Safety Assessment of Organo-Titanium Ingredients as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst

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INTRODUCTION

The safety of the following 5 organo-titanium ingredients as used in cosmetics is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment.

Isopropyl Titanium Triisostearate	Titanium Ethoxide	Titanium Salicylate
Titanium Citrate	Titanium Isostearates	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*), these organo-titanium ingredients are reported to have the following functions in cosmetics: surface modifiers, colorants, humectants, binders, film formers, opacifying agents, and preservatives.[1]

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

CHEMISTRY

Definition and General Characterization

The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.[1] The ingredients in this group are organometallic derivatives of titanium.

$$Ti^{n+}\left[R^{m-}\right]_x$$

Figure 1. This formula represents organometallic derivatives of titanium.

However, when the oxidation state of titanium is 4+ or greater ("n+" $\geq$ 4 in Figure 1) the titanium-bonding character is likely to be more covalent than ionic. Accordingly, structures for those chemicals wherein the oxidation state of titanium is known to be 4+ or greater, have been drawn with covalent-titanium bonds for the sake of convenience (Figure 2).

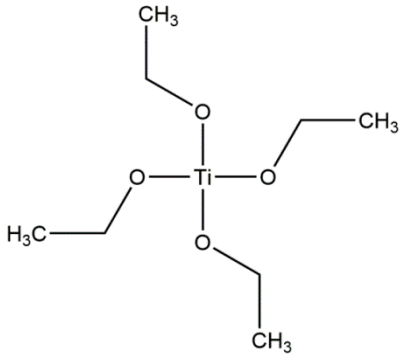


Figure 2. Titanium Ethoxide

Chemical and Physical Properties

Titanium Citrate and Titanium Ethoxide are soluble in water, and the latter ingredient has a density of 1.109. Properties of these ingredients are presented in Table 2.

Method of Manufacture

Titanium Citrate

Titanium Citrate has been prepared by mixing titanium (III) chloride with a 1.2-fold excess of sodium citrate at a pH of 3.[2] Exposure to air resulted in the quantitative oxidation of titanium (III) citrate to colorless titanium (IV) citrate.

Impurities

Impurities data on the organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

USE

Cosmetic

The safety of the organo-titanium ingredients is evaluated based on data received from the US FDA and the cosmetics industry on the expected use of this ingredient in cosmetics.[3] Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[4]

Only one of the organo-titanium ingredients is reported to be in use. According to 2018 VCRP data, Isopropyl Titanium Triisostearate is reported to be used in 580 cosmetic products (573 leave-on and 7 rinse-off products).[3] The results of a concentration of use survey conducted in 2017 indicate that Isopropyl Titanium Triisostearate is being used at concentrations up to 1.5% in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers).[4] Further use frequency and concentration of use data are presented in

Table 3.

Cosmetic products containing Isopropyl Titanium Triisostearate may be applied to the skin or, incidentally, may come in contact with the eyes (at maximum use concentrations up to1.5% in eye shadows); this ingredient is applied to mucous membranes, and could be incidentally ingested (at maximum use concentrations up to 0.42% in lipstick). Products containing Isopropyl Titanium Triisostearate may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Noncosmetic

Titanium dioxide is widely used in the preparation of anti-reflective coatings, and these titanium dioxide layers can be prepared by spin-coating a Titanium Ethoxide solution.[5] Titanium Ethoxide has also been used as a catalyst in the synthesis of *N*-acyl-*O*-ethyl-*N*,*O*-acetals.[6]

TOXICOKINETIC STUDIES

Dermal Penetration

Data on the dermal penetration of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Titanium Citrate

In an *in vitro* study using the rat (male Wistar rats) everted gut sac model, absorption (intestinal uptake) of Titanium Citrate was found to be a concentration-dependent process over the ≤ 100 µg/dl to 500 µg/dl concentration range.[2]

Human

Oral

Titanium Salicylate

Following the oral administration of titanium salicylates (~ 10 mg) to one human subject, titanium was detected in the feces and urine, with evidence that salicylate remained attached to titanium in the urine.[7] Details relating to the test protocol were not included. Though the definition of titanium salicylates is not provided in this study, it is possible that these data may be useful in evaluating the toxicokinetics of Titanium Salicylate.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Titanium Ethoxide

The acute oral toxicity of Titanium Ethoxide was evaluated at a dose of 2000 mg/kg body weight using 6 fasted female Wistar rats.[8] Dosing was followed by a 14-day observation period. Surviving animals were necropsied. None of the animals died. The mean body weight gain of animals was considered similar to that expected for non-treated animals of the same age and strain. There was no evidence of abnormalities at macroscopic postmortem examination. The authors concluded that the LD_{50} was > 2000 mg/kg body weight.

