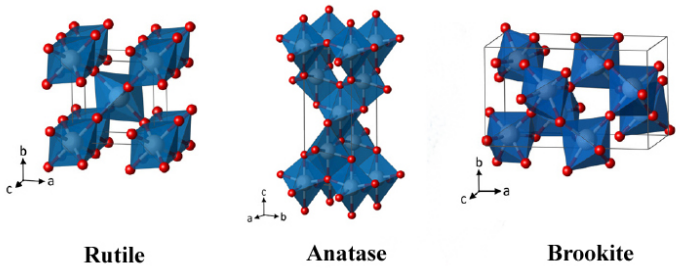
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	13463-67-7
Chemical Name	Titanium dioxide
Structural Formula	 Rutile Anatase Brookite

SUMMARY CONCLUSIONS OF THE SIAR

This report does not cover the nanoparticle form of titanium dioxide. The particle size of titanium dioxide assessed in this report is >100 nm.

Physical and Chemical Properties

Titanium dioxide exists in three different crystallographic structures: rutile, anatase and brookite. Common crystalline forms are anatase and rutile or a mixture of both forms. The crystal form is specified below if the information is available. Anatase forms brown tetragonal crystals, brookite forms white orthorhombic crystals, and rutile forms white tetragonal crystals. They have unit-cell parameters with *a*=b=4.5937 Å and *c*=2.9581 Å (rutile); *a*=*b*=3.7842 Å and *c*=9.5146 Å (anatase); *a*=9.16 Å, *b*=5.43 Å and *c*=513 Å (brookite). The melting points of titanium dioxide are 1560 °C (anatase) and 1,843 °C (rutile) and the boiling point is 2,500-3,000 °C. It has a density of 4.23 g/cm^3 (rutile), 3.90 g/cm^3 (anatase) and 4.13 g/cm^3 (brookite). Titanium dioxide is insoluble in water, hydrochloric acid, dilute sulphuric acid, nitric acid, and alcohol. It is soluble in hot concentrated sulphuric acid and hydrogen fluoride. Oxidation-reduction potential (E^o) is -0.502 V at 25 °C and 1 atm. Vapour pressure and partition coefficient are not applicable to metal-containing inorganic oxide substances. This inorganic substance does not contain relevant functional groups for which an assessment of the dissociation behaviour would be applicable.

Human Health

Toxicokinetics, Metabolism and Distribution

In an oral toxicokinetic study, the absorption, excretion and distribution of titanium dioxide in male and female rats were observed after exposure to diet containing platelet forms of thick and thin rutile and amorphous forms of rutile and anatase. The four forms of titanium dioxide were given orally at dose levels of 0 or 200 mg/kg (nominal, equivalent to approximately 30 mg/kg bw). These diets were administered to groups of three animals per sex per time-point for seven consecutive days and then were replaced by control diet for three days. After being fed with the treated diet, groups of animals were sacrificed at 1, 24, and 72 hours to analyze the titanium content in liver, kidneys, muscle, whole-blood, urine and feces. Feces was the main excretion route and the fecal excretion rate in all treated groups was similar. The mean total amounts of titanium in feces excreted in 72 hours after withdrawal from the treated diet ranged from 1.1-2.2 mg for male rats and from 1.1-1.3 mg for female rats. Urinary excretion and whole blood concentrations of titanium were below the limit of quantification (LOQ) and concentrations of titanium in liver, kidneys and muscle could not be detected for all tested groups. Based on the result from the urinary levels, this study was unable to detect differences in absorption among the four forms of titanium dioxide tested.

