

Three eye irritation studies (OECD TG 405) conducted using titanium dioxide in New Zealand White rabbits indicated that the chemical was non-irritating (conjunctival redness score of 1 or 2 at one and 24 hours examination but reversible by 24 or 48 hours after instillation in one study) to the eyes (OECD, 2013; REACH).

Titanium dioxide particles ~100 nm caused mild eye irritation (transient and reversible conjunctival redness) in rabbits (NICNAS, 2012; SCCS, 2013).

Information available suggests that eye effects could be due to mechanical irritation from the insoluble particles.

Observation in humans

Titanium dioxide in sunscreens at high concentrations over a long period has not been associated with any reporting of human skin irritation.

Sensitisation

Respiratory Sensitisation

Titanium dioxide may possibly increase respiratory sensitisation to other allergens based on results from animal tests. However, there is insufficient evidence for hazard classification.

In a non-guideline study, pregnant and non-pregnant female mice were exposed (via intranasal application) to ovalbumin (OVA) alone or OVA co-administered with titanium dioxide at 50 µg on day 14 of gestation or equivalent age. Neonates were challenged with a 3 % OVA aerosol on day four after birth. Pregnant mice were reported to have a higher level of respiratory sensitisation than non-pregnant mice. Treatment-related effects reported in offspring included increased airway hyper-responsiveness and allergic inflammation with increased allergic susceptibility (OECD, 2013).

Nanoparticles of titanium dioxide (14–29 nm primary particles) also increased pulmonary inflammation, sensitisation to allergens in mice (de Haar et al., 2006; Larsen et al., 2009) and triggered an asthmatic response in sensitised mice (Hussain et al., 2011). However, similar results were also reported with other fine particles and, therefore, these effects may not be specific to titanium dioxide (Granum et al., 2001).

Skin Sensitisation

The chemicals are not expected to be skin sensitisers.

In two skin sensitisation studies (a Buehler test in guinea pigs (OECD TG 406) and a mouse local lymph node assay—LLNA equivalent to OECD TG 429), titanium dioxide was not found to induce dermal sensitisation. Stimulation indices < 3 were reported in the LLNA at all test concentrations up to 100 % (OECD, 2013; REACH).

Observation in humans

Titanium dioxide used in sunscreens at high concentrations over a long period has not been associated with reporting of human skin sensitisation.

Repeated Dose Toxicity

Oral

The chemicals are not expected to cause serious damage to health from repeated oral exposure based on results from 28-day animal tests using titanium dioxide.

Two 28-day repeated dose oral studies (OECD TG 407) reported no significant treatment-related effects when titanium dioxide was administered to rats (n = 5/sex/dose) at concentrations of 250, 500 or 1000 mg/kg bw/day in one study; and at 24000 mg/kg bw/day in the second study. In the first study, liver and thymus weight changes, effects on some haematological and clinical chemistry parameters and coloured faeces were observed at all doses, but were not considered to be toxicologically significant. The no observed adverse effect levels (NOAELs) were reported to be the highest doses tested (1000 mg/kg bw/day and 24000 mg/kg bw/day), as there were no adverse treatment-related effects observed in either study (OECD, 2013).

No 90-day repeated dose oral toxicity studies are available.

Dermal

No data are available for the chemicals.

Inhalation

These chemicals may cause serious damage to health from repeated inhalation exposure. However, most adverse effects were due to lung overload and impaired lung clearance mechanisms, but at doses within the hazard classification range under both the HSIS Approved Criteria and the GHS. As the available information is insufficient to conclude if the intrinsic properties of the chemical caused adverse health effects, hazard classification is not warranted. If any further information becomes available to indicate severe effects from the intrinsic properties of the chemical, a further assessment may be required.

A study of CD male rats were exposed to titanium dioxide dust at concentrations of 5, 50 or 250 mg/m³ (with a MMAD of 1.9, 1.7 and 1.4 µm, respectively) for four weeks and examined for a further six months post-exposure. Persistent pulmonary effects such as inflammation and macrophage aggregation were observed throughout the six-month observation period at the 250 mg/m³ dose (Warheit et al., 1997). The study concluded that 'large dust burdens of low toxicity, low solubility dusts in the lungs of exposed rats can result in a cascade of factors which ultimately lead to a spectrum of pulmonary lesions, including pulmonary fibrosis and pulmonary tumours unique to rats,' (Warheit et al., 1997).