Parenteral

Titanium Salicylate

The injection of titanium salicylates, in water, into the skin of mice and rabbits (animal numbers and strains not stated) did not cause adverse effects.[7] However, tiny bumps were observed at injection sites and eventually disappeared. The doses administered and other details relating to the test protocol were not included. Though the definition of titanium salicylates is not provided in this study, it is possible that these data may be useful in evaluating potential acute effects on the skin that may result from the dermal application of Titanium Salicylate.

Short-Term Toxicity Studies

Oral

Titanium Salicylate

The daily oral administration of titanium salicylates (10 g) in bread fed to rabbits did not cause any adverse effects.[7] Details relating to the test protocol were not included. Though the definition of titanium salicylates is not provided in this study, it is possible that these data may be useful in evaluating the short-term toxicity of Titanium Salicylate.

Subchronic Toxicity Studies

Data on the subchronic toxicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

Chronic Toxicity Studies

Data on the chronic toxicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

Data on the genotoxicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

ANTI-TUMORIGENICITY STUDY

Titanium Citrate

The anti-tumorigenicity of Titanium Citrate in rats (number and strain not stated) was evaluated using 2 groups of 46 rats (strain not stated) with Jensen sarcoma.[9,7] One group was injected intramuscularly (i.m.) with Titanium Citrate (1 ml of 1 ppt titanium) in water, and the other group (control) was injected i.m. with ferrous citrate (1 ml of 1 ppt Fe). Long-term survivals were 88% for the group injected with Titanium Citrate and 39% for the group injected with ferrous citrate. Following 3 weeks of injections, the death rate in the control group was 5.5 times greater than in the test group, with 12% of the animals injected with Titatnium Citrate dying and 61% of the control group dying from their tumors.

OTHER RELEVANT STUDIES

Cytotoxicity

Titanium Citrate

The structural effects of Titanium Citrate on the human erythrocyte membrane were studied *in vitro* using intact erythrocytes.[10] Erythrocytes were incubated with 0.1. 0.5, or 0.8 mM Titanium Citrate for 1 h and then examined using scanning electron microscopy (SEM). Erythrocyte deformations (both echinocytic and stomatocytic types) were observed at the concentrations tested. At a concentration of 0.1 mM, slight deformation (both types) was observed in a few erythrocytes. Titanium Citrate (0.5 mM) caused both types of deformation (mostly echinocytic) in the majority of the cell population. At a concentration of 0.8 mM, some stomatocytes and a few remaining echinocytes were observed, due to the intense hemolysis that affected the great majority of the erythrocytes. Numerous erythrocytes were ruptured, resulting in empty and retracted membranes (i.e., erythrocyte ghosts).

In another study, the effect of Titanium Citrate on human erythrocytes *in vitro* (1-h incubation period) was studied using SEM.[11] For a few of the erythrocytes incubated with 0.001 mM and 0.0005 mM Titanium Citrate, the shape appeared slightly deformed when compared to controls; the cellular diameter of treated cells was described as almost normal. At a concentration of 0.0025 mM titanium citrate, most of the erythrocytes had morphological alterations. Incubation with Titanium Citrate (0.005 mM) caused damage to erythrocytes, and the cells appeared smaller and more distorted. The morphological differences between treated and control erythrocytes were statistically significant.

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation

Animal

Titanium Salicylate

The topical application of titanium salicylates to the healthy skin of rabbits (number and strain not stated) did not cause skin irritation. The test concentration and other details relating to the test protocol were not included.[7] Though the definition of titanium salicylates is not provided in this study or the following human study, it is possible that these data may be useful in evaluating the skin irritation potential of Titanium Salicylate.

Human

Titanium Salicylate

Skin irritation also was not observed following the application of Titanium Salicylates to the healthy skin of human subjects (number not stated). The test concentration and other details relating to the test protocol were not included.[7]

Sensitization

Data on the sensitization potential of the organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

OCULAR IRRITATION STUDIES

Data on the ocular irritation potential of the organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

SUMMARY

The safety of 5 organo-titanium ingredients as used in cosmetics is reviewed in this CIR safety assessment. According to the Dictionary, these ingredients are reported to have the following functions in cosmetics: surface modifiers, colorants, humectants, binders, film formers, opacifying agents, and preservatives.

