Titanium Dioxide (CAS #13463-67-7) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Washington State Department of Ecology

Prepared by:

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TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for Titanium Dioxide (CAS #13463-67-7)

Titanium dioxide is a chemical that functions as a pigment in coated fabrics, delustering agent in synthetic fiber, pigments in a variety of mediums, shrinking agent for glass fiber, sub-coating in confectionary panned goods & icings, medication, and cosmetics.

Inhalation: Titanium dioxide was assigned a GreenScreen® Benchmark Score of 1 ("Avoid-Chemical of High Concern") as it has Very High persistence (P) and High Group I Human Health hazard (carcinogenicity (C)) and High Group II* Human Health hazard (repeated dose systemic toxicity (STr*)). This corresponds to GreenScreen® benchmark classifications 1c ("vPT = very High P + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]") and 1e ("High T (Group I Human)") in CPA 2011, 2012a. Data gaps (DG) exist for endocrine activity (E), single and repeated dose neurotoxicity (Ns and Nr*), and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), titanium dioxide meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gaps. In a worst-case scenario, if titanium dioxide were assigned a High or Very High score for the data gaps endocrine activity (E), single and repeated dose neurotoxicity (Ns and Nr*), and respiratory sensitization (SnR*), it would still be categorized as a Benchmark 1 Chemical.

Oral: Titanium dioxide was assigned a GreenScreen® Benchmark Score of 3 ("Use but Still Opportunity for Improvement") as it has Moderate Group II Human Health hazard (single dose systemic toxicity (STs) and eye irritation (IrE)). This corresponds to GreenScreen® benchmark classification 3c ("Moderate T (Group II or II*") in CPA 2011, 2012a. Data gaps (DG) exist for endocrine activity (E), single and repeated dose neurotoxicity (Ns and Nr*), and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), titanium dioxide meets requirements for a GreenScreen® Benchmark Score of 3 despite the hazard data gaps. In a worst-case scenario, if titanium dioxide were assigned a High score for the data gaps endocrine activity (E), repeated dose neurotoxicity (Nr*), and respiratory sensitization (SnR*), it would be categorized as a Benchmark 1 Chemical.

Dermal: Titanium dioxide was assigned a GreenScreen® Benchmark Score of U ("Unspecified Due to Insufficient Data") as it does not meet the minimum data requirements for a Benchmark Score of 2, based on its Moderate Group II Human Health Toxicity (single dose systemic toxicity (Ns) and eye irritation (IrE)). This corresponds to GreenScreen® benchmark classification 3c ("Moderate T (Group II or II*") in CPA 2011, 2012a. Data gaps (DG) exist for carcinogenicity (C), endocrine activity (E), repeated dose systemic toxicity (STr*), single and repeated dose neurotoxicity (Ns and Nr*), and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), titanium dioxide does not meet requirements for a GreenScreen® Benchmark Score of 2 due to the hazard data gaps. In a worst-case scenario, if titanium dioxide were assigned a High score for the data gaps carcinogenicity (C), endocrine activity (E), repeated dose systemic toxicity (STr*), repeated dose neurotoxicity (Nr*), and respiratory sensitization (SnR*), it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
In order to address the route specified hazards, all exposure routes (oral, dermal, and inhalation) were evaluated separately and GreenScreen® Benchmark Scores were generated for each route of exposure.

GreenScreen® Hazard Ratings for Titanium Dioxide

Route of Exposure	Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
	C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
							single	repeated*	single	repeated*										
Inhalation	H	L	L	L	DG	L	*M*	H	DG	DG	L	DG	L	*M*	L	L	vH	L	*L*	*L*
Oral	L							L												
Dermal	DG							DG												

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Assessment for Titanium Dioxide (CAS #13463-67-7)

Method Version: GreenScreen® Version 1.2[1]
Assessment Type[2]: Certified

Chemical Name: Titanium Dioxide

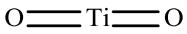
CAS Number: 13463-67-7

GreenScreen® Assessment Prepared By:
Name: Zach Guerrette, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 7, 2014
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 15, 2014

Confirm application of the *de minimus* rule[3]: N/A

Chemical Structure(s):



Also called:
CI 77891; Pigment white 6; Titanium oxide; Atlas white titanium dioxide; C 97 (oxide); C.I. 77891; C.I. Pigment White 6; CI Pigment white 6; Cosmetic Hydrophobic TiO2 9428; Cosmetic Micro Blend TiO2 9228; Cosmetic White C47-5175; Cosmetic White C47-9623; EINECS 236-675-5; Pigment White 6; Tin dioxide dust; Titanic anhydride; Titanic oxide; Titanium oxide (TiO2); Titanium peroxide; Titanium peroxide (TiO2); Titanium White; Titanium(IV) oxide (ChemIDplus 2014)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
No data were identified for the endocrine activity, neurotoxicity, and respiratory sensitization endpoints. ToxServices attempted to identify potential chemical surrogates using the structural similarity search function of ChemIDplus and the U.S. EPA's Analog Identification Methodology (AIM) software but none of the surrogates identified using these strategies possessed data for these endpoints. Therefore, the endocrine activity, neurotoxicity, and respiratory sensitization endpoints were assigned data gaps.

