Diisopropoxytitanium Bis(ethylacetoacetate) (CAS# 27858-32-8) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Washington State Department of Ecology

Prepared by:

ToxServices LLC

October 16, 2014

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for Diisopropoxytitanium bis(ethylacetoacetate) (CAS #27858-32-8)

Diisopropoxytitanium bis(ethylacetoacetate) is a chemical that is used as a catalyst and coupling agent in adhesives, sealants, inks, fillers, and flame retardants.

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it has Moderate Group I Human Toxicity (reproductive toxicity (R) and developmental toxicity (D)) and Very High Group II Human Toxicity (systemic toxicity single dose (STs)). This corresponds to GreenScreen® benchmark classifications 2e and 2f in CPA 2011. Data gaps (DG) exist for endocrine activity (E), respiratory sensitization (SnR*), and skin irritation (IrS). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), diisopropoxytitanium bis(ethylacetoacetate) meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if diisopropoxytitanium bis(ethylacetoacetate) were assigned a High score for the data gap endocrine activity (E), it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
As a standard approach for GreenScreen® evaluations, all exposure routes (oral, dermal, and inhalation) were evaluated together, so the GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Diisopropoxytitanium Bis(ethylacetoacetate)

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*										
L	**L**	*M*	*M*	DG	**L**	*vH*	**L**	*M*	*L*	*L*	DG	DG	*H*	**L**	**L**	*L*	*vL*	*L*	**M**

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 Diisopropoxytitanium Bis(ethylacetoacetate) (CAS #27858-32-8)

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

Chemical Name: Diisopropoxytitanium bis(ethylacetoacetate)

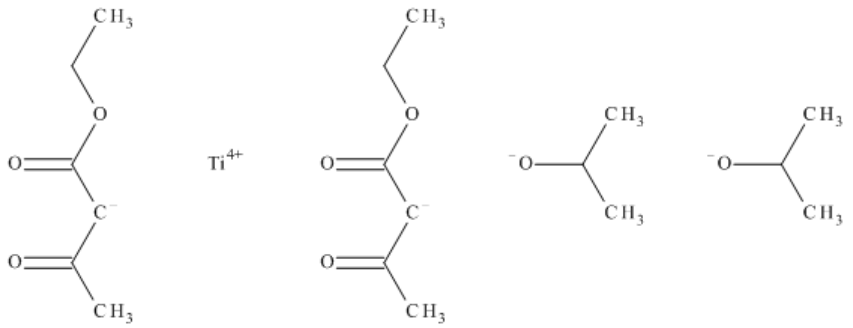
CAS Number: 27858-32-8

GreenScreen® Assessment Prepared By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 1, 2014
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 16, 2014

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

Chemical Structure(s):

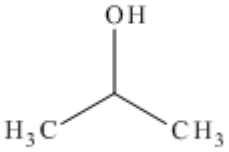


Also called: Titanium, bis(ethyl 3-(oxo-kappaO)butanoato-kappaO')bis(2-propanolato)-; Diisopropoxydi(ethoxyacetoacetyl)titanate; Bis(ethyl acetoacetato-O1',O3)bis(propan-2-olato)titanium; Titanium, bis(ethyl 3-(oxo-kappaO)butanoato-kappaO')bis(2-propanolato)-; Titanium, bis(ethyl 3-oxobutanoato-O1',O3)bis(2-propanolato)- (ChemIDplus 2014)

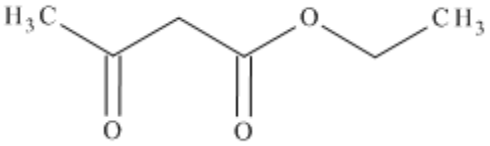
Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
Only a limited dataset was available for diisopropoxytitanium bis(ethylacetoacetate). This chemical is rapidly hydrolyzed (half-life ≤ 10 minutes) to isopropanol (CAS# 67-63-0), ethyl acetoacetate (CAS# 141-97-9), and hydrated titanium dioxide (CAS# 13463-67-7) (ECHA 2014a). Based on the structure of diisopropoxytitanium bis(ethylacetoacetate), hydrolysis is expected to produce two moles each of isopropanol and ethyl acetoacetate and 1 mole of titanium dioxide. Since *in vivo* exposure is expected for these hydrolysis products, they were used as surrogates to fill data gaps. Inhalation studies for

[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

titanium dioxide were not considered, since this compound is an inorganic solid and exposure following *in vivo* hydrolysis of diisopropoxytitanium bis(ethylacetoacetate) is likely to differ from direct inhalation exposure to titanium dioxide dust.



Isopropanol (CAS# 67-63-0)



Ethyl acetoacetate (CAS# 141-97-9)

Titanium dioxide (CAS# 13463-67-7)

Identify Applications/Functional Uses: (Capaute undated)
1. Catalyst (Wacker Chemie undated)
2. Coupling agent (Capaute undated)
3. Adhesives
4. Sealants
5. Inks
6. Fillers
7. Flame retardants

GreenScreen® Summary Rating for Diisopropoxytitanium Bis(ethylacetoacetate)[4]:
Diisopropoxytitanium bis(ethylacetoacetate) was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it has Moderate Group I Human Toxicity (reproductive toxicity (R) and developmental toxicity (D)) and Very High Group II Human Toxicity (systemic toxicity single dose (STs)). This corresponds to GreenScreen® benchmark classifications 2e and 2f in CPA 2011. Data gaps (DG) exist for endocrine activity (E), respiratory sensitization (SnR*), and skin irritation (IrS). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), diisopropoxytitanium bis(ethylacetoacetate) meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if diisopropoxytitanium bis(ethylacetoacetate) were assigned a High score for the data gap endocrine activity (E), 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 Diisopropoxytitanium Bis(ethylacetoacetate)

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*										
L	**L**	*M*	*M*	DG	**L**	*vH*	**L**	*M*	*L*	*L*	DG	DG	*H*	**L**	**L**	*L*	*vL*	*L*	**M**

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]

Diisopropoxytitanium bis(ethylacetoacetate) hydrolyzes rapidly, producing isopropanol, ethyl acetoacetate, and hydrated titanium dioxide (ECHA 2014a). Although titanium dioxide is an LT-1 chemical, this classification is based on the potential for carcinogenic effects following occupational inhalation exposure of particles of respirable size. Since titanium dioxide is only formed following hydrolysis in the environment, such exposures are not expected to occur based on the use pattern of diisopropoxytitanium bis(ethylacetoacetate). Therefore the overall benchmark score for diisopropoxytitanium bis(ethylacetoacetate) was not affected by this transformation product.

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	Feasible and Relevant?	CAS #	List Translator Results[6,7]
Unknown	Unknown	Hydrolysis	Isopropanol	Y	67-63-0	LT-U
Unknown	Unknown	Hydrolysis	Ethyl acetoacetate	Y	141-97-9	LT-U
Unknown	Unknown	Hydrolysis	Titanium dioxide	N for inhalation hazards (see justification above); Y for other hazards	13463-67-7	LT-1

[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.
[6] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2014) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[7] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

Introduction

Diisopropoxytitanium bis(ethylacetoacetate) is a titanium ethyl acetoacetate complex that is used as a catalyst (Wacker undated) and coupling agent (Capaute undated) for use in adhesives, sealants (ECHA 2014a), inks, fillers, and flame retardants (Capaute undated).

ToxServices assessed diisopropoxytitanium bis(ethylacetoacetate) 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 diisopropoxytitanium bis(ethylacetoacetate)can be found in Appendix C and a summary of the results can be found below:

- Persistence
    - Environment Canada - Domestic Substances List (DSL) DSL substances that are Persistent

PhysicoChemical Properties of Diisopropoxytitanium Bis(ethylacetoacetate)

Diisopropoxytitanium bis(ethylacetoacetate) is a clear yellow to amber liquid at room temperature with a melting point of 17ºC. It decomposes during the test for vapor pressure, and therefore vapor pressure cannot be determined. No partition coefficient was identified.