In a repeated dose inhalation study, Fischer 344 (F344) rats (n = 65 females/dose) were exposed (whole body inhalation for 13 weeks with a 52 week recovery period) to titanium dioxide (rutile; 1.44 µm MMAD) at concentrations of 0, 10, 50 or 250 mg/m³. There was reported pulmonary overload in rats at the 50 and 250 mg/m³ doses (inflammation was also observed at these doses, where inflammatory responses were elevated during post-exposure recovery period in the highest dosed group). The no observed adverse effect concentrations (NOAEC) were reported to be 10 mg/m³ based on systemic effects including inflammatory responses in the lung, lung-associated lymph node burdens and pulmonary lesions at doses ≥50 mg/m³ (OECD, 2013; REACH).

In a two-year inhalation study, CD rats were exposed to titanium dioxide (1.5-1.7 µm MMAD) at concentrations of 0, 10, 50 and 250 mg/m³ for six hours/day, five days/week. A dose-dependent increase in collagenised fibrosis in the lungs of rats exposed to titanium dioxide at 50 and 250 mg/m³ was observed, but no increase at 10 mg/m³ compared with the controls. The study concluded that 'the pulmonary response at 10 mg/m³ satisfied the biological criteria for a "nuisance dust" (Lee et al., 1985).

A 24-month inhalation study in F344 rats (n = 50/sex/dose) was conducted to evaluate the fibrogenic potency of a toner chemical using titanium dioxide (99.5 % rutile; 1.1µm MMAD at a concentration of 5 mg/m³) as the negative control. The comparative fibrogenic potency was reported to be 1 : 5 : 418 for titanium dioxide, a toner chemical and silicon dioxide, respectively (Muhle et al., 1991).

There is some evidence that inhaling large quantities of titanium dioxide nanoparticles over a long period may also cause adverse health effects such as chronic inflammation, pulmonary damage, fibrosis, and lung tumours due to impairment of normal lung clearance mechanism (NICNAS, 2012; SCCS, 2013).

Genotoxicity

Mixed results were reported for titanium dioxide in both in vitro and in vivo genotoxicity assays. Although the results were mostly negative, one in vivo assay reported significantly increased hprt (hypoxanthine-guanine phosphoribosyl transferase) mutations in alveolar type II cells of rats that received titanium dioxide at 100 mg/kg bw, but not at the 10 mg/kg bw (IARC, 2010). The weight of evidence from the available studies indicates that the chemicals are not genotoxic.

The following in vitro genotoxicity assays are available for titanium dioxide (IARC, 2010; OECD, 2013; REACH):

- negative results for bacterial mutation assays in various *Salmonella typhimurium* strains and one *Escherichia coli* strain, with or without metabolic activation;
- a negative result for *Bacillus subtilis* recombination assay (doses up to 0.5 M) without metabolic activation;
- a negative result for chromosomal aberrations in Chinese hamster ovary (CHO) cells and human lymphocyte assays with or without metabolic activation (doses up to 800 µg/mL and 100 µg/mL, respectively);
- a negative result for gene mutation assays in mouse lymphoma cells with or without metabolic activation (doses up to 500 µg/mL);
- positive results for micronucleus tests in human peripheral blood lymphocytes (doses up to 10 µg/mL) and CHO-K1 cells (doses up to 20 µg/mL) without metabolic activation; negative results for micronucleus test in CHO-K5 cells (doses up to 10 µg/mL) with or without metabolic activation; and
- positive results for sister chromatid exchange assays in CHO-K1 cells (doses up to 5 µg/mL) and human peripheral blood lymphocytes (doses up to 10 µg/mL) without metabolic activation; negative result for sister chromatid exchange assay in CHO cells (doses up to 25 µg/mL) without or without metabolic activation.

Titanium dioxide gave mostly negative results in several in vivo genotoxicity assays (non-guideline) which included the following (OECD, 2013):

- a negative result for inducing bone marrow chromosomal aberrations in mice at doses up to 2500 mg/kg bw;
- a negative result for micronuclei induction in mice at doses up to 1500 mg/kg bw;
- significantly increased mutation frequency in alveolar type II cells for a hprt gene mutation assay in rats dosed at 100 mg/kg bw, but not at 10 mg/kg bw; and
- a negative result for a sex-linked recessive lethal test in *Drosophila melanogaster* (doses up to 5680 ppm).

Potential to cause DNA damage has been clearly demonstrated for some titanium dioxide nanomaterials (SCCS, 2013).