In an inhalation toxicokinetic study, male rats were exposed to anatase or rutile titanium dioxide aerosol for

7 hours. For anatase and rutile, the aerosol concentrations were 16.5±1.7 and 19.3±3.1 mg/m^3, and the Mass Median Aerodynamic Diameters (MMAD) were 1.0 and 0.83 µm, respectively. At days 1, 8, 27, and 132 after 7-hour exposure, 8-10 animals/group were analyzed to determine the retained amount of titanium dioxide in the lung. The initial deposition was estimated to be 136±14 µg anatase/lung and 151±30 µg rutile/lung at day 0 after exposure and 23±11 µg anatase/lung and 23±9 µg rutile/lung at day 132 post exposure. The retained amounts of anatase and rutile in the lung at days 1, 8, 27, and 132 were similar, and their clearance half-lives were 51 and 53 days, respectively. Statistically significant differences were not observed between anatase and rutile groups (p<0.05). In the lung lavage test, 6 males/group received by intratracheal instillation 0 (saline), 0.5 or 5.0 mg/rat anatase or rutile and 5 males received 1 mg/rat of PbO as a positive control. Twelve lung lavages/lung were performed on excised lungs 24 hours after dosing. There were no significant differences in cell counts or differentiation between the anatase and rutile groups. At 5.0 mg/rat, the polymorphonuclear leukocytes and peroxidase positive alveolar macrophages were increased in the lavages. The positive control showed higher values for almost all parameters measured.

Acute Toxicity

The acute oral LD_{50} value was greater than 5,000 mg/kg bw for male/female mice [OECD TG 420]. The results showed significant increase of titanium dioxide in the spleen and brain. Also, neuron vacuoles in the hippocampus and hydropic degeneration and spotty necrosis in liver cells were observed. In another study, the acute oral LD_{50} value was greater than 5,000 mg/kg bw for female rats [OECD TG 425, EPA OPPTS 870.1100]. No mortality and body weight changes were observed, and no gross lesions were present in all the animals at necropsy. But 1 rat dosed at 1,750 mg/kg bw and 3 rats dosed at 5,000 mg/kg bw temporarily exhibited grey coloured feces. In a limit test [OECD TG 401, EU Method B.1], the acute oral LD_{50} was greater than 2,000 mg/kg bw in both sexes of rats.

The acute inhalation LC_{50} values in male rats exposed to titanium dioxide powders were greater than 3.43 mg/L (particle size <3.5 µm was 56%, MMAD 3.2 µm) and greater than 5.09 mg/L(particle size <3.5 µm was 20%, MMAD 7.0 µm), respectively [OECD TG 403]. No mortality, body weight changes and clinical signs were observed. Gross pathology revealed mottled lungs in 2/5 males and 3/5 females exposed to titanium dioxide (particle size <3.5 µm was 56%), as well as pale lungs in 3/8 males and 1/5 females exposed to titanium dioxide (particle size <3.5 µm was 20%).

No acute dermal studies were available.

Irritation and Sensitization

Titanium dioxide was not skin irritating. No clinical signs of toxicity were observed in a skin irritation assay performed in 3 male rabbits [OECD TG 404]. Draize scores for erythema and edema were both “0”. No dermal irritation in any of the rabbits was observed during the study. In another skin irritation assay performed in 3 rabbits/sex [equivalent to OECD TG 404], slight erythema occurred in 2/6 animals at 1 hour, 3/6 animals at 24 hours and 1/6 animals both at 48 and 72 hours. In addition, mild erythema occurred in 1/6 animals at 1 hour. No edema was observed. Titanium dioxide was considered to be a non-irritant in this study.

Acute eye irritation/corrosion test was performed according to OECD TG 405. Conjunctival redness (score of 1 or 2) observed at the 1- and 24-hour examinations. The treated eyes of three rabbits were normal by 24 or 48 hours after instillation of the test substance. Based on these results, titanium dioxide was not irritating to the eye of rabbits. In two other eye irritation studies performed under OECD TG 405, the results also showed that the test substance was not irritating to the eye of rabbits.

A Buehler test was performed with titanium dioxide using guinea pigs in accordance with OECD TG 406. Sensitization reactions were not observed in any of 20 animals treated with titanium dioxide for both 24 and 48 hours after the challenge application. No clinical signs of toxicity were observed. In a local lymph node assay [equivalent to OECD TG 429], titanium dioxide was applied to the ear of 5 female mice/group at concentrations of 0, 5, 25, 50 or 100% for three consecutive days. Stimulation indexes (SIs) of less than 3.0 were observed at all test concentrations. No clinical signs of toxicity were observed. Based on these results, titanium dioxide is not considered to be a dermal sensitizer.