Table 1: Physical and Chemical Properties of Diisopropoxytitanium Bis(ethylacetoacetate) (CAS #27858-32-8)

Property	Value	Reference
Molecular formula	C18-H32-O8-Ti	ChemIDplus 2014
SMILES Notation	O=C(OCC)[CH-]C(C)=O.[Ti+4].O=C([CH-]C(=O)OCC)C.[O-]C(C)C.[O-]C(C)C	ChemIDplus 2014
Molecular weight	424.31	ChemIDplus 2014
Physical state	Liquid	ECHA 2014a
Appearance	Clear yellow to amber	ECHA 2014a
Melting point	17°C	ECHA 2014a
Vapor pressure	Not determined (decomposes during testing)	ECHA 2014a
Water solubility	Not identified	
Dissociation constant	Not identified	
Density/specific gravity	1.094 at 25°C	ECHA 2014a
Partition coefficient	Not identified	

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for carcinogenicity based on negative carcinogenicity data for the hydrolysis products isopropanol and titanium dioxide. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and are negative for carcinogenicity, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

  - No data were identified

Isopropanol (CAS# 67-63-0)

- IARC 2012
  - Cancers in the nasal cavity were observed in workers during manufacture of isopropanol by the strong-acid processes. Isopropanol is manufactured by three methods: indirect hydration of propylene, direct hydration of propylene, and catalytic hydrogenation of acetone. In the indirect-hydration method, there are two processes, the strong acid process which uses sulfuric acid at high concentrations (>80% wt) and low temperature (20-30ºC), and the weak-acid process which uses a lower concentration of acid (60 – 80%) at higher temperatures (60 – 65ºC). A plausible mechanism of carcinogenesis of the strong-acid process to produce isopropanol involves the inhalation of inorganic acid mists that causes DNA damage. There are no data available to evaluate the carcinogenicity of strong acid mists in experimental animals. It was concluded that isopropanol manufactured by the strong-acid process is carcinogenic to humans (Group I).
- IARC 1999
  - Increased incidences of paranasal sinuses and laryngeal cancers were reported where isopropanol was manufactured by the strong-acid process. However, one case-control study did not find an association of occupational isopropanol exposure and increased cancer incidences.
  - One study with limitations in design and adequacy did not find increased tumor incidences in mice but found a slight increase in interstitial cell adenomas of the testis in male rats after chronic inhalation to isopropanol.
  - It was concluded that there is inadequate evidence for carcinogenicity of isopropanol in humans and in experimental animals.
- ECHA 2014b
  - A GLP-compliant inhalation oncogenicity study was conducted according to OECD guideline 451 in F344 rats and CD-1 mice. Animals were exposed to isopropanol vapor via whole body inhalation at 0, 500, 2,500, or 5,000 ppm for 6 hours/day, 5 days/week for 104 weeks (rats) and 78 weeks (mice). In rats (65/sex/dose for the core group and 10/sex/dose for interim sacrifice), there was a dose-related increase in interstitial cell adenomas of the testis at interim and terminal sacrifices and in males that died during the study. The authors stated that testicular adenomas are common in aged male rats with a historical incidence rate of 88% in studies conducted by the National Toxicology Program (NTP), while the incidence in control rats in the current study was 64.9%. Therefore, this tumor was

considered to be possibly spurious by the study authors. In mice (55/sex/dose for the core group, 10/sex/dose for the interim sacrifice group, and 10/sex/dose for recovery group), no treatment-related neoplastic lesions were found (Burleigh-Flayer H et al. 1997 as cited in ECHA 2014b).

Ethyl acetoacetate (CAS# 141-97-9)

- No data were identified

Titanium dioxide (CAS# 13463-37-7)

- 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 & 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
    - A 103-week carcinogenicity study (GLP status and guideline used were 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 (approx 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
    - 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, 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 hyperplasion 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.
- Based on the weight of evidence, a score of Low was assigned. Negative carcinogenicity data were obtained for the hydrolysis product isopropanol, and the hydrolysis product titanium dioxide was negative in oral toxicity studies. Authoritative listings for carcinogenicity for titanium dioxide were not considered in the assessment, as these listings apply only to occupational inhalation exposure to respirable particles. As titanium dioxide is not formed until diisopropoxytitanium bis(ethylacetoacetate) hydrolyzes upon contact with water internally, such inhalation exposures are not relevant. These negative data for the hydrolysis products in conjunction with negative genotoxicity data for diisopropoxytitanium bis(ethylacetoacetate) indicate that it is not likely to be a

carcinogen. Confidence in this score is reduced because no carcinogenicity data were available for ethyl acetoacetate.

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for mutagenicity/genotoxicity based on negative results in *in vitro* bacterial and mammalian cell mutagenicity assays and an *in vitro* mammalian cell chromosome aberration assay. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and are negative for both mutagenicity and clastogenicity, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014a
    - Diisopropoxytitanium bis(ethylacetoacetate) (purity not reported) was negative in a bacterial reverse mutation assay in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 when tested at concentrations of 1,000, 3,000, 5,000, 7,000, and 10,000 µg/plate with and without metabolic activation. No increases in mutations were seen in any strain at any dose.
    - Diisopropoxytitanium bis(ethylacetoacetate) (95-100% purity) was negative in a GLP-compliant *in vitro* mammalian cell mutagenicity assay in mouse lymphoma L5178Y cells when tested at concentrations up to 333 µg/mL with and without metabolic activation. No increase in mutations was seen in either of two independent experiments.
    - Diisopropoxytitanium bis(ethylacetoacetate) (95-100% purity) was negative in a GLP-compliant *in vitro* mammalian chromosome aberration assay in peripheral human lymphocytes when tested at concentrations up to 900 µg/mL without metabolic activation and 333 µg/mL with metabolic activation. No increase in aberrations was seen in either of two independent experiments.

Reproductive Toxicity (R) Score (H, M, or L): *M*

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Moderate for reproductive toxicity based on reproductive effects in 1-generation drinking water studies of the hydrolysis product isopropanol in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity in animals (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- No data were identified

Isopropanol (CAS# 67-63-0)

- ECHA 2014b
    - A GLP-compliant 2-generation reproductive toxicity study was conducted according to OECD guideline 416. Isopropanol was administered to Sprague-Dawley rats via daily gavage at 0, 100, 500, or 1,000 mg/kg/day. There were no treatment related changes in body weight, food consumption, reproductive performance, gross pathology, and histopathology in parental animals. Absolute and relative liver weights were statistically significantly increased in high dose P1 males. Relative liver weight was increased in the mid and high

dose females, and relative kidney weight was increased at the high dose only in females. The NOAEL for reproductive toxicity was established at 1,000 mg/kg/day by ECHA based on lack of reproductive effects (Report date: 1992).

- A GLP-compliant 1-generation reproductive toxicity study was conducted according to OECD guideline 415. Isopropanol was administered to Wistar rats in drinking water at 0, 0.5, 1.0, or 2.0%. There were no deaths, abortions, early deliveries, or dams removed from the study. Reduced water intake was observed in males at all doses, but was transient only at the lowest dose. There was also a dose-related decrease in food consumption, but body weight gain was not significantly affected in males. In females, water and food consumption decreased at the mid and high doses prior to mating, and the reduction persisted to the lactation period at the high dose. There were no treatment-related effects on male and female fertility or the length of gestation in females. The number of pups/litter on gestation day 1 decreased at the high dose. Since this effect was not replicated in the embryotoxicity portion of the study, it was proposed that pup mortality was increased during parturition of gestation followed by cannibalism of the dead pups by the dam. A slight dose-dependent reduction in red blood cells was found in males at the high dose and in females at the mid and high doses. The mean cell volume in the mid and high doses was also decreased in males. A statistically significant increase was found in absolute kidney weight and relative kidney, liver, and spleen weights in F0 high dose males, and in absolute liver and kidney weights and relative liver weights in F0 females. Increased pre-implantation loss, decreased mean litter weight and mean fetal body weight were observed at the high dose. ECHA reported a NOAEL of 0.5% for parental systemic toxicity based on reduced food and water intake, reduced body weight, changes in red blood cells, and cell volume and organ weight changes to liver, kidney, and spleen. A NOAEL of 1% (853, 1,330, and 1,948 mg/kg/day for females during premating, gestation, and postpartum phases, respectively) was reported for reproductive toxicity based on increased pre-implantation loss, decreased mean litter weight, and mean fetal body weight (Report date: 2008).
- A GLP-compliant 1-generation reproductive toxicity study was conducted according to OECD guideline 415. Wistar rats received isopropanol in drinking water at 0, 0.5, 1.25, 2, or 2.5%. Reduced water intake was found at concentrations of 1.25% and above. Body weight was reduced at 2.0 and 2.5% in both sexes. There was 100% fertility, but also evidence of embryotoxicity as demonstrated by fewer pups produced, increased pup mortality, and reduced pup weight gain at 2.0 and 2.5%. There were signs of anemia in females and all rats had increased liver and kidney weights at doses of 1.25% and higher (Report date: 1986).

<u>Ethyl acetoacetate (CAS# 141-97-9)</u>

- EC 2002
  - In a GLP-compliant reproductive and developmental toxicity screening test according to OECD Guideline 421, Sprague Dawley rats (10/sex/dose) were administered doses of 0, 50, 225, and 1,000 mg/kg/day via gavage; males were treated daily from 2 weeks before mating until the end of the mating period, and females were treated daily from 2 weeks before mating until the 4th day of lactation. In the high-dosed dams (1,000 mg/kg/day), the number of corpora lutea and implants was slightly decreased compared to the control, leading to a mean pre-implantation loss of 5.0% versus the control of 2.0%. Statistical significance of this difference was not reported. There were no effects on pre-coital time, duration of pregnancy, histopathology of reproductive organs, or parturition. The number of pups at birth and during the 4 day lactation period was slightly decreased due to the reduction in implants, which resulted in a decrease in mean birth index and live birth index compared to

concurrent controls. There were no effects on the mean viability index. EC reports that after considering the historical control data for 7 additional OECD Guideline 421 studies, the effects seen at the high dose are not considered to be toxicologically significant. EC identified a NOAEL of 1,000 mg/kg/day for reproductive toxicity based on the lack of toxicologically significant effects.