Identify Applications/Functional Uses (ESIS 2000)**:**
1. Polymer industry
2. Coloring agent
3. Construction materials
4. Cosmetics
5. Fillers

[1] Use GreenScreen® Assessment Procedure (Guidance) V1.2

[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent) or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen® Verification Program)

[3] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

6. Food/Foodstuff additives
7. Pharmaceuticals
8. Photochemicals
9. Semiconductors
10. Pigments

GreenScreen® Summary Rating for Titanium Dioxide[4]:

Inhalation: Titanium dioxide was assigned a GreenScreen® Benchmark Score of 1 ("Avoid-Chemical of High Concern") as it has Very High persistence (P) and High Group I Human Health hazard (carcinogenicity (C)) and High Group II* Human Health hazard (repeated dose systemic toxicity (STr*)). This corresponds to GreenScreen® benchmark classifications 1c ("vPT = very High P + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]") and 1e ("High T (Group I Human)") in CPA 2011, 2012a. Data gaps (dg) exist for endocrine activity (E), single and repeated dose neurotoxicity (Ns and Nr*), and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), titanium dioxide meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gaps. In a worst-case scenario, if titanium dioxide were assigned a High or Very High score for the data gaps endocrine activity (E), single and repeated dose neurotoxicity (Ns and Nr*), and respiratory sensitization (SnR*), it would still be categorized as a Benchmark 1 Chemical.

Oral: Titanium dioxide was assigned a GreenScreen® Benchmark Score of 3 ("Use but Still Opportunity for Improvement") as it has Moderate Group II Human Health hazard (single dose systemic toxicity (STs) and eye irritation (IrE)). This corresponds to GreenScreen® benchmark classification 3c ("Moderate T (Group II or II*") in CPA 2011, 2012a. Data gaps (dg) exist for endocrine activity (E), single and repeated dose neurotoxicity (Ns and Nr*), and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), titanium dioxide meets requirements for a GreenScreen® Benchmark Score of 3 despite the hazard data gaps. In a worst-case scenario, if titanium dioxide were assigned a High score for the data gaps endocrine activity (E), repeated dose neurotoxicity (Nr*), and respiratory sensitization (SnR*), it would be categorized as a Benchmark 1 Chemical.

Dermal: Titanium dioxide was assigned a GreenScreen® Benchmark Score of U ("Unspecified Due to Insufficient Data") as it does not meet the minimum data requirements for a Benchmark Score of 2, based on its Moderate Group II Human Health Toxicity (single dose systemic toxicity (Ns) and eye irritation (IrE)). This corresponds to GreenScreen® benchmark classification 3c ("Moderate T (Group II or II*") in CPA 2011, 2012a. Data gaps (dg) exist for carcinogenicity (C), endocrine activity (E), repeated dose systemic toxicity (STr*), single and repeated dose neurotoxicity (Ns and Nr*), and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), titanium dioxide does not meet requirements for a GreenScreen® Benchmark Score of 2 due to the hazard data gaps. In a worst-case scenario, if titanium dioxide were assigned a High score for the data gaps carcinogenicity (C), endocrine activity (E), repeated dose systemic toxicity (STr*), repeated dose neurotoxicity (Nr*), and respiratory sensitization (SnR*), it would be categorized as a Benchmark 1 Chemical.

[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Figure 1: GreenScreen® Hazard Ratings for Titanium Dioxide

Route of Exposure	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
							single	repeated*	single	repeated*										
Inhalation	H	L	L	L	DG	L	*M*	H	DG	DG	L	DG	L	*M*	L	L	vH	L	*L*	*L*
Oral	L							L												
Dermal	DG							DG												

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e. vH, H, M, and L) instead of three (i.e. H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[5]

Titanium dioxide is an inorganic chemical that is not susceptible to transformation. Therefore, the Benchmark Score is not adjusted by the transformation products.

Introduction

Titanium dioxide has a wide variety of uses including: pigment in coated fabrics, delustering agent in synthetic fiber, pigments in a variety of mediums, shrinking agent for glass fiber, sub-coating in confectionary panned goods and icings, medication, and cosmetics (HSDB 2009). Titanium dioxide is produced via the reaction of titanium as inorganic titanium compounds or aqueous solutions of titanium salts and oxygen, or via the oxidation or hydrolysis of organic chemicals of titanium (HSDB 2009). It may also be harvested and separated from naturally occurring minerals.

ToxServices assessed titanium dioxide against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.69 (GreenScreen® Hazard Assessment) (ToxServices 2013).

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2014) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. It checks all of the lists in the List Translator with the exception of the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b) and these should be checked separately in conjunction with running the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for titanium dioxide can be found in Appendix C and a summary of the results can be found below:

- High Hazard
  - Cancer
    - U.S. CDC (NIOSH-C) – occupational carcinogen
    - Cal/EPA – chemicals known to cause cancer and reproductive toxicity (Prop. 65) – cancer (airborne particles of respirable size – occupational setting)
  - Systemic Toxicity (repeated exposure)

[5] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

        - GHS Japan Category 1 systemic toxicant following repeat dose
- Medium Hazard
    - Cancer
        - International Agency for Research on Cancer – Group 2b: possibly carcinogenic to humans – inhaled from occupational sources
        - German MAK – carcinogen group 3A – evidence of carcinogenic effects but not sufficient to establish MAK/BAT value
    - Systemic Toxicity (single exposure)
        - GHS Japan Category 3 systemic toxicity following single dose
    - Eye Irritation
        - GHS Japan Category 2B – serious eye damage/eye irritation
    - Chronic Aquatic Toxicity
        - GHS Japan Category 4 – hazardous to the aquatic environment (chronic)
- Titanium dioxide is not listed on the U.S. DOT (2008a,b) lists.

PhysicoChemical Properties of Titanium Dioxide

Titanium dioxide is a white crystalline solid under standard temperature and pressure. It is insoluble in water based on a water solubility of 0.0034 mg/L. As an inorganic chemical, the log K_{ow} is not applicable since titanium dioxide is not likely to bioaccumulate.