In a non standard respiratory sensitization study, pregnant female mice received 50 µg/mouse intranasally of

titanium dioxide on day 14 of gestation and non-pregnant females received the same dose (9 mice in each group). On day 4 after birth, newborns from normal control females intraperitoneally received 0.1 mL of 50 µg/mL ovalbumin (OVA) with alum. On days 12 to 14 of life, these neonates were challenged three times with 3% OVA aerosol. Pregnant mice were shown to have a more significant level of respiratory sensitization than non-pregnant mice after titanium dioxide exposure. Neonates of mothers exposed to titanium dioxide showed increased allergic susceptibility. Offspring of mothers exposed to titanium dioxide showed increased airway hyperresponsiveness (AHR) and allergic inflammation (AI) with increased allergic susceptibility. Therefore, titanium dioxide may have the potential to be a respiratory sensitizer in mice.

Repeated Dose Toxicity

Repeated dose oral toxicity of titanium dioxide has been investigated in two studies. In a study following OECD TG 407, the test substance was administered via gavage to 5 rats/sex/dose at 0 (vehicle control, 1% methyl cellulose solution), 250, 500 or 1,000 mg/kg bw/day for 28 days. Additional recovery groups of 5 animals/sex were included in the control and high dose groups and observed for 14 days after treatment. No deaths were observed in either sex. Treatment related effects observed (compound-colored feces, effects on a few functional performance tests, some hematological and clinical chemistry parameters, liver and thymus weight changes) were not considered to be toxicologically significant. Therefore, the NOAEL was considered to be 1,000 mg/kg bw/day.

In another study conducted according to OECD TG 407, titanium dioxide was administered via gavage to 5 male rats/dose at 0 or 24,000 mg/kg bw/day for 28 days. No substance related effects were observed and the NOAEL was considered to be 24,000 mg/kg bw/day.

No dermal repeated dose toxicity studies are available.

In a repeated dose inhalation toxicity study, titanium dioxide (rutile) was administered via inhalation (whole body) to 80 rats/sex/concentration at 0, 10, 50 or 250 mg/m^3/day for 6 hours/day, 5 days/week for up to 2 years. Titanium dioxide particles showed a spherical configuration and a 1.5-1.7 µm MMAD. Approximately 84% of the dust particles were of respirable size (<13 µm MMAD). Exposure to titanium dioxide resulted in no excess mortality in any exposed group. Treatment related effects were observed as follows: increased haematocrit and haemoglobin in the 250 mg/m^3 treatment group, increased leukocyte and neutrophil count in all treatment groups, decreased lymphocyte count in all treatment groups, increased bilirubin content in females at 50 and 250 mg/m^3 treatment groups, decreased calcium concentrations in all treatment groups, increased lung and thymus weights in the 50 and 250 mg/m^3 treatment groups, increased incidences of pneumonia, tracheitis and rhinitis with squamous metaplasia of the anterior nasal cavity in all treatment groups. Based on the findings at 10 mg/m^3 (tracheitis, rhinitis with squamous metaplasia of the anterior nasal cavity, alveolar cell hyperplasia and broncho/bronchiolar pneumonia), the LOAEC for repeated dose inhalation toxicity was considered to be 10 mg/m^3.

In another repeated dose inhalation toxicity study (whole body), 65 female rats were exposed to 0, 10, 50 or 250 mg/m^3 of titanium dioxide (rutile) for 6 hours/day, 5 days/week for 13 weeks with recovery groups held for an additional 4, 13, 26 or 52 weeks post-exposure (MMAD: 1.44 µm, Geometric SD (GSD): 1.71, respirable fraction was not available). No deaths occurred during the exposure period. Lung and lung-associated lymph node burdens of titanium dioxide increased in a concentration-dependent manner. Pulmonary overload was achieved in rats at 50 and 250 mg/m^3. Inflammation was seen at 50 and 250 mg/m^3 by the evidence of increased numbers of macrophages and neutrophiles and incidences of soluble inflammation markers. Inflammatory responses remained elevated throughout the entire post-exposure recovery period at 250 mg/m^3. Pulmonary lesions with progressive epithelial and fibroproliferative changes were observed at 250 mg/m^3. These epithelial changes were also manifested in rats as evidenced by an increase in alveolar cell labeling at 250 mg/m^3 in cell proliferation studies. Based on these results, 10 mg/m^3 is considered as the NOAEC in this study.