Titanium dioxide (CAS# 13463-37-7)

- OECD 2013a
    - In a reproductive and developmental toxicity screening test 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.
- Based on the weight of evidence, a conservative score of Moderate was assigned based on increased pre-implantation loss, reduced number of pups produced, increased pup mortality, and decreased mean litter weight and mean fetal body weight as observed in 1-generation drinking water studies of the hydrolysis product isopropanol. Confidence in this score is reduced as no effects on reproduction were seen in the 2-generation gavage study of isopropanol, and because the other hydrolysis products, ethyl acetoacetate and titanium dioxide, were negative in reproductive toxicity screening tests.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Moderate for developmental toxicity based on developmental effects seen in oral toxicity studies of the hydrolysis product isopropanol in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity in animals (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- No data were identified

Isopropanol (CAS# 67-63-0)

- ECHA 2014b
    - In the 2-generation gavage toxicity study described above, increased mortality was observed with high dose F1 offspring from postnatal days 0-2. Several F1 weanlings (1 each at low and mid doses and 18 at the high dose) died or were euthanized prior to P2 selection. In addition, body weight was significantly decreased for F1 males at the high dose on postnatal days 0 and 1. A NOAEL of 500 mg/kg/day (LOAEL = 1,000 mg/kg/day) for offspring toxicity was identified in ECHA based on reduced body weights and increased mortality (Report date: 1992).
    - In the 1-generation drinking water toxicity study described above, a statistically significant increase in the total number of pre-implantation losses and a slight but not statistically significant decrease in mean litter and mean fetal weights were observed at 2.0%. A 40% incidence of whole body edema was found in fetuses in 3 of the 8 litters at the high dose but there were no macroscopic abnormalities of the viscera in these fetuses. A statistically significant decrease in postnatal survival and average pup weight was found at the high dose.

In the F1 generation, significant increase in relative liver weight was found at all dose levels, and a significant increase in relative kidney weight was found at the high dose only. There was also a slight but statistically significant increase in absolute brain weight and relative empty cecum weight in both sexes at the high dose (Report date 2008).

- A GLP-compliant developmental toxicity study was conducted according to OECD guideline 414. Pregnant New Zealand White rabbits (15/dose) received isopropanol via gavage during gestational day 6 to 18 at 0, 120, 240, or 480 mg/kg/day. There was significant maternal toxicity at the high dose demonstrated as mortality, reduced body weight gain, reduced food consumption, and severe clinical signs of toxicity. Only transient, relatively mild, and nonspecific clinical signs of toxicity were found at lower doses. No developmental toxicity was observed. The authors established a developmental NOAEL at 480 mg/kg/day (Report date: 1990).
- A second GLP-compliant developmental toxicity study was identified that was conducted according to OECD guideline 414. Pregnant Sprague-Dawley rats (25/dose) received isopropanol at 400, 800, or 1,200 mg/kg/day via daily gavage during gestational days 6 and 15. Signs of maternal toxicity were found at 800 and 1,200 mg/kg, including mortality and reduced maternal weight gain. Fetal body weight/litter was significantly reduced at 800 and 1,200 mg/kg/day. The authors identified a developmental NOAEL and LOAEL at 400 and 800 mg/kg/day, respectively (Report date: 1990).
- A third GLP-compliant developmental toxicity was conducted according to OECD guideline 414. Pregnant Wistar rats (20/dose) received isopropanol in drinking water at 0, 0.5, 1.25, or 2.5% during gestational days 6 and 16. Maternal toxicity was found at doses higher than 0.5%, demonstrated by reduced food and water consumption and body weight. There was a slight dose-dependent decrease in mean litter weight and a statistically significant reduction in mean fetal weight at doses higher than 0.5%. There was a statistically significant increase in skeletal variations that suggested a lower degree of ossification in treated animals. There was a dose-dependent decrease in the number of fetuses with the 4th sacral arch and an increase in the number of fetuses with less than 2 caudal arches. An increased number of fetuses with small, absent, or incompletely ossified sternebrae was also observed. A reduction in skull ossification was only observed at the low dose. There were more fetuses with forelimb proximal phalanges, less than 3 metacarpals, or unilateral sternebrae at the mid dose. Increased numbers of fetuses with dumbbell shaped sternebrae or 14 pairs of ribs were found at the low and mid doses. ECHA established a NOAEL at 0.5% (equivalent to 596 mg/kg according to ECHA) for maternal and developmental toxicity, based on reduced maternal food and water consumption and decreased body weight, and decreased mean fetal body weight (Report date: 2008).

- UNEP 1997
  - Available developmental toxicity studies found developmental toxicity in rats but not in rabbits. In rats, developmental toxicity (decreased fetal body weight) was found at maternally toxic doses. It appears that isopropanol is not a selective developmental toxicant.

<u>Ethyl acetoacetate (CAS# 141-97-9)</u>

- EC 2002
  - In the GLP-compliant reproductive and developmental toxicity screening test conducted according to OECD Guideline 421 in Sprague Dawley rats described above for reproductive toxicity, there were no effects on number of pups alive, stillbirths, sex distribution, or malformations. ToxServices identified a NOAEL of 1,000 mg/kg/day based on the lack of developmental effects at the highest dose studied.

Titanium dioxide (CAS# 13463-37-7)

- OECD 2013a
    - In the reproductive and developmental toxicity screening test conducted 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.
- Based on the weight of evidence, a conservative score of Moderate was assigned based on mortality, decreased body weight and/or delayed ossification found in rats at high doses that are maternally toxic. Data suggest that developmental toxicity is secondary to maternal toxicity. However, the possibility cannot be completely ruled out that isopropanol induces developmental toxicity through a mechanism independent of maternal toxicity. Therefore, ToxServices conservatively assigned a score of Moderate. Confidence in this score is reduced because it is possible that effects of isopropanol are due to maternal toxicity, and because the other hydrolysis products, ethyl acetoacetate and titanium dioxide, were negative in developmental toxicity screening tests.

Endocrine Activity (E) Score (H, M, or L): DG

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Data Gap for endocrine disruption based on a lack of data for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists
- 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.

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- No data were identified

Isopropanol (CAS# 67-63-0)

- No data were identified

Ethyl acetoacetate (CAS# 141-97-9)

- No data were identified

Titanium dioxide (CAS# 13463-37-7)

- No data were identified

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for acute toxicity based on an oral LD_{50} of 23,020 mg/kg in rats. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when the oral LD_{50} is greater than 2,000 mg/kg (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014c
    - *Oral*: LD_{50} (rat, male Chr:CD) = 23,020 mg/kg

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
Group II Score (single dose)* (vH, H, M, or L): *vH
Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Very High for systemic toxicity (single dose) based on GHS Category 1 classification of the hydrolysis product isopropanol. GreenScreen® criteria classify chemicals as a Very High hazard for systemic toxicity (single dose) when the chemical is classified to GHS Category 1 (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- No data were identified

Isopropanol (CAS# 67-63-0)

- NITE 2006
    - Isopropanol is classified as GHS Category 1 in Japan based on effects on central nervous system, kidneys, and systemic toxicity.
- HSDB 2012
    - In humans, signs of acute toxicity after inhalation, ingestion, or skin absorption of isopropanol include vomiting, abdominal pain, hematemesis, depressed respirations, and oliguria followed by diuresis. Generalized tenderness, induration, and edema of muscles may also occur. In addition, cardiovascular system effects include tachycardia and hypotension associated as the result of peripheral vasodilation. Cases of acute tubular necrosis, hepatic dysfunction, hemolytic anemia, myoglobinuria, and mild hypothermia have also been reported.
- UNEP 1997
    - In humans, symptoms of acute exposure to isopropanol usually reside in the absence of shock.

Ethyl acetoacetate (CAS# 141-97-9)

- ECHA 2014c
    - *Dermal*: In a GLP-compliant acute dermal toxicity study according to OECD Guideline 402, Wistar rats (5/sex) were dermally administered a single dose of 2,000 mg/kg ethyl acetoacetate under semiocclusion for 24 hours and were observed for 14 days. There were no deaths, signs of systemic toxicity, effects on body weight, or gross abnormalities.

Titanium dioxide (CAS# 13463-37-7)

- ECHA 2014d
    - *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 doses of 3,400, 5,000, and 7,500 mg/kg had weight loss of up to 6% one day after dosing. No other findings were reported.
- Based on the weight of evidence, a conservative score of Very High was assigned, due to GHS classification of the hydrolysis product isopropanol as GHS Category 1 for effects on the kidneys and systemic toxicity in humans. Confidence in this score is reduced as no adverse effects were seen for the other two hydrolysis products.