Table 1: Physical and Chemical Properties of Titanium Dioxide (CAS #13463-67-7)

Property	Value	Reference
Molecular formula	O2-Ti	ChemIDplus 2014
SMILES Notation	[Ti](=O)=O	ChemIDplus 2014
Molecular weight	79.865 g/mol	ChemIDplus 2014
Physical state	Solid	ECHA 2014
Appearance	White, crystalline	ECHA 2014
Melting point	1,560-1,843°C	ECHA 2014
Vapor pressure	Not identified	
Water solubility	0.0034 mg/L at 21.9°C	ECHA 2014
Dissociation constant	Not identified	
Density/specific gravity	3.9 - 4.17 g/cm^3 at 20°C	ECHA 2014
Partition coefficient	Not applicable, inorganic chemical	ECHA 2014
Particle size	Nano particles are < 100 nm Less than 1 µm to greater than 10 µm	OECD 2013 HSDB 2009
Structure	Crystalline – rutile, anatase, or brookite	OECD 2013
Bioavailability	Not bioavailable via the oral route	OECD 2013

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): H (inhalation), **L** (oral), DG (dermal)

Titanium dioxide was assigned a score of High for carcinogenicity via the inhalation route based on authoritative lists. GreenScreen® criteria classify chemicals as a High hazard for carcinogenicity when they are listed as occupational carcinogens by the U.S. CDC (NIOSH-C) or are known to the State of California to cause cancer or reproductive toxicity (CPA 2012a). Titanium dioxide was assigned a score

of Low for carcinogenicity via the oral route based on negative results in oral carcinogenicity studies. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when negative results, no structural alerts, and no GHS classification are available (CPA 2012a). Titanium dioxide was assigned a score of Data Gap for carcinogenicity via the dermal based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:*
        - U.S. CDC (NIOSH-C) – occupational carcinogen
        - Cal/EPA – chemicals known to cause cancer and reproductive toxicity (Prop. 65) – cancer (airborne particles of respirable size – occupational setting)
        - International Agency for Research on Cancer – Group 2b: possibly carcinogenic to humans – inhaled from occupational sources
        - German MAK – carcinogen group 3A – evidence of carcinogenic effects but not sufficient to establish MAK/BAT value
    - *Screening:* Not listed on any screening lists for this endpoint.
- Pharos 2014
    - Titanium dioxide is classified as an LT-1 chemical based on its presence on authoritative lists for carcinogenicity (US CDC – Occupational Carcinogens (NIOSH-C) Occupational carcinogen; Cal/EPA – Chemicals Known to Cause Cancer and Reproductive Toxicity (Prop 65) Cancer (airborne particles of respirable size – occupational setting); International Agency for Research on Cancer – Cancer Monographs (IARC) Group 2b: Possibly carcinogenic to humans – inhaled from occupational sources; German MAK – List of Substances (MAK); Carcinogen Group 3A – Evidence of carcinogenic effects but not sufficient to establish MAK/BAT value).
- NCI 1979
    - *Oral*: A 103-week carcinogenicity study (GLP status and guidelines used are not reported) was conducted using male and female Fischer 344 rats and B6C3F1 mice (50/sex/group). Animals were administered doses of 25,000 and 50,000 ppm (~1,875 and 3,750 mg/kg for rats and 3,750 and 7,500 mg/kg for mice) of titanium dioxide (≥ 98% purity) in the food daily for 103 weeks. Examinations conducted include: body weights, clinical signs, mortality, and pathology. In female rats, increases in C-cell adenomas or carcinomas of the thyroid were reported (1/48 in controls, 0/48 in low-dose, and 6/44 in high-dose). However, comparison between the control and high dose group ($p = 0.043$) indicate that they did not reach statistical significance by the Bonferroni criteria ($p = 0.025$). Therefore, the tumors were not considered by the study authors to be related to the administration of the test substance. No statistically significant increases in tumors were reported for male rats, or male and female mice. The study authors concluded that under the conditions of the bioassay titanium dioxide was not carcinogenic by the oral route to Fischer 344 rats or B6C3F1 mice.
- ESIS 2000
    - *Oral*: A 130- week carcinogenicity study (GLP status and guideline used are not reported) was conducted using male and female Fischer 344 rats (60/sex/group). Rats were administered doses of 0, 750, 1,500, and 3,700 mg/kg of titanium dioxide (purity not reported) in the food daily for 130 weeks. Examinations conducted include: mortality; body weights; clinical chemistry; and histopathology. A slight increased incidence of adrenal medullary hyperplasia was reported in male rats. However, no dose-response relationship was established. The study authors concluded that under the conditions of the experiment no evidence of carcinogenic effects were found. No further details were reported for this study.

  - *Inhalation*: A 24-month inhalation carcinogenicity study (GLP status and guidelines were not reported) was conducted using male and female CD rats (200/group). Rats were exposed to concentrations of 10, 50, and 250 mg/m^3 of titanium dioxide for 5 days/week, 6 hours/day, for 24 months. Type II pneumocytes hyperplasia was present in the 50 and 250 mg/m^3 exposure groups with minute collagenized fibrosis. In the 250 mg/m^3 group, there was evidence of excessive dust loading and the presence of bronchoalveolar adenomas and cystic keratinizing squamous cell carcinomas.
  - *Inhalation*: Fischer 344 rats (number/sex not reported) were exposed to concentrations of 5 mg/m^3 of titanium dioxide for 5 days/week, 6 hours/day for 2 years. No increases in tumors were reported. No other information was provided.
- Heinrich et al. 2005
  - *Inhalation*: Female Wistar rats and NMRI mice were exposed to varying concentrations (7.2 to 14.8 mg/m^3) of titanium dioxide for 30 and 24 months, respectively. No evidence of tumor formation was found in mice. Rats developed tumors in the lungs. Limited data were available for this study, and no further information was found.
- NIOSH 2011
  - *Inhalation*: Chronic inhalation studies have been identified in both rats and mice, but the rat is the only species in which tumors were observed. Lung tumors observed in CD rats following chronic inhalation exposure include squamous cell keratinizing cysts, bronchioalveolar adenomas, squamous cell carcinomas, and adenocarcinomas of the alveolar ducts. Squamous cell keratinizing cystic tumors are most prevalent in female rats, but they have been extensively reviewed by multiple groups and determined to be irrelevant to human pathology. Other types of tumors (adenomas, adenocarcinoma, and squamous cell carcinoma) do occur in humans. The most likely mechanisms of action for titanium dioxide and other poorly water-soluble particles in the lung involve particle overload, sustained inflammation, production of reactive oxygen species, depletion of antioxidants, and/or impairment of other defense mechanisms, cell proliferation, and gene mutations. This is considered a secondary genotoxic mechanism, as opposed to a primary genotoxic mechanism where the agent directly interacts with DNA. This mechanism is also believed to be responsible for the carcinogenic effects of other poorly soluble respirable particles such as carbon black and talc. The pathological progression of carcinogenesis in rodents includes accumulation of particle laden macrophages, increased lung weight, infiltration of neutrophils, increased epithelial permeability, increased transfer of particles to lymph nodes, persistent inflammation, lipoproteinosis, fibrosis, alveolar epithelial cell hyperplasia, and (eventually in rats) metaplasia, and non-neoplastic and neoplastic tumors.
- Available studies indicate that titanium dioxide is not carcinogenic via the oral route of exposure, but is carcinogenic via inhalation through a mechanism involving insoluble particle overload of the lung. The inhalation route of exposure is only relevant under the occupational setting in humans.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