According to 2018 VCRP data, Isopropyl Titanium Triisostearate is reported to be used in 580 cosmetic products (573 leave-on and 7 rinse-off products). The results of a concentration of use survey conducted in 2017 indicate that Isopropyl Titanium Triisostearate is being used at concentrations up to 1.5% in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers).

Titanium Citrate has been prepared by mixing titanium (III) chloride with sodium citrate, followed by exposure to air, which resulted in the quantitative oxidation of titanium (III) citrate to colorless titanium (IV) citrate. Methods of manufacture for the remaining organo-titanium ingredients in this safety assessment were not found.

Following the oral administration of titanium salicylates (~ 10 mg) to one human subject, titanium was detected in the feces and urine, with evidence that salicylate remained attached to titanium in the urine. Though the definition of titanium salicylates is not provided in this study, it is possible that these data may be useful in evaluating the toxicokinetics of Titanium Salicylate. Data on titanium salicylates relating to short-term oral toxicity, systemic toxicity, and skin irritation potential are included in some of the study summaries below.

In an acute oral toxicity study of Titanium Ethoxide involving female Wistar rats, the LD_{50} was > 2000 mg/kg body weight, and there was no evidence of abnormalities at macroscopic postmortem examination. The injection of titanium salicylates, in water, into mice and rabbits (animal numbers and strains not stated) did not cause adverse effects.

The short-term oral administration of titanium salicylates (10 g) in bread fed to rabbits did not cause any adverse effects. Chronic toxicity studies on the organo-titanium ingredients reviewed in this safety assessment were not found in the published literature.

The topical application of titanium salicylates (concentration not stated) to the healthy skin of rabbits or humans did not cause skin irritation. Studies on the ocular irritation potential or skin sensitization potential of organo-titanium ingredients were not found.

Rats with Jensen sarcoma were treated with injections of Titanium Citrate in an anti-tumorigenicity study, and 3-week survival rates were 88% and 39% for test and control groups, respectively.

The hemolytic activity of Titanium Citrate in human erythrocytes *in vitro* has been observed at concentrations ranging from 0.0025 to 0.4 mM.

DATA NEEDS

CIR is seeking any additional data, specifically those listed below, on the organo-titanium ingredients reviewed in this safety assessment. This information would help the CIR Expert Panel assess the safety of these ingredients as used in cosmetics, and would improve the resulting safety assessment.

1. Method of manufacture and impurities data
2. Chemical characterization data
3. Dermal absorption data; if absorbed, additional data (e.g., a 28-day dermal toxicity study or DART data) may be needed
4. Irritation and sensitization data (at use concentrations) on all ingredients

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[1; *CIR Staff*]