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for systemic toxicity (repeated dose) based on repeated dose studies of the hydrolysis products isopropanol, ethyl acetoacetate, and titanium dioxide. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data are available and no adverse effects are seen below the guidance values of 100 mg/kg/day for an oral study and 1 mg/L for an inhalation study (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

<u>Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)</u>

- No data were identified

<u>Isopropanol (CAS# 67-63-0)</u>

- ECHA 2014b
    - *Inhalation*: In a GLP-compliant subchronic inhalation toxicity study conducted according to OECD guideline 413, F344 rats (10/sex/dose at 100 ppm and 25/sex/dose for the other groups) and CD-1 mice (10/sex/dose) were exposed to isopropanol via whole-body inhalation at 0, 100, 500, 1,500, or 5,000 ppm for 6 hours/day, 5 days/week for 13 weeks (equivalent to 0, 0.18, 0.88, 2.6, and 8.8 mg/L/6h/day). In rats, there were decreased absolute body weight and body weight gain and changes in hematology parameters (suggestive of a transient slight anemia) at 1,500 and 5,000 ppm. Relative liver weight was increased in both sexes at 5,000 ppm. Histological examination revealed hyaline droplets in the kidneys of all male rats including controls, with a non-dose-related increase in size and frequency of these droplets. The biological significance of this kidney pathology is unclear. In mice, increased body weight and body weight gain were observed at 5,000 ppm in females only. Changes in hematology were observed in female mice at 5,000 ppm, indicative of a slight dehydration effect. Increased relative liver weight was found in female mice at 5,000 ppm. No other effects were noted. ToxServices established the NOAEL and LOAEL of 1,500 (2.6 mg/L/6h/day) and 5,000 ppm (8.8 mg/L/6h/day), respectively, based

on changes in body weight and liver weight, and in hematology parameters (Report date: 1991).

- *Inhalation*: A GLP-compliant combined repeated dose and carcinogenicity study was conducted according to OECD guideline 451. Fisher 344 rats (65/sex/dose for the core group and 10/sex/dose for interim sacrifice) were exposed to isopropanol via whole body inhalation at 0, 500, 2,500, or 5,000 ppm for 6 hours/day, 5 days/week for 104 weeks (equivalent to 0, 0.88, 4.4, and 8.8 mg/L/6h/day). Changes in body weight and urinalysis parameters indicative of kidney changes (decrease in osmolality and increase in total volume and/or protein) were found at 2,500 and 5,000 ppm. Increased absolute and relative kidney weight was observed in males at 2,500 ppm and in females at 5,000 ppm. There were macroscopic changes such as granular kidney in males and females at the mid and high concentrations. Microscopically, a number of lesions were reported, with the most significant being in the kidney (details not provided for males). In females, there was increased severity of glomerulosclerosis and increased renal disease at the highest concentration. ECHA considered the kidney effects species-specific and not adverse, and established the NOAEC at 5,000 ppm for systemic toxicity. Although it appears that the kidney lesions (hyaline droplets) in male rats may be associated with the α2μ-globulin mechanism that is specific to male rats and not relevant to humans, kidney effects were also observed in female rats, including changed kidney weight, increased severity of glomerulosclerosis, and renal disease. With limited details provided in this study, ToxServices established the LOAEL at 5,000 ppm (8.8 mg/L/6h/day) based on kidney effects in female rats (Burleigh-Flayer H et al. 1997 as cited in ECHA 2014).
- *Inhalation*: A GLP-compliant combined repeated dose and carcinogenicity study was conducted according to OECD guideline 451. CD-1 mice (55/sex/dose for the core group and 10/sex/dose for interim sacrifice) were exposed to isopropanol via whole body inhalation at 0, 500, 2,500, or 5,000 ppm for 6 hours/day, 5 days/week for 78 weeks (equivalent to 0, 0.88, 4.4, and 8.8 mg/L/6h/day). A concentration-related increase in body weight and body weight gain was reported for male mice, with statistical significance reached at 2,500 and 5,000 ppm. There was a concentration related increase in absolute and relative liver weight in female mice that reached statistical significance at 5,000 ppm. ECHA established a NOEC at 500 ppm (0.88 mg/L/6h/day) and LOEC at 2,500 ppm (4.4 mg/L/6h/day) based on increased body weight and body weight gain (Burleigh-Flayer H et al. 1997 as cited in ECHA 2014).
- A GLP-compliant range-finding 14 week study equivalent to OECD guideline 412 was identified, but was not described here as the exposure duration was only 9 days.

- UNEP 1997
  - A few additional repeated dose toxicity studies were identified through oral (two subchronic oral toxicity studies established NOELs > 600 mg/kg/day) and inhalation routes. It was summarized that the only target organ was the kidney. In rats, accumulation of hyaline droplets in proximal tubule cells (males) and an exacerbation of chronic progressive nephropathy (males and females) was found, a spontaneous disease common in aged rats (male and females) of unknown etiology. In mice, effects were minimal to mild, including renal tubular proteinosis and tubular dilation in chronic studies. There was not concentration-related increase in severity and frequency for renal tubular proteinosis, and no corresponding evidence of alterations to the glomeruli. Tubular dilation was observed in a small number of females at 2,500 and 5,000 ppm, but was statistically significant only at 5,000 ppm. This effect was not seen in males, and was not accompanied by tubular cell degeneration or urinary outflow obstruction.

- NITE 2006
    - Isopropanol was classified to GHS category 2 based on effects on blood vessel, liver, and spleen in a 86-day inhalation toxicity study in rats (Report date: 1990). No further details were available and the study could not be located.

Ethyl acetoacetate (CAS# 141-97-9)

- ECHA 2014c
    - *Oral*: A 28-day study was conducted in rats. Animals (16/sex/dose) were administered doses of 0, 100, 300, and 1,000 mg/kg via oral feed daily. A NOAEL of 1,000 mg/kg/day was established, as there were no adverse treatment-related effects observed on clinical signs, body weight, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, organ weights, or gross pathology and histopathology. This value is compared to a tripled guidance value due to the 28-day length of the study.
    - *Oral*: A 28-day study was conducted in Sprague-Dawley rats. Animals (5/sex/dose) were administered doses of 0, 50, 225, and 1,000 mg/kg/day (purity not reported) via gavage, daily. A NOAEL of 1,000 mg/kg/day was established, as there were no adverse treatment-related effects on clinical signs, body weight, food consumption, hematology, clinical chemistry, or microscopic and macroscopic pathology observed. This value is compared to a tripled guidance value due to the 28-day length of the study.

Titanium dioxide (CAS# 13463-37-7)

- ECHA 2014d
    - *Oral*: A subacute oral toxicity study (GLP status 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 NOAEL 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 included: mortality, body weights, clinical chemistry, and histopathology. Administration of titanium dioxide had no effect on body weights in males or females at any dose. The only clinical sign related to treatment in either gender 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.
- Based on the weight of evidence, a score of Low was assigned. Although the study identified in NITE (conducted prior to 1990) may potentially classify isopropanol to GHS Category 2, the actual study or its summary could not be found. In addition, in more recent GLP-compliant subchronic inhalation studies in rats, no adverse effects were identified on blood vessels, liver or spleen. Therefore, this study was not considered in this evaluation. As none of the studies for isopropanol, ethyl acetoacetate, or titanium dioxide reported effects below the guidance values, a score of Low was assigned.

Neurotoxicity (N)

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Moderate for neurotoxicity (single dose) based on transient narcotic effects of the hydrolysis product isopropanol. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when available data indicate that GHS Category 3 classification is warranted (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- No data were identified

Isopropanol (CAS# 67-63-0)

- Pharos 2014
    - Isopropanol is associated with EU H336: May cause drowsiness or dizziness, EU R67: Vapor may cause drowsiness and dizziness, Grandjean & Landrigan: Known to be neurotoxic in man, and Patty's Toxicology - Boyes Neurotoxicants: Neurotoxic.
- HSDB 2012
    - The principal effect of acute isopropyl poisoning in humans is CNS depression, demonstrated by symptoms such as areflexia, headache, mental depression, hallucinations, distorted perceptions, dizziness, poor coordination, confusion that progress to stupor and deep coma, and loss of deep tendon reflexes in serious cases. The CNS effects often persist for 24 hours. Lethality cases were reported from acute inhalation and oral exposure to isopropanol.

Ethyl acetoacetate (CAS# 141-97-9)

- No data were identified

Titanium dioxide (CAS# 13463-37-7)

- No data were identified
- Based on the weight of evidence, a score of Moderate was assigned. The typical effect from acute exposure to isopropanol is narcotic effects in humans. According to GHS criteria, human evidence of narcotic effects classifies chemicals to GHS category 3. Confidence in this score is reduced as no data were available for the other hydrolysis products.

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for neurotoxicity (repeated dose) based on a lack of effects below the guidance value for subchronic inhalation studies of the hydrolysis product isopropanol in rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and no neurological effects are seen below the guidance value of 1 mg/L for an inhalation study (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- No data were identified

Isopropanol (CAS# 67-63-0)

- ECHA 2014b
    - *Inhalation*: In the GLP-compliant subchronic inhalation toxicity study conducted according to OECD guideline 413 as detailed previously, F344 rats (10/sex/dose at 100 ppm and 25/sex/dose for the other groups) were exposed to isopropanol via whole-body inhalation at 0, 100, 500, 1,500, or 5,000 ppm for 6 hours/day, 5 days/week for 13 weeks (equivalent to 0, 0.18, 0.88, 2.6, and 8.8 mg/L/6h/day). Neurobehavioral examination was carried out, including functional observational battery (FOB) at weeks 0, 1, 2, 4, 9, and 13, and motor activity evaluations at weeks 0, 4, 9, and 13. No changes were observed regarding FOB, but an increase in motor activity was reported in females at 5,000 ppm at weeks 8 and 13.