Carcinogenicity

Based on the information available, titanium dioxide is not considered to be carcinogenic due to its intrinsic properties. However, particle overload conditions in the lung impairing the clearance mechanism have shown to induce specific lung tumours in rats. The intrapulmonary particle retention patterns and tissue reactions in rats were considered not predictive of these patterns/reactions in primates exposed to poorly soluble particles at high concentrations (Warheit and Frame, 2006). If new data become available, a further assessment may be required to assess the potential for carcinogenicity.

Based on reports in some rodent studies of increased lung tumours after inhalation of titanium dioxide (range of crystalline structures and ultra fine to fine particle sizes: 50 nm to 1.5 µm), the International Agency for Research on Cancer (IARC) has classified titanium dioxide and related polymorphs as 'Possibly carcinogenic to humans (Group 2B)', based on inadequate evidence in humans and limited evidence in animals (IARC, 2010).

Two inhalation studies were conducted in rats with exposure to titanium dioxide (rutile; 1.1–1.7 µm MMAD) dust (whole body) or dry aerosol (whole body) for two years. The treatment-related effects in one study (dust exposure) included bronchioalveolar adenomas, squamous metaplasias, pulmonary keratin cysts and squamous cell carcinoma observed at the 250 mg/m³, but the effects were reported to be secondary to particle overload due to an impaired clearance mechanism of the lung. No treatment-related lung tumours were observed at 10 or 50 mg/m³ (Lee et al., 1985; OECD, 2013). The other study (OECD TG 453) showed no difference in the incidence of lung tumours in treated rats (dry aerosol exposure at 5 mg/m³ - the only dose tested) compared with the control group (OECD, 2013).

A further microscopic review has been conducted on proliferative squamous lesions that were diagnosed as cystic keratinizing squamous cell carcinoma in the lungs of rats exposed to pigment grade titanium dioxide for two years (see above). The review concluded that 'These keratin cysts are a species-specific lesion that is unique to the rat lung under conditions of particle overload exposure' (Warheit and Frame, 2006). The intrapulmonary particle retention patterns and tissue reactions in rats were considered not predictive of this effect in primates exposed to poorly soluble particles at high concentrations.

Carcinogenicity studies in rats and mice showed no treatment-related tumour effects from titanium dioxide, when administered in the diet at doses up to 50000 ppm (equivalent to 6500 mg/kg bw/day in mice and 2500 mg/kg bw/day in rats) for 103 weeks (OECD, 2013).

Reproductive and Developmental Toxicity

The chemicals are not expected to have reproductive or developmental toxicity.

In a reproductive and developmental study (OECD TG 421), titanium dioxide was administered by oral gavage doses to SD rats (n = 10/sex) two weeks before mating to the end of the mating period in males, and from two weeks before mating to day three of lactation including the gestation period in females. No treatment-related adverse effects on reproductive and developmental parameters were observed at doses up to 1000 mg/kg bw/day. The NOAEL was stated as 1000 mg/kg bw/day for reproductive and developmental toxicity (OECD, 2013; REACH).

Risk Characterisation

Critical Health Effects

The chemicals in this group are considered non-hazardous. However, when inhaled in large quantities (under lung overload conditions) for long periods of time, adverse health effects can be expected (refer to **Repeated dose toxicity: Inhalation** section).

Public Risk Characterisation

Cosmetics and sunscreens used by the public will allow exposure through dermal (e.g. body lotions) and inhalation (e.g. cosmetic powders) routes. Limited incidental oral exposure is also possible. However, given the low bioavailability and low toxicity of the chemicals, significant risks are not expected. Hence, the public risk from use of these chemicals is not considered to be unreasonable.

Occupational Risk Characterisation

Based on the available data, the chemicals are not likely to be hazardous to human health. The current exposure standard for titanium dioxide is considered adequate to protect workers from lung overload conditions and should be applicable to all the chemicals in this group. Therefore, the chemicals are not considered to pose an unreasonable risk to the health of workers.

The US National Institute for Occupational Safety and Health (NIOSH) recommends airborne exposure limits of 2.4 mg/m³ TWA for fine (≥ 100 nm) of titanium dioxide, based on chronic inhalation studies in rats (refer to **Repeated dose toxicity: Inhalation** section) used to predict lung tumour risks in humans (NIOSH, 2011). The differences between rats and humans, with respect to particle deposition in the alveolar region, should also be considered and quantified in an exposure standard (NIOSH, 2011, Safe Work Australia, 2012). In the absence of further data, this exposure standard cannot be supported.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory.