Titanium dioxide was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity in a battery of *in vitro* tests and an *in vivo* test. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative results for mutagenicity and clastogenicity, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.

- CCRIS 2010
    - *In vitro*: Several Bacterial Reverse Mutation assays have been conducted utilizing *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA102, TA1537, TA1537, and *E.coli* tester strains WP2 UVRA in the presence and absence of metabolic activation at concentrations ranging from 1 to 10,000 µg/plate. Titanium dioxide was negative for mutagenicity under all tested conditions. No further details were available.
    - *In vitro*: Three chromosomal aberration assays were conducted utilizing Chinese Hamster Ovary (CHO) cells in the presence and absence of metabolic activation at concentrations ranging from 0.25 to 25 µg/mL. Titanium dioxide was negative for clastogenicity under all tested conditions. No further details were available.
- ESIS 2000
    - *In vitro*: An Ames Bacterial Reverse Mutation assay was conducted utilizing *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of metabolic activation. Titanium dioxide was reported to be negative for mutagenicity. No further information was available.
    - *In vitro*: Limited data were available for genetic toxicity studies in the IUCLID document. Titanium dioxide was reported as testing negative for mutagenicity/clastogenicity and DNA damage following: mouse lymphoma assay, sister chromatic exchange assay, unscheduled DNA synthesis, *E.coli* reverse mutation assay, and a DNA synthesis test.
    - *In vivo*: Reported data indicate that titanium dioxide was reported negative for mutagenicity following a somatic mutation assay.

Reproductive Toxicity (R) Score (H, M, or L): L
Titanium dioxide was assigned a score of Low for reproductive toxicity based on the lack of reproductive effects in a rat screening test. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when negative results, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- OECD 2013
    - In a reproductive and developmental toxicity screening test conducted according to OECD Guideline 421 in rats (strain not specified), animals (10/sex/dose) were administered 0 or 1,000 mg/kg/day titanium dioxide via gavage for 2 weeks prior to mating, during mating, and for either 2 weeks post mating (males) or through gestation and lactation day 3 (females). There were no effects on clinical signs, body weights, food consumption, mating, gestation, delivery, organ weights, necropsy, or histopathology in parental animals. There was no evidence of reproductive toxicity (no details were provided). OECD established a NOAEL of 1,000 mg/kg/day based on the lack of effects on reproduction.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L
Titanium dioxide was assigned a score of Low for developmental toxicity based on the lack of developmental effects observed in a rat screening test. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when negative results, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.

- OECD 2013
    - In the reproductive and developmental toxicity screening test according to OECD Guideline 421 in rats described above for reproductive toxicity, there were no effects on clinical signs, body weights, viability index, external malformations, or sex ratios in pups. OECD established a NOAEL of 1,000 mg/kg/day based on the lack of effects on pup development.

Endocrine Activity (E) Score (H, M, or L): DG
Titanium dioxide was assigned a score of Data Gap for endocrine disruption based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- No data were identified for this endpoint.