ToxServices established the NOAEC and LOAEC at 1,500 (2.6 mg/L/6h/day) and 5,000 ppm (8.8 mg/L/6h/day), respectively, based on increased motor activity in females (Report date: 1991).

- *Inhalation*: A GLP-compliant developmental neurotoxicity study was conducted according to OECD guideline 426. Pregnant Sprague-Dawley rats (64/dose) were exposed to isopropanol by daily oral gavage from gestation day 6 to postnatal day 21, at the doses of 0, 200, 700, or 1,200 mg/kg/day. Motor activity of the pups was evaluated on days 13, 17, 21, 47, and 58. Auditory startle reflex habituation was evaluated on days 22 and 60. Active avoidance test was conducted on days 60-64. At study termination, brain weight was measured and histopathological examination was performed on tissues from the control and high dose pups. Isopropanol did not lead to any observed neurotoxic effects. Therefore, ECHA established the NOAEL at 1,200 mg/kg/day for developmental neurotoxicity (Report date: 1991).
- *Inhalation*: A GLP-compliant neurotoxicity study was conducted according to OECD guideline 413. Female Fischer 344 rats (30/group) were exposed to isopropanol via inhalation at 5,000 ppm for 6 hours/day, 5 days/week for 9 or 13 weeks. There was no mortality during the study. Clinical signs included hypoactivity and lack of a startled reflex. Decreased body weight and body weight gain were noted at the beginning of the study, but gradually improved. There was an increase in total motor activity (ambulation, fine motor activity, and rearing activity) and mean cumulative motor activity (the sum of total activity across the 90-min test session). ToxServices identified the LOAEC at 5,000 ppm (8.8 mg/L/6h/day).

Ethyl acetoacetate (CAS# 141-97-9)

- No data were identified

Titanium dioxide (CAS# 13463-37-7)

- No data were identified
- Based on the weight of evidence, a score of Low was assigned. Although acute exposure to isopropanol led to narcosis, repeated lower dose exposure does not appear to adversely affect neurological parameters irreversibly. The lowest LOAEC was 8.8 mg/L/6h/day based on motor activity increase in female rats. Therefore a Low was assigned. Confidence in this score is reduced as no data were available for the other hydrolysis products.

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for skin sensitization based on negative modeling results. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and are negative for sensitization, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014
  - In a non-guideline dermal sensitization test in albino guinea pigs (sex and strain not specified), animals (10/test group, 9/control) were induced with a series of 4 weekly intradermal injections of 0.1 mL of a 1% solution of diisopropoxytitanium bis(ethylacetoacetate) (>98% purity). Animals were challenged dermally on shaved shoulder skin with 0.05 mL of a 50% and 5% solution after a 2-week rest period, and skin was evaluated after 24 and 48 hours. For the animals challenged with the 50% solution, 6/10 had positive responses at 24 hours and 2/10 had positive responses at 48 hours

(compared to 3/9 at 24 and 48 hours for the negative control). For the animals challenged with the 5% solution, no animals had positive responses at either the 24 or 48 hour observations. Authors concluded that the substance is not sensitizing. This study is reported with a Klimisch score of 3 (Not reliable) for reliability as the method is not validated and the documentation is insufficient for assessment.

- OECD 2013b
  - Diisopropoxytitanium bis(ethylacetoacetate) is predicted to not be a skin sensitizer using the OECD Toolbox model using the read-across methodology, Reliability in the prediction is reduced because the value of the target chemical for log K_{ow} (-0.990) is out of the range of the values for neighbors (-0.960-2.56). See Appendix D for justification.
- Payne and Walsh 1994
  - Diisopropoxytitanium bis(ethylacetoacetate) is not predicted to be a skin sensitizer based on the absence of structural alerts identified by Payne and Walsh. See Appendix E for a complete list of structural alerts.
- ToxTree 2013
  - Diisopropoxytitanium bis(ethylacetoacetate) is predicted to not be a skin sensitizer using the ToxTree model using decision tree methodology. This chemical has not been identified as a substrate for any of the 5 electrophilic mechanisms known to produce a skin sensitization reaction. See Appendix F for justification.
- Based on the weight of evidence, a score of Low was assigned. The guinea pig study was not weighed heavily in the assessment as it was a non-guideline study, did not include positive controls, and showed some positive responses in negative control animals. Diisopropoxytitanium bis(ethylacetoacetate) does not contain structural alerts for sensitization, and ToxTree did not identify any electrophilic mechanisms known to cause reactions. Although OECD Toolbox results were of reduced reliability, the read-across analysis demonstrates that compounds that share similar organic functional groups were negative for sensitization. Based on the modeling results, a score of Low was assigned. Confidence in this score is reduced because it is based on modeling.

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Data Gap for respiratory sensitization based on a lack of data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

<u>Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)</u>

- No data were identified

<u>Isopropanol (CAS# 67-63-0)</u>

- No data were identified

<u>Ethyl acetoacetate (CAS# 141-97-9)</u>

- No data were identified

<u>Titanium dioxide (CAS# 13463-37-7)</u>

- No data were identified

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Data Gap for skin irritation/corrosivity based on a lack of adequate data for this endpoint

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists

- *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014
  - Diisopropoxytitanium bis(ethylacetoacetate) (>98% purity) was slightly irritating when 0.05 mL of a 5% or 50% solution (in dimethyl phthalate) was administered to two separate areas of the shaved shoulder skin of 10 albino guinea pigs (sex and strain not specified) for 24 or 48 hours (coverage not specified). Mild irritation was seen in 2 animals at the 24 hour observation and 3 animals at the 48 hour observation. Authors concluded that the substance was not irritating. This study is reported with a Klimisch score of 3 (Not reliable) for reliability as the method is not validated and the documentation is insufficient for assessment.
- Based on the weight of evidence, a Data Gap was assigned. The only available study for diisopropoxytitanium bis(ethylacetoacetate) was a non-guideline study in guinea pigs that was not described in detail, and only tested up to a 50% solution of diisopropoxytitanium bis(ethylacetoacetate). Authors concluded that the substance was not irritating, but based on the aforementioned study limitations, these data are insufficient to assign a score of Low.

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of High for eye irritation/corrosivity based on self-classification in ECHA with the H-statement H319: Causes serious eye irritation. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when the chemical is associated with H319 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014a
  - Diisopropoxytitanium bis(ethylacetoacetate) (>98% purity) was judged to be slightly irritating to rabbits (sex and strain not specified) when 0.1 mL was instilled into the eye of one rabbit for 20 seconds followed by washing by 1 minute and into the eye of a second rabbit without washing. Observations were made at 1 and 4 hours and days 1, 2, and 3. In the animal that received washing, localized slight dulling of the cornea was seen at 1 hour and slight opacity was seen at 4 hours. Mild redness was seen from 4 hours-2 days, slight to mild swelling was seen at 1 hour-2 days, and mild to moderate discharge was seen from 4 hours-1 day. In the animal that did not receive washing, localized slight opacity was seen from 1-4 hours and increased to a small area of slight opacity at 1 day, mild redness was seen from 1 hour-2 days, slight swelling was seen from 1 hour-2 days, mild discharge was seen from 1-4 hours, and moderate discharge was seen from 1-2 days. All effects resolved by day 3. No effects were seen on the iris of either animal. This study is reported with a Klimisch score of 3 (Not reliable) for reliability as the method is not validated and the documentation is insufficient for assessment.
  - Diisopropoxytitanium bis(ethylacetoacetate) was self-classified by notifiers with the H-Statement H319: Causes serious eye irritation.

Isopropanol (CAS# 67-63-0)

- Pharos 2014
  - Isopropanol is associated with the H-Statement H319: Causes serious eye irritation.
- Based on the weight of evidence, a score of High was assigned. No irritation scores were reported, but irritation in rabbit eyes was described as slight and resolved by day 3, which indicates that this

substance is not corrosive. The notifiers self-classified this chemical with H-Statement H319: Causes serious eye irritation. The hydrolysis product isopropanol, which is likely to form in the moist eye environment, is also classified with this H-statement, which corresponds to a score of High. Therefore a score of High was conservatively assigned. Confidence in this score is reduced because there are no reliable ocular irritation studies available for diisopropoxytitanium bis(ethylacetoacetate).