The chemicals are not recommended for classification and labelling under the current approved criteria and adopted GHS. The current exposure standard is considered adequate to protect workers from lung overload conditions and should be applicable to all the chemicals in this group. This does not consider classification of physical hazards and environmental hazards.

Further assessment of these chemicals may be necessary if new hazard data become available specifically on carcinogenicity and/or repeated dose inhalation toxicity.

Regulatory Control

Work Health and Safety

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction. Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemicals has not been undertaken as part of this assessment.

References

ChemIDPlus Advanced. Accessed April 2015 at <http://chem.sis.nlm.nih.gov/chemidplus/>

Cosmetic Ingredients and Substances (CosIng). Accessed April 2015 at <http://ec.europa.eu/consumers/cosmetics/cosing/>

de Haar C, Hassing I, Bol M et al. 2006. Ultrafine but not fine particulate matter causes airway inflammation and allergic airway sensitisation to co-administered antigen in mice. *Clin Exp Allergy* 36:1469-79.

Galleria Chemica. Accessed April 2015 at <http://jr.chemwatch.net/galleria/>

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Granum B, Gaarder PI, Groeng E et al. 2001. Fine particles of widely different composition have an adjuvant effect on the production of allergen-specific antibodies. *Toxicol Lett* 118:171-81.

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed April 2015 at <http://toxnet.nlm.nih.gov>

Hussain S Vanoirbeek JA, Luyts K et al. 2011. Lung exposure to nanoparticles modulates an asthmatic response in a mouse model. *Eur Respir J* 37:299-309.

International Agency for Research on Cancer (IARC) 2010. Carbon Black, Titanium Dioxide, and Talc, IARC Monographs Volume 93. Accessed at <http://monographs.iarc.fr/ENG/Monographs/vol93/mono93.pdf>

KEMI, Swedish Chemical Agency 2010. KEMI Report 3/10: Hazardous substances in tattoo inks, Accessed April 2015 at http://www.kemi.se/Documents/Publikationer/Trycksaker/Rapporter/Rapport3_10.pdf

Larsen ST, Roursgaard M, Jensen KA et al. 2009. Nano titanium dioxide particles promote allergic sensitization and lung inflammation in mice. *Basic Clin Pharmacol Toxicol* 106:114-7.

Lee KP, Trochimowicz HJ and Reinhardt CF. 1985. Pulmonary Responses of Rats Exposed to Titanium Dioxide (TiO₂) by Inhalation for Two Years. *Toxicol Appl Pharmacol* 79:179-92

Muhle H, Bellmann B, Creutzenberg O et al. 1991. Pulmonary response to toner upon chronic inhalation exposure in rats. *Fundam Appl Toxicol* 17:280-99

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2012. Nano Titanium dioxide Health Hazard Review Technical Information Sheet. Available at <http://www.nicnas.gov.au/communications/issues/nanomaterials-nanotechnology/nicnas-technical-activities-in-nanomaterials/nano-titanium-dioxide-human-health-hazard-review>

NICNAS 2006. Australian High Volume Industrial Chemicals List (AHVICL). Accessed February 2015 at http://www.nicnas.gov.au/_data/assets/pdf_file/0019/6661/NICNAS_AHVICL_2006_PDF.pdf

Organisation for Economic Cooperation and Development (OECD) 2013. SIDS Initial Assessment Profile (SIAP) on Titanium dioxide (CAS No. 13463-67-7). Accessed April 2015 at <http://webnet.oecd.org/Hpv/UI/handler.axd?id=1f6be49d-48b6-4909-8e0d-a6f5e48503d3>

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. 13463-67-7. Accessed May 2015 at <http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances>

Safe Work Australia (SWA). Approved Criteria for Classifying Hazardous Substances, 3rd Edition [NOHSC: 1008 (2004)]. Accessed January 2015 at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed March 2015 at <http://hsis.safeworkaustralia.gov.au/HazardousSubstance>.