Group II and II* Human Health Effects (Group II and II* Human)
Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M, or L): L
Titanium dioxide was assigned a score of Low for acute toxicity based on oral LD_{50} values of greater than 5,000 mg/kg, dermal LD_{50} values greater than 10,000 mg/kg, and inhalation LC_{50} values greater than 6.82 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg and inhalation LC_{50} values greater than 5 mg/L for dusts (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ESIS 2000
    - *Oral*: LD_{50} (rats) = greater than 10,000 to greater than 25,000 mg/kg.
    - *Dermal*: LD_{50} (rabbits) = greater than 10,000 mg/kg.
    - *Dermal*: LD_{50} (hamsters) = at least 10,000 mg/kg.
    - *Inhalation*: 4-hour LC_{50} (rats) = greater than 2.29 to greater than 6.82 mg/L.
- ECHA 2014
    - *Oral*: LD_{50} (female Crl: CD (SD) rats) = greater than 5,000 mg/kg.
    - *Oral*: LD_{50} (male and female Sprague-Dawley rats) = greater than 2,000 mg/kg
    - *Oral*: LD_{50} (male and female Sprague-Dawley rats) = greater than 5,000 mg/kg.
    - *Oral*: LD_{50} (male ChR-CD rats) = greater than 25,000 mg/kg.
    - *Oral*: LD_{50} (male Crl:DC BR rats) = 11,000 mg/kg.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M, or L):** *M*
Titanium dioxide was assigned a score of Moderate for systemic toxicity (single dose) based on screening lists. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified as Category 3 systemic toxicants following single dose by GHS Japan (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS Japan Category 3 systemic toxicity following single dose
- ECHA 2014
  - *Oral*: In an acute oral toxicity study in female Crl:CD (SD) rats, single oral doses of 175, 550, 1,750 or 5,000 mg/kg titanium dioxide did not lead to any adverse effects. The only effects noted were grey colored feces in animals at 1,750 and 5,000 mg/kg doses.
  - *Oral*: In an acute oral toxicity study in Sprague-Dawley rats of both sexes, titanium dioxide was given by single gavage at 10, 200 or 2,000 mg/kg. No signs of systemic toxicity were observed in the study.
  - *Oral*: In an acute oral toxicity study in Sprague-Dawley rats of both sexes, titanium dioxide was given by single gavage at 10 or 5,000 mg/kg. Animals were observed for 14 days after exposure. No signs of systemic toxicity were observed in the study. No mortality or gross post mortem abnormalities were observed and body weight gain was normal. At 0.5 h-7 days after dosing, only piloerection was observed.
  - *Oral*: In an acute oral toxicity study in male ChR-CD rats, titanium dioxide was given by single gavage at 2,250, 5,000, 7,500, 11,000, 17,000 or 25,000 mg/kg. Weight loss was observed at doses of 2,250 mg/kg and above for only 1-2 days. Diarrhea (compound and/or metabolite excreted with feces) was found on the day of dosing and wet perineal area on the day after dosing was found in animals at doses of 5,000 mg/kg and above. No mortality information was reported. ToxServices conservatively established the LOAEL at 2,250 mg/kg based on reversible decrease in body weight.
  - *Oral*: In an acute oral toxicity study in male Crl:DC BR rats (1/dose), titanium dioxide was given by single gavage at 6 doses ranging from 670-11,000 mg/kg. No deaths occurred during the study and no clinical signs of toxicity were found. Rats at 3,400, 5,000, and 7,500 mg/kg had weight loss of up to 6% 1 day after dosing. No other findings were reported.

***Group II* Score (repeated dose)* (H, M, or L): H** (inhalation), **L** (oral), DG (dermal)
Titanium dioxide was assigned a score of High for systemic toxicity (repeated dose) via the inhalation route based on the lowest LOAEC of 0.002 mg/L/6h/day in a subchronic mouse study. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when inhalation LOAECs for dusts are no greater than 0.02 mg/L (CPA 2012a). Titanium dioxide was assigned a score of Low for systemic toxicity (repeated dose) via the oral route based on the lowest LOAEL of 3,700 mg/kg/day in a two-year rat carcinogenicity study. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when oral LOAELs are greater than 100 mg/kg/day (CPA 2012a). Titanium dioxide was assigned a score of Data Gap for systemic toxicity (repeated dose) via the dermal route based on the lack of data available for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:*

    - GHS Japan Category 1 systemic toxicant following repeated dose
- ECHA 2014
    - *Oral*: A sub-acute oral toxicity study (GLP status was not reported) was conducted according to OECD TG 407. Male Crl:CD(SD) IGS BR rats (5/group) received titanium dioxide via daily gavage for 29 days at 0 or 24,000 mg/kg. Cage side observation, clinical observation, food consumption, body weight, hematological analysis, clinical chemistry analysis, gross pathology, and histopathology were performed. No adverse effects were noted and ECHA established the NOEL at 24,000 mg/kg/day.
    - *Oral*: A 130-week carcinogenicity study (GLP status and guideline used were not reported) was conducted using male and female Fischer 344 rats (60/sex/group). Rats were administered doses of 0, 750, 1,500 or 3,700 mg/kg of titanium dioxide (purity not reported) in the food daily for 130 weeks. Examinations conducted include: mortality, body weights, clinical chemistry, and histopathology. Administration of titanium dioxide had no effect on body weights in males or females of either species. The only clinical sign related to treatment in either species was the appearance of white feces. No additional adverse effects at any dose were reported. ToxServices established the NOAEL at 3,700 mg/kg/day.
    - *Inhalation*: A 24-month inhalation carcinogenicity study (non-GLP) was conducted using male and female CD rats (100/sex/dose). Rats were exposed to concentrations of 10, 50 or 250 mg/m^3 of titanium dioxide for 5 days/week, 6 hours/day, for 24 months. An LOEC of 10 mg/m^3 (equivalent to mg/L/6h/day[6]) was established for non-neoplastic changes in this study by ECHA, based on alveolar cell hyperplasia and broncho/bronchiolar pneumonia.
    - *Inhalation*: A non-GLP chronic/carcinogenicity study was conducted using female NMRI and C57BL/6N mice. Animals (1,140 NMRI mice and 585 C57BL/6N mice) were exposed to ultrafine titanium dioxide particles via whole body inhalation at concentrations of 0 or 10 mg/m^3 for 18 hours/day, 5 days/week for 24 months. A significantly decreased life-span was found compared to control. ToxServices established an LOAEC at 10 mg/m^3 (equivalent to 0.021 mg/L/6h/day[7]) for this study.
    - *Inhalation*: A GLP-compliant subchronic study was conducted using female Syrian hamsters. Animals were exposed to titanium dioxide via whole-body inhalation at 0, 10, 50 or 250 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. NOAEC and LOAEC were established by ECHA at 10 and 50 mg/m^3, respectively (equivalent to 0.007 and 0.035 mg/L/6h/day[8]), based on a statistically significant increase in the number of neutrophils recovered by lung lavage (BAL) at the end of the study.
    - *Inhalation*: A GLP-compliant subchronic study was conducted in female F344 rats. Animals (65/dose) were exposed to titanium dioxide via whole-body inhalation at 0, 10, 50 or 250 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. NOAEC and LOAEC were established by ECHA at 10 and 50 mg/m^3, respectively (equivalent to 0.007 and 0.035 mg/L/6h/day[9]), based on lung and lymph node titanium dioxide particle burdens and histopathological alterations.
    - *Inhalation*: A GLP-compliant subchronic study was conducted in female B3C3F1/CrlBR mice. Animals (73/dose) were exposed to titanium dioxide via whole-body inhalation at approximately 0, 10, 50 or 250 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. NOAEC and LOAEC were established by ECHA at 10 and 50 mg/m^3, respectively (equivalent to 0.007 and 0.035 mg/L/6h/day[10]), based on a statistically significant increase in the number of