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L
Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for acute aquatic toxicity based on LC/EC_{50} values of greater than 100 mg/L in fish, daphnia, and algae. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when the most conservative LC/EC_{50} values are greater than 100 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2014a
  - 96-hour LC_{50} (*Danio rerio*, zebrafish) > 100 mg/L (nominal)
  - 48-hour EC_{50} (*Daphnia magna*, water flea) > 100 mg/L (nominal)
  - 72-hour EC_{50} (*Desmodesmus subspicatus*, green algae) > 100 mg/L (nominal) (growth and biomass)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): L
Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for chronic aquatic toxicity based on a NOEC of 100 mg/L in algae. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 100 mg/L and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014a
  - 72-hour NOEC (*Desmodesmus subspicatus*, green algae) = 100 mg/L (nominal) (growth and biomass)
- No data were identified for fish and algae, but acute toxicity data do not indicate that these trophic levels are more sensitive than algae. Therefore a score of Low was assigned based on the NOEC for algae.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *L*
Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for persistence based on a hydrolysis half-life of less than 10 minutes. GreenScreen® criteria classify chemicals as a Low hazard for persistence when the half-life is less than 16 days in water, soil, or sediment (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists

  - *Screening:* Environment Canada - Domestic Substances List (DSL) DSL substances that are Persistent

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014a
  - Diisopropoxytitanium bis(ethylacetoacetate) is hydrolytically unstable based on a GLP-compliant study conducted according to OECD Guideline 111. Alternative methods, which included testing at 20 °C, 30 °C, and 50 °C with an amount of test substance above the water solubility, were applied as needed since the test substance is highly reactive in water. A hydrolysis half-life of ≤ 10 minutes at 20 °C, ≤ 5 minutes at 30 °C, and ≤ 2 minutes at 50 °C was determined. The half-life at 25 °C and each pH (4, 7, 9) was estimated to be ≤ 10 minutes. The expected hydrolysis products are ethyl acetoacetate, isopropyl alcohol, and insoluble titanium oxides.
- Based on the weight of evidence, a score of Low was assigned. Although it is classified as persistent on the DSL, the underlying persistence data were modeled using EPISuite (OECD 2014) and this program does not perform well for organometallic compounds (U.S. EPA 2012). No biodegradation data are available, but a hydrolysis study measured a half-life of ≤ 10 minutes. This indicates that diisopropoxytitanium bis(ethylacetoacetate) is not likely to persist in the environment, but is instead expected to rapidly hydrolyze to form ethyl acetoacetate, isopropyl alcohol, and insoluble titanium oxides. Therefore a score of Low was assigned, as the half-life is expected to be less than 16 days in water, soil, and sediment. Confidence in this score is reduced because it is based on expert judgment.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Very Low for bioaccumulation based on expert judgment, as it is hydrolytically unstable. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the BCF is less than 100 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2014a
  - The PBT assessment in the REACH dossier explains that diisopropoxytitanium bis(ethylacetoacetate) is not bioaccumulative as it is hydrolytically unstable, with a hydrolysis half-life of ≤ 10 minutes. The hydrolysis products isopropanol and ethyl acetoacetate are not bioaccumulative.
- Based on the weight of evidence, a score of Very Low was assigned. Diisopropoxytitanium bis(ethylacetoacetate) is hydrolytically unstable, and will undergo hydrolysis in both the aquatic environment and *in vivo*. Therefore it is not expected to bioaccumulate. Furthermore, as explained in the REACH dossier, the hydrolysis products are not bioaccumulative. Diisopropoxytitanium bis(ethylacetoacetate) is expected to have a BCF < 100. Confidence in this score is reduced as it is based on expert judgment.

Physical Hazards (Physical)

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Low for reactivity based on an MSDS reporting that it is not reactive. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when the chemical is not reactive and is not present on authoritative lists (CPA 2012a).

- Authoritative and Screening Lists

- *Authoritative:* Not present on any authoritative lists
- *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014a
  - Diisopropoxytitanium bis(ethylacetoacetate) is stable under normal conditions. It has no unusual reactivity.

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

Diisopropoxytitanium bis(ethylacetoacetate) was assigned a score of Moderate for flammability based on its flash point of 36 °C. GreenScreen® criteria classify chemicals as a Moderate hazard for flammability when available data indicate that the chemical warrants GHS Category 3 classification as a flammable solid (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

Diisopropoxytitanium bis(ethylacetoacetate) (CAS# 27858-32-8)

- ECHA 2014a
  - Diisopropoxytitanium bis(ethylacetoacetate) had a measured flash point of 36 °C in a test conducted according to ASTM D-93 (non-equilibrium method closed cup Pensky Martens Closed Cup method).
  - Diisopropoxytitanium bis(ethylacetoacetate) had a measured flash point of 37 °C in a test conducted according to ASTM D-93 (non-equilibrium method closed cup Pensky Martens Closed Cup method).
- Based on the weight of evidence, a score of Moderate was assigned. A flash point of 36-37°C corresponds to GHS Category 3 classification which applies to chemicals with a flash point > 23°C and < 60°C. .

References

Capaute Chemical. Undated. Organimetallic Coupling Agents. Available at: http://www.capatue.com/english/images/Titanate.pdf.

ChemIDplus. 2014. Entry for itanium, bis(ethyl 3-(oxo-kappaO)butanoato-kappaO')bis(2-propanolato)-(CAS #27858-32-8). United States National Library of Medicine. Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp.

Clean Production Action (CPA). 2011. The GreenScreen® for Safer Chemicals Version 1.2 Benchmarks. Dated October 2011. Available at: http://www.greenscreenchemicals.org/.

Clean Production Action (CPA). 2012a. The GreenScreen® for Safer Chemicals Version 1.2 Criteria. Dated: November 2012. Available at: http://www.greenscreenchemicals.org/.

Clean Production Action (CPA). 2012b. List Translator. Dated February 2012. Available at: http://www.greenscreenchemicals.org/.

Clean Production Action (CPA). 2013. The GreenScreen® for Safer Chemicals Chemical Hazard Assessment Procedure. Version 1.2 Guidance. Dated August 31, 2013. Available at: http://www.greenscreenchemicals.org/.

European Chemicals Agency (ECHA). 2014a. REACH Dossier for bis(ethyl acetoacetato-O1',O3)bis(propan-2-olato)titanium (CAS# 27858-32-8). Available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-dceb8f5b-f7c2-1ff2-e044-00144f67d031/AGGR-3278871b-7149-4dfc-9b14-2be558de0b15_DISS-dceb8f5b-f7c2-1ff2-e044-00144f67d031.html#section_3_5.

European Chemicals Agency (ECHA). 2014b. REACH Dossier for propan-2-ol (CAS# 67-63-0). Available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d82bbf7-98d2-11d2-e044-00144f67d249/DISS-9d82bbf7-98d2-11d2-e044-00144f67d249_DISS-9d82bbf7-98d2-11d2-e044-00144f67d249.html.

European Chemicals Agency (ECHA). 2014c. REACH Dossier for Ethyl Acetoacetate (CAS# 141-97-9). Available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-a1342699-c924-4314-e044-00144f67d031/DISS-a1342699-c924-4314-e044-00144f67d031_DISS-a1342699-c924-4314-e044-00144f67d031.html.

European Chemicals Agency (ECHA). 2014d. REACH Dossier for Titanium Dioxide (CAS# 13463-67-7). Available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eaff323-014a-482f-e044-00144f67d031/DISS-9eaff323-014a-482f-e044-00144f67d031_DISS-9eaff323-014a-482f-e044-00144f67d031.html.

European Chemical Substances Information System (ESIS). 2000. Titanium dioxide IUCLID dataset. European Commission Joint Research Center. Available at: http://esis.jrc.ec.europa.eu/doc/IUCLID/datasheet/13463677.pdf.

European Commission (EC). 2002. Ethyl acetoacetate European Union Risk Assessment Report. Final Report. Available at: http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/ethylacetoacetatereport012.pdf.

Grandjean, P. and P.J. Landrigan. 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368: 2167-2178.

Grandjean, P. and P.J. Landrigan. 2014. Neurobehavioral effects of developmental toxicity. The Lancet 13: 330-338.

Hazardous Substances Data Bank (HSDB). 2012. Isopropanol. National Library of Medicine. Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+67-63-0.

International Agency for Research on Cancer (IARC). 1999. Isopropanol (Group 3). Vol. 71 (p1027). 5. Summary of data reported and evaluation. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf.

International Agency for Research on Cancer (IARC). 2012. Isopropyl alcohol manufacture by the strong-acid process. Chemical agents and related occupations. Volume 100 F. A review of human carcinogens. IARC monographs on the evaluation of carcinogenic risks to humans. Available at: http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F.pdf.

National Cancer Institute (NCI). 1979. Bioassay of titanium dioxide for possible carcinogenicity.

National Institute of Technology and Evaluation (NITE). 2006. GHS classification for 2-propanol. ID928. Available at: http://www.safe.nite.go.jp/english/ghs_index.html#results.

Organization for Economic Cooperation and Development (OECD). 2013a. SIDS Initial Assessment Profile. Titanium Dioxide (CAS# 13463-67-7). CoCAM 4, 16-18 April 2013. Available at: http://webnet.oecd.org/hpv/UI/handler.axd?id=0D893DAD-1B1B-4ADC-9816-FF805B1E892F. .