In another inhalation study, male rats were exposed to aerosols of titanium dioxide (rutile) at concentrations of 0, 25 or 50 mg/m^3. Rats were exposed by whole-body inhalation 7 hours/day, 5 days/week (25 mg/m^3 exposure for 209 days, and 50 mg/m^3 for 118 days). The MMAD (GSD) for titanium dioxide was 2.1 µm (2.2). There were 6 time points and generally 12 animals/concentration were used. The lung burdens at the final exposure points were 24 and 17 mg/g for the high and low-dose groups, respectively. The mean lymph node burdens and number of polymorphonuclear cells (PMN) were raised with increasing exposure. The

higher levels of inflammation occurred concurrently with the higher lymph node burdens, after 69 and 139 days in the 50 and 25 mg/m^3 group. The predicted averages for percent PMN were, for the high and low-dose groups, respectively, 28% and 16%. The mean numbers of alveolar macrophages obtained did not change significantly compared to control animals. Titanium dioxide showed no significant fibrogenic activity. Therefore, the LOAEC for titanium dioxide was considered to be 25 mg/m³ based on the increased mean number of neutrophils with exposure-related lymph-node burdens.

In another study, female rats were exposed for 6 hours/day, 5 days/week for 4 weeks by nose-only inhalation to 0, 0.1, 1.0, or 10 mg/m^3 of titanium dioxide (MMAD: 1.3 µm , GSD: 2.6, respirable fraction was not available) and the lung burdens were determined at 1 week after the end of the exposure. The lungs were evaluated by analysis of bronchoalveolar lavage fluid (BALF) at 1, 8, and 24 weeks after the end of the exposure and by histopathology at 24 weeks. With lung burdens up to 420 µg/g lung, titanium dioxide elicited no changes in BALF parameters at any time after exposure, nor were any histopahological findings observed. Therefore, the NOAEC was considered to be 10 mg/m^3.

In another inhalation study following OECD TG 453, the test substance (rutile) was administered via inhalation (dry aerosol, whole body) to 50 rats/sex/concentration at 0 or 5 mg/m^3 for 6 hours/day, 5 days/week for 24 months. The MMAD (GSD) was 1.1 µm (1.6) and the respirable fraction was 78%, equivalent to 3.87±0.28 mg/m^3. A 5% incidence of lung fibrosis was seen in the titanium dioxide-exposed groups. After exposure, minor changes were observed in the cytologic pattern of the BALF. A lymphoid hyperplasia of the lung-associated lymph nodes was observed in the titanium dioxide-exposed group. Thus, the LOAEC was considered to be 5 mg/m^3 in rats.

A repeated dose inhalation study was conducted to examine burdens of titanium dioxide (rutile) in the lung and lung associated lymph nodes and selected lung responses in mice and hamster (73 females/concentration). Animals were exposed to 0, 10, 50 or 250 mg/m^3 pigmentary titanium dioxide for 6 hours/day, 5 days/week for 13 weeks with recovery groups held for an additional 4, 13, 26 or 52 weeks (46 weeks for hamster) post-exposure (MMAD: 1.39 µm in mice, 1.36 µm in hamster). Pulmonary parameters including inflammation, cytotoxicity, lung cell proliferation, and histopathologic alterations were assessed. Pigmentary titanium dioxide burdens in the lung and lymph nodes increased in a concentration-dependent manner. Inflammation was noted at 50 and 250 mg/m^3, as evidenced by increase in macrophage and neutrophil numbers and in soluble indices of inflammation in BALF. Based on the results, the NOAEC for mice and hamsters was 10 mg/m^3.