[6] 10 mg/m^3 for 6 hours/day, 5 days/week is equivalent to 10 mg/m^3 x 6 /6h x 5/7 day x 10^{-3} m^3/L = 0.007 mg/L/6h/day.
[7] 10 mg/m^3 for 18 hours/day, 5 days/week is equivalent to 10 mg/m^3 x 18 /6 h x 5 /7day x 10^{-3} m^3/L = 0.021 mg/L/6h/day.
[8] 10 mg/m^3 for 6 hours/day, 5 days/week is equivalent to 10 mg/m^3 x 6 /6h x 5/7 day x 10^{-3} m^3/L = 0.007 mg/L/6h/day.
[9] 10 mg/m^3 for 6 hours/day, 5 days/week is equivalent to 10 mg/m^3 x 6 /6h x 5/7 day x 10^{-3} m^3/L = 0.007 mg/L/6h/day.
[10] 10 mg/m^3 for 6 hours/day, 5 days/week is equivalent to 10 mg/m^3 x 6 /6h x 5/7 day x 10^{-3} m^3/L = 0.007 mg/L/6h/day.

neutrophils recovered by lung lavage (BAL) at the end of the study and increased lactate dehydrogenase and protein in BAL.

- *Inhalation*: A GLP-compliant subchronic study was conducted in female Syrian hamsters. Animals (25/dose) were exposed to titanium dioxide via whole-body inhalation at 0, 0.53, 2.1 or 10.7 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. NOAEC and LOAEC were established by ECHA at 2.1 and 10.7 mg/m^3, respectively (equivalent to 0.002 and 0.008 mg/L/6h/day[11]), based on statistically significant increases in the number of neutrophils recovered by lung lavage (BAL) and in terminal bronchiolar cell replication.
- *Inhalation*: A GLP-compliant subchronic study was conducted in female F344 rats. Animals (25/dose) were exposed to titanium dioxide via whole-body inhalation at 0, 0.52, 2.1 or 10.5 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. NOAEC and LOAEC were established by ECHA at 0.52 and 2.1 mg/m^3, respectively (equivalent to 0.0004 and 0.002 mg/L/6h/day[12]), based on a statistically significant increase in terminal bronchiolar cell replication, and histopathological alterations such as progressive epithelial and fibroproliferative changes related to inflammatory responses.
- *Inhalation*: A GLP-compliant subchronic study was conducted in female B3C3F1/CrlBR mice. Animals (25/dose) were exposed to titanium dioxide via whole-body inhalation at 0, 0.54, 2.2 or 10.8 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. NOAEC and LOAEC were established by ECHA at 2.2 and 10.8 mg/m^3, respectively (equivalent to 0.002 and 0.008 mg/L/6h/day[13]), based on statistically significant increases in the number of neutrophils, lactate dehydrogenase and protein levels recovered by lung lavage (BAL), statistically significant changes in the cytological profile of cells (elevated number of macrophages, neutrophils and lymphocytes) recovered by BAL, a statistically significant increase in terminal bronchiolar cell replication, and histopathological changes comprised of little epithelial changes with aggregations of heavily particle-laden macrophages moving into interstitial areas and perivascular lymphoid proliferation.
- *Inhalation*: A combined chronic/carcinogenicity study was conducted in male and female F344 rats. Animals (number/dose was not reported) were exposed to titanium dioxide as a negative control for toner exposure by whole body inhalation at 0 or 5 mg/m^3 for 6 hours/day, 5 days/week for 24 months. Body weight, clinical chemistry, food consumption and organ weights were normal and ECHA established the NOAEL at 5 mg/m^3 (equivalent to 0.004 mg/L/6h/day[14]).

- ESIS 2000
  - *Inhalation*: Several inhalation toxicity studies have been identified ranging from 4-days to 24-months. Limited details were available for these studies. A NOAEL value of greater than 10 mg/m^3 has been established by study authors in rats based on a 2- and 4-month study. Additional studies in which NOAELs were not established, reported no adverse effects in rats at titanium dioxide concentrations up to and including 250 mg/m^3. These data collectively show that titanium dioxide is of low inhalation toxicity.
- Basis for Rating: Titanium dioxide is assigned a score of High for the inhalation route based on the lowest LOAEC of 0.002 mg/L/6h/day in a subchronic study in female B3C3F1/CrlBR mice. A score of Low for the oral route was assigned based on the lowest NOAEL of 3,700 mg/kg/day. A data gap was assigned for the dermal route based on lack of data.

[11] 2.1 mg/m^3 for 6 hours/day, 5 days/week is equivalent to 2.1 mg/m^3 x 6 /6h x 5/7 day x 10^{-3} m^3/L = 0.002 mg/L/6h/day.
[12] 0.52 mg/m^3 for 6 hours/day, 5 days/week is equivalent to 0.52 mg/m^3 x 6 /6h x 5/7 day x 10^{-3} m^3/L = 0.0004 mg/L/6h/day.
[13] 2.2 mg/m^3 for 6 hours/day, 5 days/week is equivalent to 2.1 mg/m^3 x 6 /6h x 5/7 day x 10^{-3} m^3/L = 0.002 mg/L/6h/day.
[14] 5 mg/m^3 for 6 hours/day, 5 days/week is equivalent to 5 mg/m^3 x 6 /6h x 5/7 day x 10^{-3} m^3/L = 0.004 mg/L/6h/day.

Neurotoxicity (N)

***Group II Score (single dose)* (vH, H, M, or L):** DG

Titanium dioxide was assigned a score of Data Gap for neurotoxicity (single dose) based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- No data were identified for this endpoint.