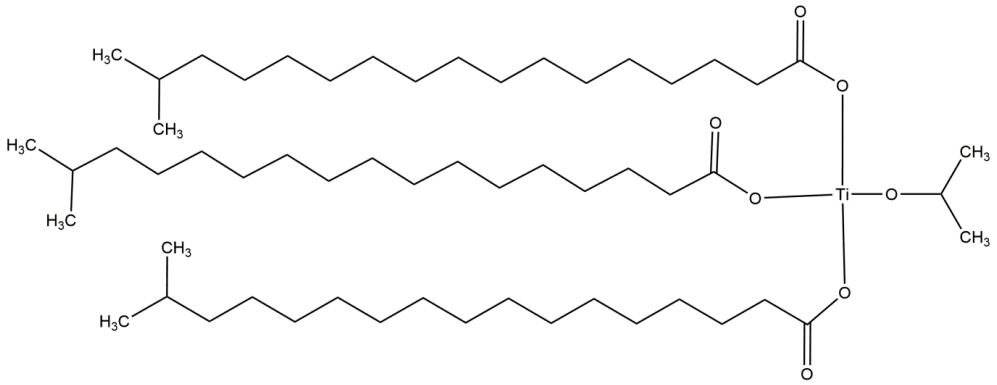
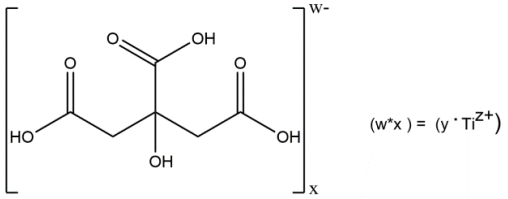
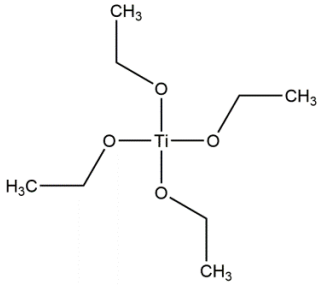
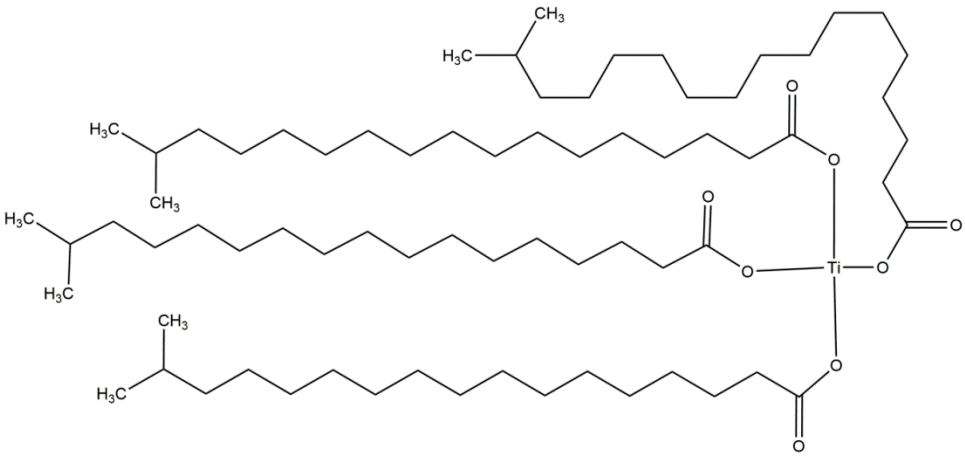
Ingredient CAS No.	Definition & Structures	Function(s)
Isopropyl Titanium Triisostearate 61417-49-0	Isopropyl Titanium Triisostearate is the organic compound that conforms to the formula: 	Surface Modifiers
Titanium Citrate	Titanium Citrate is the salt of titanium and citric acid prepared by electrolysis. 	Colorants; Humectants
Titanium Ethoxide 3087-36-3	Titanium Ethoxide is the organic salt that conforms to the formula: 	Binders
Titanium Isostearates	Titanium Isostearates is the product formed by the reaction of titanium tetraethoxide and isostearic acid. 	Film Formers; Opacifying Agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[1; *CIR Staff*]

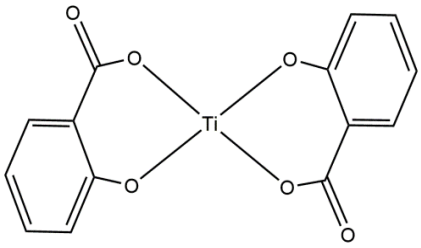
Ingredient CAS No.	Definition & Structures	Function(s)
Titanium Salicylate	Titanium Salicylate is the titanium salt of salicylic acid. 	Preservatives

Table 2. Chemical and Physical Properties of Organo-Titanium Ingredients

Property	Value/Results	Reference
Isopropyl Titanium Triisostearate		
Formula Weight (Da)	972.42	
Titanium Citrate		
Solubility	Soluble in water	12
Dissociation	Dissociation of free citrate increased with rise in pH (i.e., increased alkalinity).	12
Titanium Ethoxide		
Form	white solid light-yellow liquid	13 8
Odor	Similar to alcohol	13
Formula Weight (Da)	228.11	
Melting Point (ºC)	54	13
Flash Point (ºC)	43	
Density (g/cm^3)	1.109	8
Vapor Pressure (hPa)	57.26	8
$logK_{ow}$	- 0.3	8
Water solubility (mg/l)	789,000	8
Hydrolysis	Hydrolysis half-life = < 3 minutes to < 2 h.	8
Titanium Isostearates		
Formula Weight (Da)	1196.81	
Titanium Salicylate		
Formula Weight (Da)	320.08	

Table 3. Frequency and Concentration of Use According to Duration and Type of Exposure.[3,4]

	Isopropyl Titanium Triisostearate	
	# of Uses	Conc. (%)
Totals/Conc. Range	580	0.00002-1.5
Duration of Use		
Leave-On	573	0.00002-1.5
Rinse off	7	0.0023-0.3
Diluted for (bath) Use	NR	NR
Exposure Type		
Eye Area	100	0.00002-1.5
Incidental Ingestion	271	0.08-0.42
Incidental Inhalation- Sprays	5*	NR
Incidental Inhalation- Powders	20	0.25-0.75
Dermal Contact	279	0.0002-1.5
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	7	0.001-0.18
Mucous Membrane	275	0.08-0.42
Baby Products	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.

*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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