Mutagenicity

In an Ames test [OECD TG 471] with multiple strains of *Salmonella typhimurium*, and one strain of *Escherichia coli*, titanium dioxide did not induce gene mutations *in vitro* with and without metabolic activation. In a mammalian cell gene mutation assay [OECD TG 476] with mouse lymphoma L5178Y TK +/- cells, titanium dioxide was not mutagenic both with and without metabolic activation. Titanium dioxide did not induce chromosomal aberrations [OECD TG 473] in *in vitro* Chinese Hamster Ovary (CHO) cells and human lymphocytes with and without metabolic activation. In *in vitro* sister chromatid exchange (SCE) assays, titanium dioxide induced increasing SCE frequencies in CHO-K1 cells and human lymphocytes but did not induce any effects of SCE in CHO cells. In CHO-K5 cells, titanium dioxide did not induce micronucluses but induced it in CHO-K1 cells and human lymphocytes. In a recombination assay with *Bacillus subtilis* H17 (rec+) and M45 (rec-), titanium dioxide showed a negative result.

In an *in vivo* study [no guideline followed], titanium dioxide did not induce chromosome aberrations in mouse bone marrow cells and did not significantly elevate levels of micronuclei in the bone marrow cells of mice. However, it is not clear whether there was any exposure of the target tissues. In an *in vivo* sex-linked recessive lethal (SLRL) test with *Drosophila melanogaster*, it was suggested that titanium dioxide showed a negative result. In a non-standard *hprt* gene mutation assay, the *hprt* mutation frequency was significantly increased in alveolar type II cells of rats after *in vivo* exposure to titanium dioxide.

Based on the results from mutagenicity studies *in vitro*, the majority of the studies were negative (Ames, chromosome aberration and mammalian cell gene mutation tests). Positive results were observed in two micronucleus studies and two Sister Chromatid Exchange assays *in vitro* and were thought to be a consequence of oxidative stress mediated DNA damage. *In vivo* the results of somatic cell studies were negative, however it is not possible to conclude on the *in vivo* genotoxic potential of titanium dioxide due to

a positive result observed in a non-standard *in vivo* site of contact study in alveolar cells.

Table 1. Summary of genotoxicity results

Type of genotoxicity	**Type of study**	**Concentration range**	**Result**
In vitro			
Gene mutation assay	mouse lymphoma L5178Y TK +/- cells	31-500 µg/mL (±S9)	negative
	mouse lymphoma L5178Y cells, clone 3.7.2C	1.56-50 µg/mL (±S9)	negative
Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 and *Escherichia coli* WP2*uvr*A	100-5,000 µg/plate (±S9)	negative
	S. typhimurium strains TA1535, TA1537, TA98 and TA100 and *E. coli* strains WP2 and WP2*uvr*A	100-5,000 µg/plate (±S9)	negative
	Salmonella typhimurium TA1535, TA97, TA98 and TA100 and *Escherichia coli* WP2*uvr*A	100-10,000 µg/plate (±S9)	negative
Chromosomal aberration test	CHO cells	125-2,500 µg/mL (±S9)	negative
	CHO cells	1st trial: 68.72-800 µg/mL (-S9) and 167.8-800 µg/mL (+S9), 2nd trial: 167.8-800 µg/mL (+S9)	negative
	human lymphocytes	10-100 µg/mL (±S9)	negative
	CHO cells	15-25 µg/mL (±S9)	negative
Micronucleus test	human peripheral blood lymphocytes	1-10 µM	enhance oxidative stress-mediated DNA damage *in vitro*
	CHO-K1 cells	1-20 µM	positive
	CHO-K5 cells	0.025-10.0 µg/mL (-S9), 0.25-10.0 µg/mL (+S9)	negative
Sister chromatid exchange assay	CHO-K1 cells	1-5 µM	positive (1.59-fold to that of the control)
	CHO cells	2.5-25 µg/mL (±S9)	negative
	human peripheral blood lymphocytes	1-10 µM	enhance oxidative stress-mediated DNA damage *in vitro* (2-fold increase at 10 µM)
Bacillus subtilis recombination assay	*Bacillus subtilis* H17 (rec+), M45 (rec-)	0.005-0.5M	negative
In vivo			