***Group II* Score (repeated dose)* (H, M, or L):** DG

Titanium dioxide was assigned a score of Data Gap for neurotoxicity (repeated dose) based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- No data were identified for this endpoint.

Skin Sensitization (SnS) Group II* Score (H, M, or L): L

Titanium dioxide was assigned a score of Low for skin sensitization based on negative results for skin sensitization in *in vivo* tests and human patch tests. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when negative results, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ESIS 2000
  - Titanium dioxide was reported as non-sensitizing following a Maurer Optimization test and a Human Patch test. No further details were available
- ECHA 2014
  - Titanium dioxide was not a dermal sensitizer in a GLP-compliant Buehler test conducted according to OECD TG406, EU Method B.6 and EPA OPP 81-6 in male Hartley guinea pigs.
  - Titanium dioxide was not a dermal sensitizer in a mouse local lymph node assay (LLNA) (GLP status not reported) conducted similar to OECD TG 429 in female CBA/JHsd mice.

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): DG

Titanium dioxide was assigned a score of Data Gap for respiratory sensitization based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- No data were identified for this endpoint.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): L

Titanium dioxide was assigned a score of Low for skin irritation/corrosivity based on negative results in humans, rats, and guinea pigs. GreenScreen® criteria classify chemicals as a Low hazard for skin

irritation/corrosivity when negative results, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ESIS 2000
  - Titanium dioxide is reported as being non-irritating to the skin of humans, rats, and guinea pigs. No further details were reported.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): *M*

Titanium dioxide was assigned a score of Moderate for eye irritation/corrosivity based on screening lists. GreenScreen® criteria classify chemicals as a Moderate hazard for eye irritation/corrosivity when they are classified as Category 2B eye irritants by GHS Japan (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS Japan Category 2B – serious eye damage/eye irritation
- ESIS 2000
  - Titanium dioxide is reported as being non-irritating to the eyes of rabbits. No further details were reported.
- ECHA 2014
  - Titanium dioxide produced reversible conjunctival redness (score of 1 in two animals and 2 in one animal) in the eye of all three rabbits. No corneal injury was found. It was considered not irritating by the EU standard.
  - Titanium dioxide produced reversible conjunctival redness (score = 1) in the eye of all three rabbits. No corneal injury was found. It was considered minimally irritating to the eye by the EU standard (no explanation was provided regarding why the conclusion was different from that of the study above).
  - Reversible minimal conjunctival redness (score =1) and chemosis (score = 1) were observed in all three rabbits. Titanium dioxide was considered not irritating by EU standard.
  - Titanium dioxide exposure caused only very slight conjunctival redness (max score = 1) in rabbits 1-24 hours after treatment, but no effect was seen at 48 and 72 hours.
  - Titanium dioxide caused reversible conjunctival redness (score = 1 or 2) and chemosis (score = 1). Only two rabbits were used.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L

Titanium dioxide was assigned a score of Low for acute aquatic toxicity based on the acute aquatic toxicity values exceeding the water solubility of titanium dioxide. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when no acute aquatic toxicity is observed at saturation (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ESIS 2000
  - 96-hour LC_{50} (fish) = greater than 1,000 mg/L.
- ECHA 2014

- 95-hour LC_{50} (fish) = greater than 100 mg/L (nominal) in multiple studies in freshwater, brackish water, and saltwater.
- 48-hour LC_{50} (multiple aquatic invertebrate species) = greater than 100 mg/L (nominal) in freshwater and saltwater.
- 720hour LC_{50} (green algae) = greater than 100 mg/L (nominal) in multiple studies.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): L
Titanium dioxide was assigned a score of Low for chronic aquatic toxicity based on chronic aquatic toxicity values greater than the water solubility of titanium dioxide. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when no chronic aquatic toxicity is observed at saturation (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS Japan Category 4 – hazardous to the aquatic environment (chronic)
- ESIS 2000
  - 30-day NOEC (fish) = 1,000 mg/L.
  - 30-day NOEC (daphnia) = greater than 3 mg/L.
- ECHA 2014
  - 30-day reproduction – day of first reproduction LOEC (daphnia) = 10 mg/L (nominal).
  - The water solubility of titanium dioxide is 0.0034 mg/L at 21.9°C.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vH
Titanium dioxide was assigned a score of Very High for persistence based on it being an inorganic chemical and recalcitrant. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when chemicals are recalcitrant (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:*
    - Environment Canada Domestic Substance List (DSL) – persistent
- U.S. EPA 2008
  - Chemicals that are or contain inorganics, such as metal ions, are expected to be found in the environment for longer than 60 days after release.

Bioaccumulation (B) Score (vH, H, M, L, or vL): L
Titanium dioxide was assigned a score of Low for bioaccumulation based on BCF values of up to 352. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when BCF values are greater than 100 to 500 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
  - In a non-GLP, non-guideline 14-day study in rainbow trout, fish were exposed to titanium dioxide at 0-1 mg/L. Titanium concentrations in various tissues were tested, which decreased with increasing concentrations of titanium dioxide. BCFs ranged from 14-352.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*

Titanium dioxide was assigned a score of Low for reactivity based on it not being classified as reactive under GHS criteria (2013). GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification can be assigned (CPA 2012a). The confidence in the classification is reduced, as it is not based on data or an authoritative list.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ESIS 2000
  - Titanium dioxide is reported as being non-explosive. No further details were reported.
- Sigma-Aldrich 2014
  - A material safety data sheet for titanium dioxide identifies a reactivity rating of 0 from the NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") and HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").
- Based on the MSDS identified above stating that titanium dioxide is non-reactive, ToxServices did not classify titanium dioxide as a reactive chemical based on GHS criteria (UN 2013).