Organization for Economic Cooperation and Development (OECD). 2013b. OECD QSAR Toolbox for Grouping Chemicals into Categories Version 3.1.0.21. Available at: http://toolbox.oasis-lmc.org/?section=download&version=latest.

Organization for Economic Cooperation and Development (OECD). 2014. Categorization Results from the Canadian Domestic Substance List. Titanium, bis(ethyl 3-oxobutanoato-o1 ,o3)bis(2-propanolato)- (CAS# 27858-32-8). Available at: http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=0BC72734-39AF-4872-95F5-5D0AB99E285A.

Payne, M.P and P.T. Walsh. 1994. Structure-activity relationships for skin sensitization potential: development of structural alerts for use in knowledge-based toxicity prediction systems. J Chem Inf Comput Sci. 34:154-161.

Pharos. 2014. Pharos Chemical and Material Library. Available at: http://www.pharosproject.net/material/.

ToxServices. 2013. SOP 1.69: GreenScreen® Hazard Assessments. Dated: August 17, 2013.

ToxTree. 2013. Estimation of Toxic Hazard- A Decision Tree Approach v2.6.0. Available at: http://toxtree.sourceforge.net

United Nations Environmental Programme (UNEP). 1997. OECD SIDS initial assessment profile for 2-propanol. Available at: http://www.chem.unep.ch/irptc/sids/OECDSIDS/67630.pdf

United States Department of Transportation (U.S. DOT). 2008a. Chemicals Listed with Classification. 49 CFR § 172.101. Available at: http://www.gpo.gov/fdsys/pkg/CFR-2008-title49-vol2/pdf/CFR-2008-title49-vol2-sec172-101.pdf

United States Department of Transportation (U.S. DOT). 2008b. Classification Criteria. 49 CFR § 173. Available at: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title49/49cfr173_main_02.tpl

United States Environmental Protection Agency (U.S. EPA). 2012. Technical Working Group on Pesticides (TWG) (Q)uantitative Structure Activity Relationship [(Q)SAR] Guidance Document. Available at: http://www.epa.gov/oppfead1/international/naftatwg/guidance/qsar-guidance.pdf.

Wacker Chemie. Undated. SILRES® MSE 100. Available at: http://www.wacker.com/cms/media/publications/downloads/6871_EN.pdf.

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 Diisopropoxytitanium Bis(ethylacetoacetate) (CAS #27858-32-8)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

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**
No	**Diisopropoxytitanium bis (ethylacetoacetate)**	**27858-32-8**	*L*	**L**	*M*	*M*	DG	**L**	*vH*	**L**	*M*	*L*	*L*	DG	DG	*H*	**L**	**L**	*L*	*vL*	*L*	**M**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Diisopropoxytitanium bis (ethylacetoacetate)	2

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

Table 6

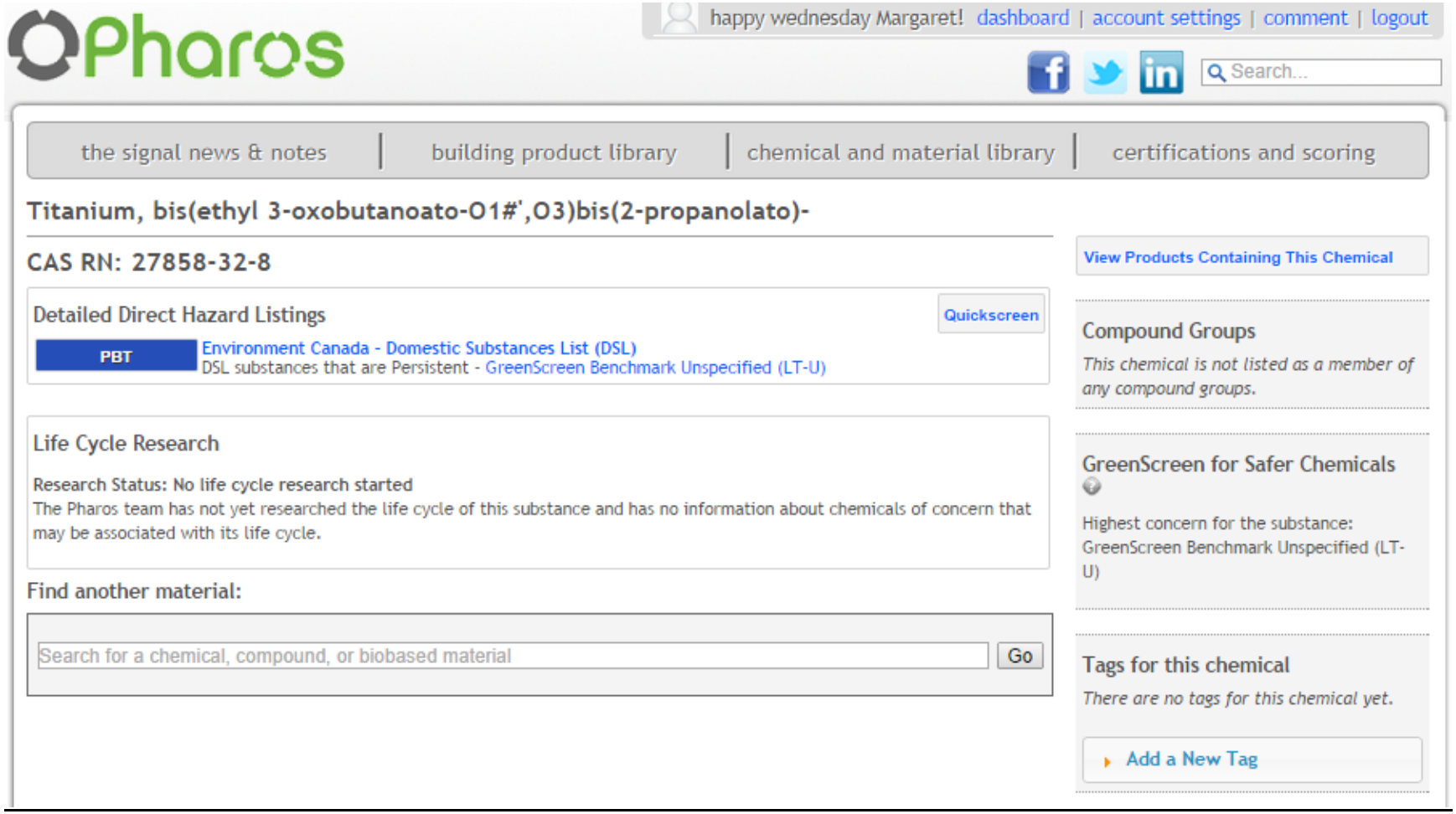
Chemical Name	Final GreenScreen® Benchmark Score
Diisopropoxytitanium bis (ethylacetoacetate)	2

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

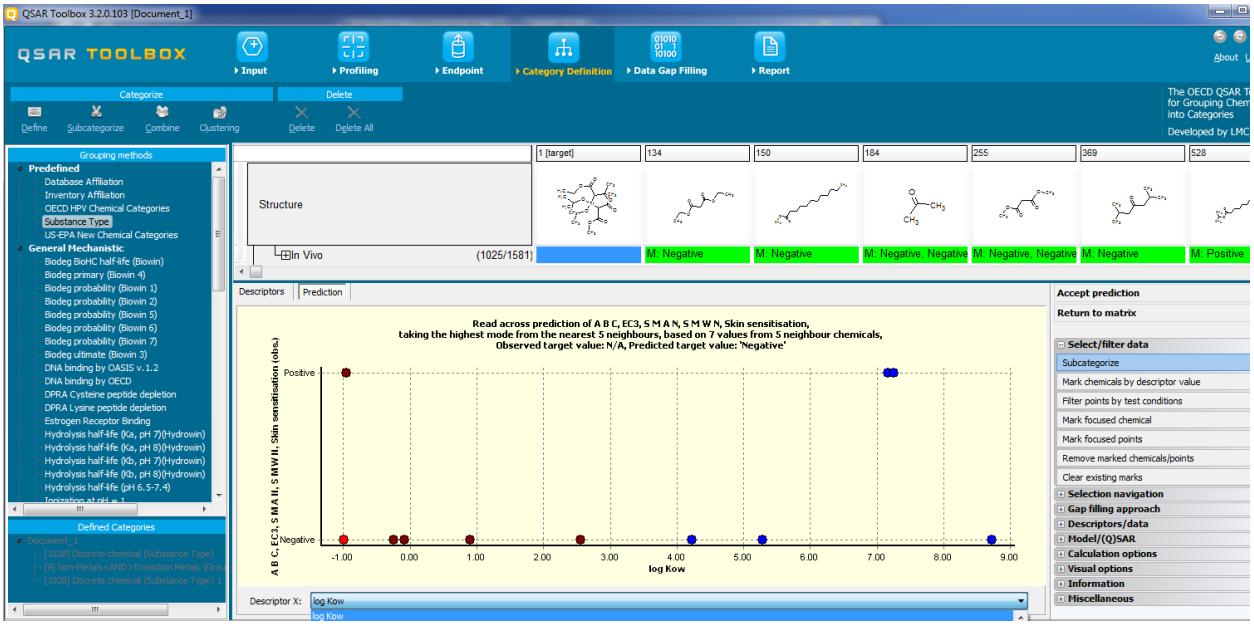
Table 5: Data Gap Assessment Table

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

APPENDIX C: Pharos Output for Diisopropoxytitanium Bis(ethylacetoacetate) (CAS #27858-32-8)