Chromosomal aberration test	mouse bone marrow cells	625- 2,500 mg/kg	negative
Micronucleus test	mouse bone marrow cells	1st trial: 0-1,000 mg/kg bw 2nd trial: 0-1,500 mg/kg bw	negative
Sex-linked recessive lethal (SLRL) test	*Drosophila melanogaster*	Feeding: 1,500 ppm Injection: 5,680 ppm	negative
hprt *gene mutation assay*	alveolar type II cells in rats	10 and 100 mg/kg bw	positive

Carcinogenicity

In an oral carcinogenicity study, titanium dioxide was administered via the diet to 50 mice and 50 rats (per sex and per dose) at 0, 25,000 or 50,000 ppm (equivalent to 0, 3,250 and 6,500 mg/kg bw/day in the mice and 0, 1,250 and 2,500 mg/kg bw/day in rats) for 7 days/103 weeks. In mice, mortality results in female showed a significantly (p=0.001) positive dose-related trend. There was no effect on the mean body weight. No tumors occurred in dosed groups at incidences that were significantly higher than those for control groups. In rats, there was no excess mortality in any dosed groups and no effect on the mean body weight. Observed histopathological findings were not considered to be related to administration of titanium dioxide. Therefore, there was no evidence of carcinogenicity at any dose level in the oral studies.

There are three inhalation carcinogenicity studies of titanium dioxide in rats. In one study, the test substance was administered via inhalation (whole body) to 80 rats/sex/concentration at 0, 10, 50 or 250 mg/m^3/day for 6 hours/day for 5 days/week for up to 2 years. Titanium dioxide particle (rutile) was a spherical configuration and a 1.5-1.7 µm MMAD. Approximately 84% of the dust particles were of respirable size (<13 µm MMAD). No excess death was observed in either sex. Bronchioloalveolar adenomas, squamous metaplasias, pulmonary keratin cysts and squamous cell carcinomas were observed in the 250 mg/m^3 treatment group, while no compound-related lung tumors were found in rats exposed either to 10 or 50 mg/m^3. At 250 mg/m^3/day, the tumor findings are considered to be the result of prolonged inflammation and fibrogenesis as a result of particle overload of the clearance mechanism of the lung.

In another study following OECD TG 453, the test substance (99.5% rutile, MMAD: 1.1 µm, GSD: 1.6, respirable fraction was 78% which equivalent to 3.87±0.28 mg/m^3) was administered via inhalation (dry aerosol, whole body) to 50 rats/sex/concentration at 0 or 5 mg/m^3/day (limit test), for 6 hours/day and 5 days/week for up to 2 years. The incidence of primary lung tumors among the titanium dioxide-exposed rats (2/100; one adenoma and one adenocarcinoma) was comparable to the air-only controls (3/100; two adenoma and one adenocarcinoma).

In another study, groups of 50 male and 50 female rats were exposed by inhalation to 0 or 15.95 mg/m^3 titanium dioxide (99.9%, <0.5 µm) for 6 hour/day, 5 days/week for 12 weeks. At the end of the study, 78% of control and 88% of treated males and 90% of control and treated females survived. No significant differences in body weights or incidence of tumors were observed between control and treatment groups (lung and other respiratory tract tumors were benign; other neoplasms seen in the lung were metastases from tumors of other sites).

Based on the results from inhalation studies, the tumors observed in rats (such as bronchioloalveolar adenomas, squamous metaplasias, pulmonary keratin cysts and squamous cell carcinoma were observed in 250 mg/m^3), are thought to be secondary to particle overload. Therefore, titanium dioxide treated via inhalation was considered to have carcinogenic potential.

Titanium dioxide is classified by IARC (2010)as group 2B (Possibly carcinogenic to humans).