Safe Work Australia 2012. Guidance on the interpretation of workplace exposure standards for airborne contaminants. Accessed March 2015 at <http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/interpretation-airborne-contaminants-guide>

Scientific Committee on Consumer Safety (SCCS) 2013. Opinion on Titanium Oxide (nano-form). Adopted by written procedure on 22 July 2013. Accessed April 2015 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_136.pdf

Substances in Preparations in Nordic Countries (SPIN). Accessed January 2015 at <http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx>

Therapeutic Goods Administration (TGA) 2013. Sunscreens: information for consumers. Accessed May 2015 at <https://www.tga.gov.au/community-qa/sunscreens-information-consumers>

US Department of Health and Human Services, Household Products Database, Health and safety information on household products. Accessed June 2014 at <http://householdproducts.nlm.nih.gov/>

US National Institute for Occupational Safety and Health (NIOSH) 2011. Occupational Exposure to Titanium Dioxide. Accessed March 2015 at <http://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf>

Warheit DB 2013. How to measure hazards/risks following exposures to nanoscale or pigment-grade titanium dioxide particles. *Toxicol Lett* 220:193-04

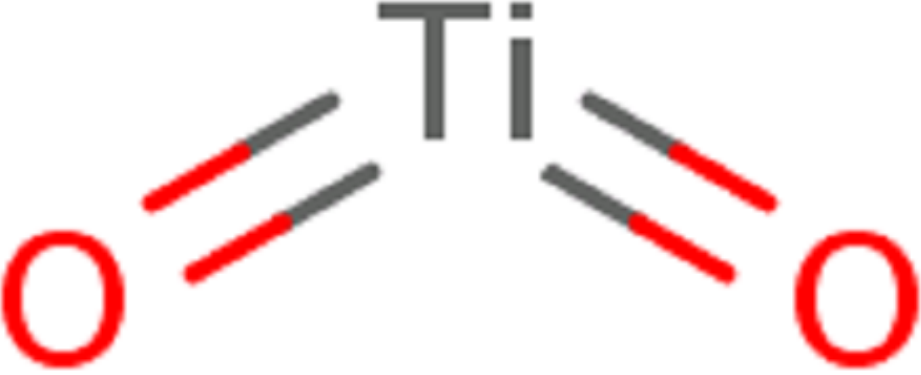
Warheit DB and Frame SR 2006. Characterization and reclassification of TiO₂-related pulmonary lesions. *J Occup Env Med* 48:1308-13

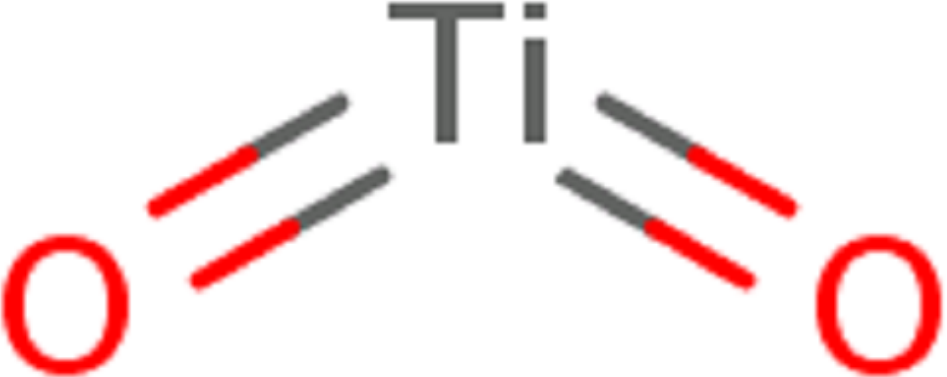
Warheit DB, Hansen JF, Yuen IS et al. 1997. Inhalation of High Concentrations of Low Toxicity Dusts in Rats Results in Impaired Pulmonary Clearance Mechanisms and Persistent Inflammation. *Toxicol Appl Pharmacol* 145:10-22

Last Update 01 July 2016

Chemical Identities

Chemical Name in the Inventory and Synonyms	Anatase (TiO₂) titanium dioxide C.I. pigment white 6 tioxide A-HR octahedrite
CAS Number	1317-70-0
Structural Formula	

	
Molecular Formula	O2Ti
Molecular Weight	79.87

Chemical Name in the Inventory and Synonyms	Rutile (TiO₂) titanium dioxide austiox R-CR JR 600A sagenite unitane
CAS Number	1317-80-2
Structural Formula	
Molecular Formula	O2Ti
Molecular Weight	79.87

Chemical Name in the Inventory and Synonyms	Titanium oxide (TiO₂) titanium dioxide CI 77891 pigment white 6 C.I. pigment white 6
CAS Number	13463-67-7
Structural Formula	



Molecular Formula	O ₂ Ti
Molecular Weight	79.87

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