Flammability (F) Score (vH, H, M, or L): *L*

Titanium dioxide was assigned a score of Low for flammability based on it not being classified as a flammable solid under GHS criteria (UN 2013). GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is assigned for this endpoint (CPA 2012a). The confidence in the classification is adjusted as it is not based on data or an authoritative list.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ESIS 2000
  - Titanium dioxide is reported as being non-flammable. No further details were reported.
- Sigma-Aldrich 2014
  - A material safety data sheet for titanium dioxide identifies a flammability rating of 0 from the NFPA ("Materials that will not burn under typical fire conditions") and HMIS ("Materials that will not burn").
- Based on the MSDS identified above stating that titanium dioxide is non-flammable, ToxServices did not classify titanium dioxide as a flammable chemical based on GHS criteria (UN 2013).

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Titanium Dioxide (CAS #13463-67-7)

GreenScreen® Score Inspector for Inhalation Exposure

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
Yes	Titanium Dioxide	13463-67-7	H	L	L	L	DG	L	*M*	H	DG	DG	L	DG	L	*M*	L	L	vH	L	*L*	*L*

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	Yes	No	Yes		
2	STOP						
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Titanium Dioxide	1

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Titanium Dioxide	1

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												1
2												
3												
4												

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector for Oral Exposure

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
Yes	**Titanium Dioxide**	**13463-67-7**	**L**	**L**	**L**	**L**	DG	**L**	*M*	**L**	DG	DG	**L**	DG	**L**	*M*	**L**	**L**	**vH**	**L**	*L*	*L*

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	No	No	No
3	No	No	Yes	No			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Titanium Dioxide	3

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Titanium Dioxide	3

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2												
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		3
4												

TOXSERVICES
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GreenScreen® Score Inspector for Dermal Exposure

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
Yes	**Titanium Dioxide**	**13463-67-7**	DG	**L**	**L**	**L**	DG	**L**	*M*	DG	DG	DG	**L**	DG	**L**	*M*	**L**	**L**	**vH**	**L**	*L*	*L*

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	No	No	No
3	No	No	Yes	No			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Titanium Dioxide	3

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Titanium Dioxide	U

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2												
3	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes		U
4												

APPENDIX C: Pharos Output for Titanium Dioxide (CAS #13463-67-7)

Titanium dioxide

CAS RN: 13463-67-7

Detailed Direct Hazard Listings — Quickscreen

CANCER	US CDC - Occupational Carcinogens (NIOSH-C) Occupational carcinogen - GreenScreen Benchmark 1 (LT-1) - occupational hazard only - HPD
CANCER	Cal/EPA - Chemicals Known to Cause Cancer & Reproductive Toxicity (Prop 65) Cancer (airborne particles of respirable size - occupational setting) - GreenScreen Benchmark 1 (LT-1) - occupational hazard only - HPD
CANCER	Intnl Agency for Rsrch on Cancer - Cancer Monographs (IARC) Group 2b: Possibly carcinogenic to humans - inhaled from occupational sources - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only - HPD
CANCER	German MAK - List of Substances (MAK) Carcinogen Group 3A - Evidence of carcinogenic effects but not sufficient to establish MAK/BAT value - GreenScreen Benchmark Unspecified (LT-U) - HPD
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Specific target organs/systemic toxicity following repeated exposure - Category 1 - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Québec CSST - WHMIS Classifications (WHMIS) Class D2A - Very toxic material causing other toxic effects - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Specific target organs/systemic toxicity following single exposure - Category 3 - GreenScreen Benchmark Unspecified (LT-U)
EYE IRRITATION	Japan METI/MOE - GHS Classifications (GHS-Japan) Serious eye damage / eye irritation - Category 2B - GreenScreen Benchmark Unspecified (LT-U)
CHRON AQUATIC	Japan METI/MOE - GHS Classifications (GHS-Japan) Hazardous to the aquatic environment (chronic) - Category 4 - GreenScreen Benchmark Unspecified (LT-U)
PBT	Environment Canada - Domestic Substances List (DSL) DSL substances that are Persistent - GreenScreen Benchmark Unspecified (LT-U)
RESTRICTED LIST	CA SCP Candidate Chemicals Full Candidate Chemical List - Not included in GreenScreen
RESTRICTED LIST	Environment Canada - Domestic Substances List (DSL) Inherently Toxic to Humans: DSL substances that meet human health categorization criteria - GreenScreen Benchmark Unspecified (LT-U)
EXEMPT	German FEA - Substances Hazardous to Waters (VwVwS) Non-Hazardous to Water (Water Hazard Class 0 NWG) - Not included in GreenScreen

Sources to Check for GreenScreen® Hazard Assessment

Note: For a GreenScreen® Hazard Assessment, data queries should be initially limited to the following references. If data gaps exist after these references have been checked, additional references may be utilized.

U.S. EPA High Production Volume Information System (HPVIS):
http://www.epa.gov/hpvis/index.html

UNEP OECD Screening Information Datasets (SIDS):
http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html

OECD Existing Chemicals Database: http://webnet.oecd.org/hpv/ui/SponsoredChemicals.aspx

European Chemical Substances Information System IUCLID Chemical Data Sheets:
http://esis.jrc.ec.europa.eu/index.php?PGM=dat

National Toxicology Program: http://ntp.niehs.nih.gov/

International Agency for the Research on Cancer:
http://monographs.iarc.fr/ENG/Classification/index.php

Human and Environmental Risk Assessment (HERA) on ingredients of household cleaning products:
http://www.heraproject.com/RiskAssessment.cfm

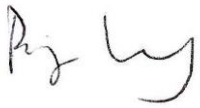
European Chemicals Agency (ECHA) REACH Dossiers: http://echa.europa.eu/

Licensed GreenScreen® Profilers

Titanium Dioxide GreenScreen® Evaluation Prepared by:

Zach Guerrette, Ph.D.
Toxicologist
ToxServices LLC

Titanium Dioxide GreenScreen® Evaluation QC'd by:



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