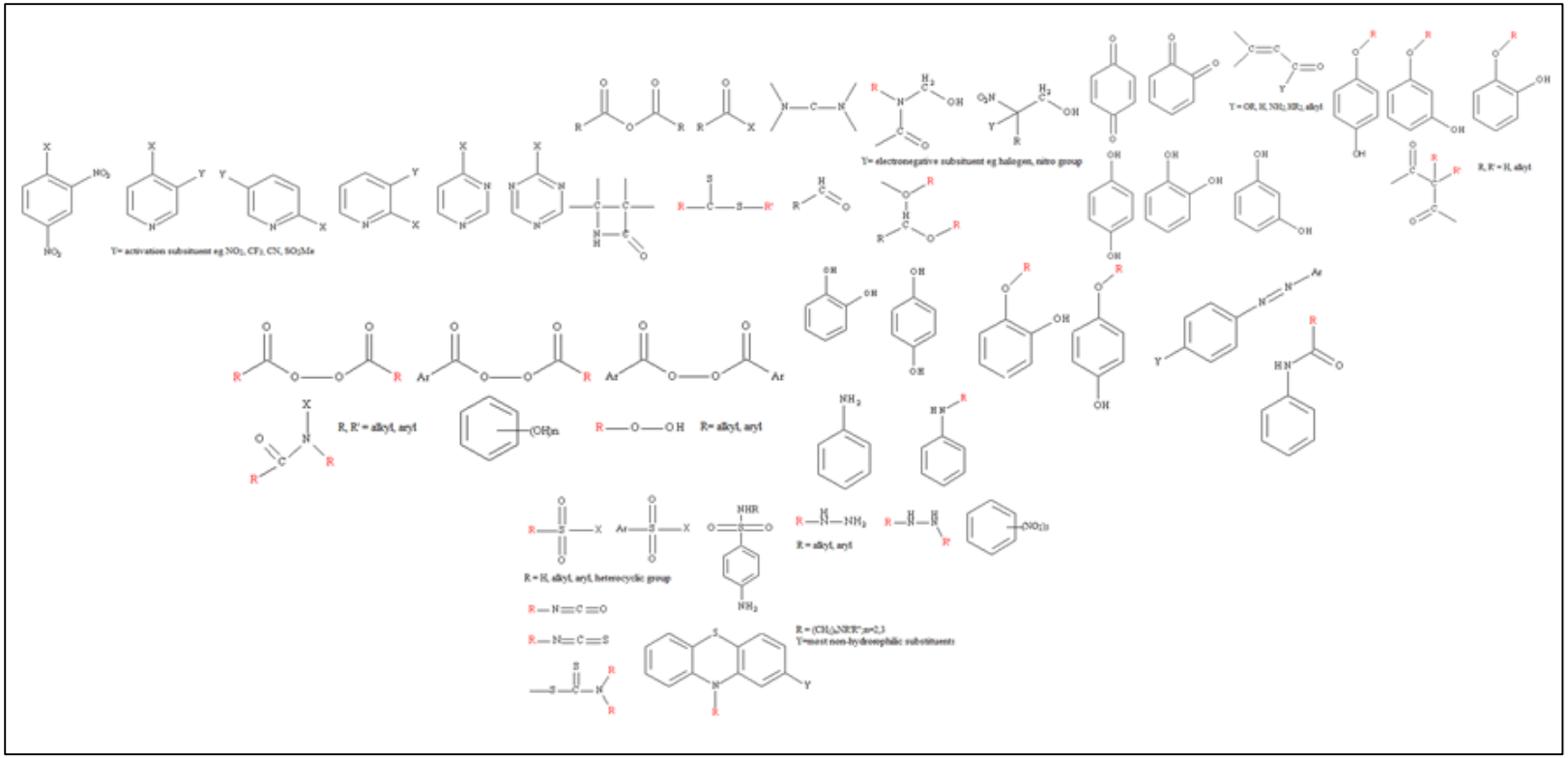


APPENDIX D: OECD Toolbox Skin Sensitization Results for Diisopropoxytitanium Bis(ethylacetoacetate) (CAS #27858-32-8)

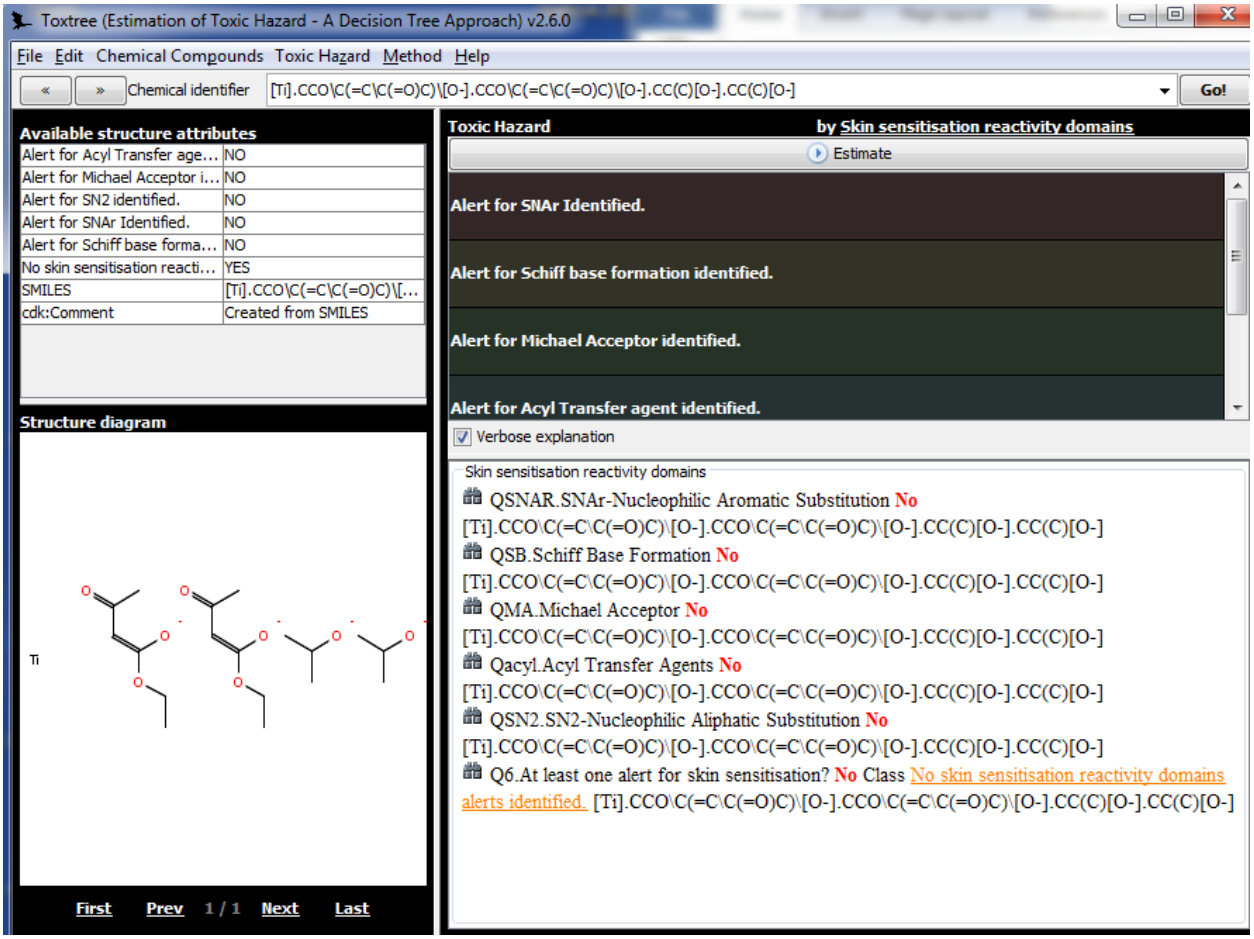


APPENDIX E: Known Structural Alerts for Skin Sensitization

Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). Diisopropoxytitanium bis(ethylacetoacetate) does not possess any known structural alerts.



APPENDIX F: ToxTree Skin Sensitization Results for Diisopropoxytitanium Bis(ethylacetoacetate) (CAS #27858-32-8)



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

Diisopropoxytitanium Bis(ethylacetoacetate) GreenScreen® Evaluation Prepared by:

Jennifer Rutkiewicz, Ph.D.
Toxicologist
ToxServices LLC

Diisopropoxytitanium Bis(ethylacetoacetate)GreenScreen® Evaluation QC'd by:

Bingxuan Wang, Ph.D.
Toxicologist
ToxServices LLC