Reproductive and Developmental Toxicity

Titanium dioxide has been investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 421]. Titanium dioxide was administered by oral gavage to 10 animals/sex at 0 or 1,000 mg/kg bw/day (limit test), to male rats from two weeks prior to mating, during the mating period and,

approximately, two weeks post mating, and to female rats from two weeks prior to mating, during the mating period, gestation period and 3 days after lactation. During the observation period, there were no dose related effects on clinical signs, body weights, food consumption, mating, gestation, delivery, organ weights, necropsy and histopathology in parents. No dose-related changes in clinical signs, body weights, viability index, external malformations and sex ratios were noted in pups. This study found no indication of any reproductive toxicity in parent animals or developmental toxicity in pups. Therefore, the NOAEL for reproductive and developmental toxicity was 1,000 mg/kg bw/day.

Titanium dioxide possesses properties indicating a hazard for human health (potential genotoxicity, repeated dose toxicity and carcinogenicity via inhalation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

Photodegradation is not applicable to metal-containing inorganic oxide substances that possess negligible vapour pressure such as titanium dioxide. Titanium dioxide is expected to be stable in water due to the absence of water-reactive functional groups, and due to its insolubility in water. Biodegradation, and environmental fate analysis based on log K_{ow} and log K_{oc}, are not applicable for inorganic substances such as titanium dioxide.

For the aquatic toxicity test, a water-accommodated fraction (WAF) was prepared with bulk titanium dioxide under OECD Series on Testing and Assessment Number 23. Test concentrations were expressed as a loading rate. The analysis results of the test substance in the test solution showed that the concentration was <LOQ of 0.1 mg/L for algae and <LOQ of 0.02 mg/L for fish and invertebrate.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Oryzias latipes*, OECD TG 203]	96 h LL_{50}>100 mg/L (nominal; static)
Invertebrate [*Daphnia magna*, OECD TG 202]	48 h EL_{50}>100 mg/L (nominal; static)
	48 h EC_{50}>100, 48 h EC_{10}=91.2 mg/L (nominal; dispersion; static)
Algae [*Pseudokirchneriella subcapitata*, OECD TG 201]	
	72 h E_rL_{50} >100 mg/L (growth rate, nominal; static)
	72 h E_yL_{50} >100 mg/L (yield, nominal; static)

Titanium dioxide has a low hazard for the environment (acute aquatic toxicity > 100 mg/L). Adequate screening-level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Exposure

In the Republic of Korea (sponsor country), the production, use and import volumes of titanium dioxide were 63,239, 227,446 and 126,748 tonnes in 2010, respectively. In Sweden, Denmark, Norway and Finland estimated use volumes of titanium dioxide were approx. 73,085, 148,816, 54,968, 49,855 and 75,988 tonnes in 2006, 2007, 2008, 2009 and 2010, respectively.

In the sponsor country, titanium dioxide is mainly used as a pigment in paints and paint additives. Titanium dioxide is used as a white pigment, opacifying agent in coatings, inks, adhesives, synthetic resins, plastic, rubber products and paper products. It is also used as a white colorant in foods, cosmetics and drugs, sunscreen, textiles and toothpaste.

For consumer exposure, the use of titanium dioxide is limited to a coloring agent in food and pharmaceuticals in the sponsor country. The general public may be exposed to small quantities of titanium dioxide by the

consumption of some food/foodstuff additives and intended use of products such as toothpastes (especially by children) and others. Titanium dioxide is acceptable for general food use with no established ADI. However, the US FDA suggests the quantity of titanium dioxide should not exceed 1 percent by weight of the food.

The most common industrial manufacturing process is as follows: ilmenite is treated using sulfuric acid and the titanium sulfate is further processed to titanium dioxide. The product is primarily the anatase form. Rutile is chlorinated and the titanium tetrachloride converted to the rutile form of titanium dioxide by vapour-phase oxidation.

In use facilities of the sponsor country, titanium dioxide is handled in closed systems and is used commercially as a powder. According to monitoring data, titanium dioxide was not detected in the workplace from 2009 to 2011. Occupational exposure is managed with personal protective equipment such as a gas mask with dustproof filter in the workplace.

Titanium dioxide may be released into water, the atmosphere and soil from the use and disposal of titanium dioxide containing products.